THE EFFECT OF EXERCISE TRAINING ON SLEEP QUALITY IN HEART FAILURE

Jessica Mary Suna
Bachelor of Nursing, Bachelor of Applied Science (Human Movement Studies), Graduate Certificate in Clinical Trial Management

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School of Exercise and Nutrition Sciences
Faculty of Health
Queensland University of Technology
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Keywords

Depression, exercise, heart failure, insomnia, mass, physical activity, resistance training, sleep.
Abstract

Background: Heart failure is a serious condition estimated to affect 1.5-2.0% of the Australian population with a point prevalence of approximately 1% in people aged 50-59 years, 10% in people aged 65 years or more and over 50% in people aged 85 years or over (National Heart Foundation of Australian and the Cardiac Society of Australia and New Zealand, 2006). Sleep disturbances are a common complaint of persons with heart failure. Disturbances of sleep can worsen heart failure symptoms, impair independence, reduce quality of life and lead to increased health care utilisation in patients with heart failure. Previous studies have identified exercise as a possible treatment for poor sleep in patients without cardiac disease however there is limited evidence of the effect of this form of treatment in heart failure.

Aim: The primary objective of this study was to examine the effect of a supervised, hospital-based exercise training programme on subjective sleep quality in heart failure patients. Secondary objectives were to examine the association between changes in sleep quality and changes in depression, exercise performance and body mass index.

Methods: The sample for the study was recruited from metropolitan and regional heart failure services across Brisbane, Queensland. Patients with a recent heart failure related hospital admission who met study inclusion criteria were recruited. Participants were screened by specialist heart failure exercise staff at each site to ensure exercise safety prior to study enrolment. Demographic data, medical history, medications, Pittsburgh Sleep Quality Index score, Geriatric Depression Score, exercise performance (six minute walk test), weight and height were collected at Baseline. Pittsburgh Sleep Quality Index score, Geriatric Depression Score, exercise performance and weight were repeated at 3 months.

One hundred and six patients admitted to hospital with heart failure were randomly allocated to a 3-month disease-based management programme of education
and self-management support including standard exercise advice (Control) or to the same disease management programme as the Control group with the addition of a tailored physical activity program (Intervention). The intervention consisted of 1 hour of aerobic and resistance exercise twice a week. Programs were designed and supervised by an exercise specialist. The main outcome measure was achievement of a clinically significant change (≥3 points) in global Pittsburgh Sleep Quality score.

Results: Intervention group participants reported significantly greater clinical improvement in global sleep quality than Control (p=0.016). These patients also exhibited significant improvements in component sleep disturbance (p=0.004), component sleep quality (p=0.015) and global sleep quality (p=0.032) after 3 months of supervised exercise intervention. Improvements in sleep quality correlated with improvements in depression (p<0.001) and six minute walk distance (p=0.04). When study results were examined categorically, with subjects classified as either “poor” or “good” sleepers, subjects in the Control group were significantly more likely to report “poor” sleep at 3 months (p=0.039) while Intervention participants were likely to report “good” sleep at this time (p=0.08).

Conclusion: Three months of supervised, hospital based, aerobic and resistance exercise training improved subjective sleep quality in patients with heart failure. This is the first randomised controlled trial to examine the role of aerobic and resistance exercise training in the improvement of sleep quality for patients with this disease. While this study establishes exercise as a therapy for poor sleep quality, further research is needed to investigate the effect of exercise training on objective parameters of sleep in this population.
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<tbody>
<tr>
<td>AACVPR</td>
<td>American Association of Cardiovascular and Pulmonary Rehabilitation</td>
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<tr>
<td>ACE-I</td>
<td>Angiotensin converting enzyme inhibitor</td>
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<td>ACSM</td>
<td>American College of Sports Medicine</td>
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<td>ANOVA</td>
<td>One way analysis of variance</td>
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<td>AHI</td>
<td>Apnoea hypopnoea index</td>
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<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<td>ATS</td>
<td>American Thoracic Society</td>
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<td>AV</td>
<td>Atrioventricular</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CBT</td>
<td>Cognitive Behavioural Therapy</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CPAP</td>
<td>Continuous positive air pressure</td>
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<td>CRT</td>
<td>Cardiac Resynchronisation Therapy</td>
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<td>CSA</td>
<td>Central sleep apnoea</td>
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<td>DEXA</td>
<td>Dual Energy X-ray Absorptiometry</td>
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<td>DMP</td>
<td>Disease management programme</td>
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<td>ECG</td>
<td>Electrocardiograph</td>
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<td>EF</td>
<td>Ejection fraction</td>
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<tr>
<td>EJCTION: HF</td>
<td>Exercise Joins Education Combined Therapy to Improve Outcomes in Newly discharged Heart Failure</td>
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<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
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<tr>
<td>FITT</td>
<td>Frequency, intensity, time, type</td>
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<td>GDS</td>
<td>Geriatric Depression Scale</td>
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<td>GLM</td>
<td>General Linear Model</td>
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<td>HF</td>
<td>Heart failure</td>
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<td>HR</td>
<td>Heart rate</td>
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<td>HREC</td>
<td>Human research ethics committees</td>
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<tr>
<td>ICH-GCP</td>
<td>International Conference on Harmonisation – Good Clinical Practice</td>
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<tr>
<td>IQR</td>
<td>Inter Quartile range</td>
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<td>ITT</td>
<td>Intention to Treat</td>
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<td>KG</td>
<td>Kilogram</td>
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<td>LV</td>
<td>Left Ventricular</td>
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<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
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<tr>
<td>NHF</td>
<td>National Heart Foundation</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>OSA</td>
<td>Obstructive sleep apnoea</td>
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<td>PA</td>
<td>Physical Activity</td>
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<td>PI</td>
<td>Pacific Islander</td>
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<tr>
<td>PLMD</td>
<td>Periodic limb movement disorder</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<td>PSQI</td>
<td>Pittsburgh Sleep Quality Index</td>
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<td>QLD</td>
<td>Queensland</td>
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<td>QOL</td>
<td>Quality of Life</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<td>RIP</td>
<td>Rest in Peace</td>
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<td>RLS</td>
<td>Restless legs syndrome</td>
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<td>RPE</td>
<td>Rating of perceived exertion</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SDB</td>
<td>Sleep disordered breathing</td>
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<td>SOL</td>
<td>Sleep onset latency</td>
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<td>6MWT</td>
<td>Six minute walk test</td>
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<tr>
<td>SPSS</td>
<td>Statistical Package for Social Science</td>
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<tr>
<td>sTNF-R</td>
<td>Soluble tumour necrosis factor-alpha receptor</td>
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<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor-alpha</td>
</tr>
<tr>
<td>TSI</td>
<td>Torres Strait Islander</td>
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<tr>
<td>VO₂</td>
<td>Maximal oxygen consumption</td>
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Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Signature: [Signature]
Date: 8th May 2013
Presentations and Awards

Conference Papers


Awards

Best clinical poster award, Royal Brisbane and Women's Hospital Healthcare Symposium, 10-14th October 2011.

Young investigator award and first prize nursing investigator session, European Society of Cardiology Heart Failure Congress 2012, 19-22 May 2012.
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Finally a special thanks to the many heart failure patients who participated in this project. Improving the lives of patients is what inspired this research.
1.1 BACKGROUND

1.1.1 Heart Failure

Heart failure (HF) is an increasingly common, chronic condition in which the heart is unable to fill with or eject sufficient blood to meet the demands of the body (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, Updated October 2011.). This condition affects approximately 1.5–2% of Australians and accounts for the majority of hospital admissions and GP consultations in persons 70 years or older ("Australia's health 2012," 2012). The prevalence of heart failure increases markedly with age (Mosterd & Hoes, 2007) with a point prevalence of approximately 1% in people aged 50-59 years, 10% in people aged 65 years or more and greater than 50% in people aged 85 years or over (National Heart Foundation of Australian and the Cardiac Society of Australia and New Zealand, 2006).

In order to keep up with the needs of the body and to mediate the effects of impaired circulation the heart employs a number of compensatory mechanisms. Clinical changes include cardiac enlargement, increased heart rate and blood pressure and arterial constriction. While these changes serve to maintain output in the short term, they have serious cardiac consequences if sustained over a long duration. These changes lead to reduced quality of life, declining functional capacity, increased hospital admission and premature death (McMurray & Pfeffer, 2005; Stewart, MacIntyre, Hole, Capewell, & McMurray, 2001).

The most common symptoms of heart failure are breathlessness, fatigue, fluid retention and reduced exercise tolerance (Davie, Francis, Caruana, Sutherland, & McMurray, 1997; Fonseca, 2006; Mant et al., 2009; Oudejans et al., 2011). Other symptoms include orthopnoea (breathlessness when lying down) and paroxysmal
nocturnal dyspnoea (attacks of breathlessness at night) (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2006).

Frequently described co-morbidities of heart failure include anaemia, angina, chronic obstructive pulmonary disease (COPD), cancer, depression, diabetes, gout, hyperlipidaemia, hypertension, obesity and sleep disturbance (Akashi, Springer, & Anker, 2005; Eschenhagen et al., 2011; J. M. Hare et al., 2008; Kasai & Bradley, 2011; MacDonald et al., 2010; O'Connor et al., 2010). These co-morbidities are associated with reduced clinical status and are predictors of poor prognosis in heart failure.

**Treatment of Heart Failure**

Management of heart failure typically includes pharmacological treatment, device therapy, coronary revascularization and surgery (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, Updated October 2011.). Improvements in heart failure medication and device therapy in recent years combined with improved survival rates from myocardial infarction have resulted in an increase in the prevalence of heart failure (National Health Service Information Centre, 2010). These factors have contributed to an increase in health care utilisation in this population. In light of the chronic nature and large costs associated with this disease, a great deal of effort has been put into examining ways to enhance patient’s ability to manage their disease outside of hospital. Multidisciplinary disease management programmes (DMPs) have been established to meet this need (Gonseth, Guallar-Castillon, Banegas, & Rodriguez-Artalejo, 2004; McAlister, Stewart, Ferrua, & McMurray, 2004; C. Phillips et al., 2004; Roccaforte, Demers, Baldassarre, Teo, & Yusuf, 2005; Taylor et al., 2005).

DMPs vary in their details, but important elements appear to include a skilled, multidisciplinary approach; inpatient and outpatient components; medical optimisation according to guidelines; intense education and counselling; close follow-up after hospital discharge with attention to early signs of de-compensation
and a plan for management (e.g. drug titration protocols and rapid-access specialist review) (Yu, Thompson, & Lee, 2006).

**Exercise Training**

At the same time, support has grown for the provision of exercise training as part of comprehensive disease management for HF. Several systemic reviews and meta-analyses of small studies have shown that exercise training improves heart failure symptoms, exercise tolerance, quality of life and hospitalisation rates in patients with heart failure (Piepoli, Davos, Francis, & Coats, 2004; van der Meer et al., 2012). In a more recent randomised controlled trial (RCT) investigators offered participants 36 supervised aerobic exercise sessions in addition to usual care for 3 months followed by home based training. Adjusted analysis found that exercise training according to protocol, led to an 11% reduction in all-cause mortality or hospitalisation (Flynn et al., 2009; O'Connor et al., 2009). These researchers also found that exercise resulted in improvements in self-reported health status including quality of life in patients with systolic heart failure (LVEF < 35%) (Flynn, et al., 2009).

While this evidence suggests exercise therapy is beneficial in heart failure, studies failed to recruit elderly patients with heart failure. Furthermore, the only trial that identified a treatment effect was obtained following an intensive treatment regime which may not be clinically practical to deliver. In order to examine the benefit of early exercise rehabilitation in a more representative HF population the EJECTION: HF (Exercise Joins Education Combined Therapy to Improve Outcomes in Newly discharged Heart Failure) study was developed. While conducting this study difficulty sleeping was identified as a frequent and debilitating symptom of patients.

### 1.1.2 Sleep Disorders in Heart Failure

Sleep disorders are a collection of conditions associated with disturbance in amount, quality and timing of sleep. Disorders of sleep can be both a cause and a
consequence of disease in HF (Edell-Gustafsson, Gustavsson, & Yngman Uhlin, 2003; Manocchia, Keller, & Ware, 2001; Parish, 2009). Explanatory mechanisms for the coexistence of these diseases include prolonged sympathetic activation, intrathoracic pressure changes, systemic inflammation, oxidative stress, coagulation factors, endothelial damage, and platelet activation (Bradley & Floras, 2003a, 2003b).

These conditions have major social, economic and medical costs (Brostrom, Stromberg, Dahlstrom, & Fridlund, 2003; D'Ambrosio, Bowman, & Mohsenin, 1999; Guilleminault, Stoohs, Clerk, Cetel, & Maistros, 1993). Disturbances of sleep worsen symptoms, impair independence and quality of life (QOL) and lead to increased morbidity and mortality in this already complex disease (Ferrier et al., 2005; Mared, Cline, Erhardt, Berg, & Midgren, 2004; Sin & Man, 2003; Trupp, 2004; Yamamoto et al., 2007).

**Diagnosis of Sleep Disturbance**

Due to the different causative mechanisms of disorders of sleep in this population, diagnostic methods also vary. Diagnosis is complicated as symptoms of HF often obscure symptoms of sleep disturbance due to their similarities (Arzt et al., 2006; Erickson, Westlake, Dracup, Woo, & Hage, 2003; Gary & Lee, 2007; Macey, Woo, Kumar, Cross, & Harper, 2010; Montemurro et al., 2012; Trupp, 2004). Detailed examination of SDB is also challenging as gold standard diagnosis through polysomnography (PSG) can be expensive, labour intensive and difficult to access (Ferrier, et al., 2005; Rao & Gray, 2005).

**Types of Sleep Disturbance in Heart Failure**

A variety of sleep disorders are commonly reported in patients with heart failure. The most common disorders of sleep in HF are insomnia, sleep associated movement disorders and sleep disordered breathing (SDB). **Insomnia** is a sleep problem that includes difficulty initiating, maintaining or non-restorative sleep that results in distress or impairment in functioning. Almost 33% of patients with HF experience insomnia (Brostrom & Johansson, 2005; Trupp, 2004; Trupp et al.,
Heart failure related factors which may contribute to insomnia include; pain, dyspnoea, paroxysmal nocturnal dyspnoea, associated mood disorders, physical exhaustion, stress, depression, anxiety, co-morbid sleep disorders such as sleep apnoea or from medications used in HF treatment (Collop, 2010; Eddy & Walbroehl, 1999; Parish, 2009; Yeh et al., 2008). Insomnia is linked with increasing age, obesity, depression, RLS, PLMD and circadian sleep disturbance (D. Hayes, Jr., Anstead, Ho, & Phillips, 2009; Johansson et al., 2010; Redeker et al., 2010). Nocturnal symptoms of insomnia include difficulty falling asleep or waking frequently during the night. Day time symptoms can include poor concentration, difficulty with memory, impaired motor coordination and irritability (Eddy & Walbroehl, 1999; D. Hayes, Jr., et al., 2009). Some sufferers of insomnia however do not describe daytime sleepiness (Redeker, et al., 2010).

Treatment of insomnia is dependent upon the cause of the problem. Behavioural recommendations for insomnia treatment include maintaining good sleep hygiene and sleep restriction which involves limiting the time spent in bed for sleeping only (Lande & Gragnani, 2010). Good sleep hygiene involves undertaking regular exercise, keeping a constant sleep routine, avoidance of caffeine, alcohol and smoking, maintaining a good sleep environment and resolving stress prior to sleep (Erickson, et al., 2003; Hoch et al., 2001). Other treatment options for insomnia include short term sedative medication and cognitive behavioural therapy (CBT).

Sleep disordered breathing (SDB) is a well-recognised co-morbidity of cardiovascular disease and comprises of obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) syndrome (Brostrom & Johansson, 2005; Redeker, 2008; Walters & Rye, 2009). OSA occurs due to a partial or complete collapse of the airway during sleep (Bradley & Floras, 2003a) while CSA arises due to reductions in central respiratory drive (Naughton et al., 1995). Both conditions are highly prevalent in HF with OSA suggested to occur in up to 37% of patients (Sin et al., 1999) and CSA between 33% and 40% (Javaheri et al., 1998; Sin, et al., 1999).
OSA is thought to be a causative factor in the development of HF with one study showing a two-fold increase in the likelihood of having HF in patients with OSA (Bradley & Floras, 2003a; Bucca et al., 2007; Ferrier, et al., 2005; Kasai & Bradley, 2011; Redeker, 2008; S. S. Smith, Doyle, Pascoe, Douglas, & Jorgensen, 2007). CSA on the other hand is thought to occur as a consequence of HF (Bradley & Floras, 2003b). Risk factors for OSA include obesity, male gender, increasing age, family history, ethnicity (African), a narrowed airway, use of alcohol, sedatives or tranquilizers, smoking and nasal congestion (Young, Skatrud, & Peppard, 2004). Risk factors for CSA include increasing age, male gender, hypocapnia and atrial fibrillation (Bradley & Floras, 2003b; Sin & Man, 2003).

SDB is associated with accelerated disease progression and poor prognosis in heart failure (Floras, 2009). This is largely due to the combined effects of sympathetic nervous system over-activation which characterise the two conditions (Solin et al., 2003). In heart failure, increases in sympathetic activity result as a compensatory mechanism of the autonomic nervous system to maintain cardiac output in the failing heart (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, Updated October 2011.). In SDB, sympathetic activation occurs as a consequence of the periods of apnoea that typify OSA and CSA. These apnoeic events trigger a drop in oxygen levels, a rise in carbon dioxide levels, and a spike in blood pressure, heart rate, and hormones as the body employs autonomic systems in an effort to reinstate breathing and ultimately restore oxygen levels to normal (Bradley & Floras, 2003a, 2003b).

There are several types of receptors that drive the autonomic nervous system. These receptors play an important role in sympathetic over-activity in coexisting heart failure and sleep disordered breathing. Chemoreceptors detect levels of carbon dioxide and oxygen in the blood (Schultz, Li, & Ding, 2007). Baroreceptors are stretch sensitive mechanoreceptors that detect pressure changes of blood flow and increase or decrease peripheral resistance to alter cardiac output (Narkiewicz et al., 1998). Ergoreceptors are a type of metaboreceptor/mechanoreceptor that are activated during muscle contraction and promote respiratory and circulatory
responses to physical work (Ponikowski et al., 2001; Scott, 2000). These receptors all work to send information to the respiratory centre in the brain which in turn sends a message to sympathetic ganglia that promotes surges of sympathetic activity to terminate the apnoeic event, elicit arousal and reinstate the oxygen levels. Such effects occur in contrast to the usual decreases in muscle sympathetic nervous system activity (MSNA), BP and HR that generally characterise the sleep state (Solin, et al., 2003). Recent findings of Spaak and colleagues have identified in fact, an additive effect of sympathetic activity in patients with both conditions that persists into the waking hours (Spaak et al., 2005).

Symptoms of OSA can include snoring, choking, snorting or gasping for breath during sleep and daytime sleepiness (Bradley & Floras, 2003a). Symptoms of CSA include observed episodes of long pauses in breathing during sleep, abrupt awakenings with shortness of breath, shortness of breath that is relieved by sitting up, difficulty getting to sleep, daytime sleepiness, difficulty concentrating, morning headaches and snoring (Bradley & Floras, 2003b).

Treatments for OSA include weight reduction, abstinence from alcohol and sedatives, continuous positive airway pressure (CPAP), sleeping in a non-supine position and mandibular advancement devices (Bradley & Floras, 2003b; Spieker & Motzer, 2003). As CSA is thought to be a sign of advanced HF the main treatment consideration is to improve the underlying disease by optimizing heart failure drug therapy (Redeker, 2008). Additional treatment methodologies include provision of nocturnal supplemental oxygen, CPAP and atrial overdrive pacing (Bradley & Floras, 2003b; Javaheri, Ahmed, Parker, & Brown, 1999; Sinha et al., 2004; Spieker & Motzer, 2003).

Sleep-associated movement disorders are a group of conditions associated with either motor activity during sleep or a lack of reduction in motor tone during sleep (Schaffernocker, Ho, & Hayes, 2009). The most commonly reported sleep associated movement disorders in heart failure are periodic limb movement disorder and restless legs syndrome. The causes of both of these diseases are not
clear (Earley, Allen, & Hening, 2011). In a study of male patients with severe HF, up to 52% were found to exhibit moderately severe periodic limb movement during sleep (Hanly & Zuberi-Khokhar, 1996). Symptoms of restless legs syndrome include uncomfortable sensations in the legs particularly when sitting or lying down, accompanied by an irresistible urge to move the affected limb (Earley, et al., 2011). Sufferers of this condition also report poor sleep quality and daytime sleepiness (Earley, et al., 2011). Treatment of PLMD and RLS is centred upon pharmacotherapy including iron replacement therapy (Silber et al., 2004; Tarsey & Sheon, 2012). Non-pharmacological treatment options include mental alerting activities, avoidance of aggravating factors such as coffee, nicotine and alcohol, stretching, heat and massage (Silber, et al., 2004; Tarsey & Sheon, 2012).

Issues with Treatment for Sleep Disturbance

While several treatment modalities for sleep disturbance exist, none are without issues. For example, several studies have found that while CPAP decreases the number of apnoeas and hypopnoeas and improves sympathetic activity it fails to improve cardiovascular variables and survival in HF (Khayat et al., 2008; Randerath, Galetke, Kenter, Richter, & Schafer, 2009). Patients also often report a lack of compliance due to difficulty using the machine, titration, noise, nasal dryness and nasal congestion (Caples & Somers, 2007; Javaheri, 2006; Steiner, Schueller, Schannwell, Hennersdorf, & Strauer, 2007).

The optimisation of HF pharmaceutical therapy has also been suggested to improve sleep (Bordier, 2009; Erickson, et al., 2003; Goldberg et al., 2009; Krachman, D'Alonzo, Permut, & Chatila, 2009). Although this alleviates many symptoms of HF, studies suggest this form of therapy only produces minor improvements in sleep (Sinha, et al., 2004; Wang, Chen, Li, Hao, Gu, et al., 2009; Wang, Chen, Li, Hao, Pang, et al., 2009). In fact, many HF medications have been linked with sleep disturbance (Erickson, et al., 2003). For example, diuretics may increase the incidence of nocturia and beta blockers are suggested to cause insomnia and vivid nightmares (D. Hayes, Jr., et al., 2009).
Potential treatments for insomnia include sedative therapy and cognitive behavioural therapy (CBT). These treatments are also problematic. Sedatives are not recommended for long term use and have been linked with a number of adverse effects, particularly in the elderly and include side effects such as confusion and falls (Singh, Clements, & Fiatarone, 1997). Cognitive behavioural therapy can be costly to deliver and difficult to access as it requires the skills of clinical psychologists or psychiatrists which are not necessarily available at all health care institutions.

**Exercise as a Treatment for Sleep Disturbance**

Exercise training has been recommended as a non-pharmacological treatment for sleep disturbances in healthy individuals, based largely on epidemiological studies which show a positive association between exercise training and sleep parameters (Lande & Gragnani, 2010; Quan et al., 2007; Sherrill, Kotchou, & Quan, 1998; Vuori, Urponen, Hasan, & Partinen, 1988; S. K. Youngstedt, C., 2006). A number of experimental studies have also examined various forms of exercise training in the elderly, persons with existing sleep complaints and patients with other health conditions. These papers suggest an improvement in sleep quality, fatigue, total sleep time, deep sleep and sleep interruptions following exercise, resulting in greater overall sleep efficiency (Afshar, Emany, Saremi, Shavandi, & Sanavi, 2011; Norman, Von Essen, Fuchs, & McElligott, 2000; Payne, Held, Thorpe, & Shaw, 2008; Sakkas et al., 2008; Sengul, Ozalevli, Oztura, Itil, & Baklan, 2011; Tang, Liou, & Lin, 2010; Young-McCaughan et al., 2003).

Several mechanisms are proposed for the effect of exercise on sleep, however the causal mechanism by which exercise exerts its beneficial effect on sleep has yet to be established (Erickson, et al., 2003; Gary & Lee, 2007; Yamamoto, et al., 2007). The first way in which exercise is thought to improve sleep is through reductions in depression and anxiety. Because there is strong evidence that disorders of sleep are both a risk factor and consequence of depression and anxiety (S. D. Youngstedt, 2005) it follows that exercise could improve sleep through its antidepressant and anxiety reducing effects (Arcos-Carmona et al., 2011; Singh, et al., 1997; S. D. Youngstedt, 2005). The second theory is that exercise may improve SDB via reductions in weight. This theory asserts that the reductions in weight
which accompany exercise reduce fluid accumulation in the neck and lead to reductions in obstructive sleep apnoea. Sleep is also suggested to be related to physical function with the improvements in physical function which accompany exercise suggested to improve sleep (Sabbagh, Iqbal, Vasilevsky, & Barre, 2008). The fourth theory asserts the thermo-regulative effects of exercise can lead to increased slow wave or deep sleep (Horne & Moore, 1985; Horne & Staff, 1983). The fifth hypothesis is based on the belief that sleep serves as a period of energy conservation and body restoration. Exercise is thought to improve sleep depth and duration because of its effect on energy expenditure, body temperature elevation and tissue breakdown (Driver & Taylor, 2000). Another theory asserts that exercise influences sleep through its influence on circadian rhythm (Reilly, 1990). Exercise may influence circadian rhythm through exposure to phase-shifting stimuli such as bright light (Shiotani, Umegaki, Tanaka, Kimura, & Ando, 2009). Exercise potentially increases cytokines, such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-a), and soluble tumour necrosis factor-alpha receptor (sTNF-R), which may improve sleep (Sprod et al., 2010). Exercise may also present a potential method for improvement in sleep through the modulation of autonomic abnormalities by reducing sympathetic activation and increasing vagal tone (Rosenwinkel, Bloomfield, Arwady, & Goldsmith, 2001).

Issues with Current Literature Regarding Exercise as a Treatment for Sleep Disturbance

While literature regarding exercise therapy for sleep disorders suggests exercise as a potential treatment option it has many limitations. The causal mechanism by which exercise exerts its beneficial effect on sleep has yet to be established (Basta et al., 2008; Reeder, Franklin, & Bramley, 2007). Many alternative explanations for the observed relationship between exercise and sleep exist. For example, improved sleep may lead to an increased likelihood of exercise (S. D. Youngstedt, 2005) and improved well-being associated with better sleep may also lead to a higher probability of exercise. Furthermore, good health may be inaccurately linked with improved sleep when in fact the real explanation may be associations with physical adaptations from exercise. In addition, it is theorised that persons who exercise are more likely to practice other healthy behaviours favourable
Early studies examining the effect of exercise on sleep have excluded patients with chronic illnesses such as HF, in whom sleep disturbance may be due to a range of disease and treatment-related factors which may be less amenable to exercise effects. Exercise prescription is more complex in the chronically ill, but there is now strong evidence that exercise is safe and beneficial in a range of chronic illnesses (American College of Sports Medicine & American Diabetes Association, 2010; S. C. Hayes, Spence, Galvao, & Newton, 2009; Selig et al., 2010). Exercise initiation and adherence remains a major challenge in HF patients (E. M. Phillips, Schneider, & Mercer, 2004). However, these patients often have multiple contacts with healthcare providers, presenting opportunities to recommend and reinforce the benefits of exercise. Better understanding of the role of exercise in relieving common and troubling symptoms may improve patient motivation to initiate or maintain exercise.

1.2 AIM OF TAILORED LITERATURE REVIEW

Sleep disturbances are a common co morbidity of patients with HF and impair function, mood and QOL. Exercise training has demonstrated health benefits in this condition, and has been shown to improve objective and subjective measures of sleep in several studies of sedentary healthy adults. The aim of this literature review was to identify the evidence for the effect of exercise training as a non-pharmacological intervention to improve sleep in patients with HF.
1.2.1 Method

A search of electronic databases including Medline, CINAHL, PubMed, ScienceDirect, EBSCO host and the Cochrane database from 1981 to 2012 was performed. Search terms included exercise, exercise training, exercise therapy, physical activity, sleep, sleep disorders, sleep quality, insomnia, sleep initiation and maintenance disorders, RLS, and sleep apnoea. Review articles, epidemiological surveys and observational studies were excluded. Studies were included if they described a clinical trial which used a structured exercise training program prescription (specifying type, frequency, duration) as the intervention and reported objective and/or subjective measures of sleep as outcomes. Studies were excluded if they were not conducted in participants with HF. References from retrieved papers were examined to identify additional studies.

1.2.2 Results

Two hundred and seventeen studies were examined for inclusion. Six studies were conducted in patients with HF. Table 1.1 provides details of the studies included.
Figure 1. Identification and selection of studies in literature review.
Table 1.1

Details of Studies Included in Literature Review

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design/ objectives</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Intervention</th>
<th>Results</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tr>
<td>(Yeh, Mietus, et al., 2008)</td>
<td>Retrospective analysis of RCT data to examine effect of tai chi on sleep</td>
<td>18 stable, LV systolic HF patients (EF&lt;=40%)</td>
<td>1) Sleep (sleep spectrogram) 2) QOL (MLHF) 3) Exercise capacity (6MWT + V02 max)</td>
<td>Study group 1 (n=8): 3 months @ 2/week 1 hour Tai Chi  Control group (n=10): Usual care</td>
<td>Study group: Significant increase in high-frequency coupling (stable sleep) + reductions in low-frequency coupling (unstable sleep) (p=0.04 and p&lt;0.01) Improved exercise capacity (mean 76m) (p&lt;0.01) and QOL (p&lt;0.01). Significant correlation between QOL and sleep stability (increased high-frequency coupling associated with better QOL)</td>
<td>Study undertaken in often under-represented population</td>
<td>Small sample size, Use of sleep spectrogram</td>
</tr>
<tr>
<td>(Gary &amp; Lee, 2007)</td>
<td>RCT to test effects of home-based exercise on sleep</td>
<td>23 women with stable diastolic HF (EF&gt;= 45%)</td>
<td>1) Sleep (actigraphy + sleep diary) 2) Physical function (6MWT) 3) QOL (MLHFQ) 4) Depression (GDS)</td>
<td>Study group (n=13): 3 months @ 3/week Self-monitored graded outdoor walking  Control group (n=10): 12 week 1/week educational home visit</td>
<td>Study group: Significant increase in TST (p&lt;0.01) Improved QOL (p&lt;0.05)</td>
<td>Study undertaken in often under-represented population</td>
<td>Small sample size, Female only, Confounding SQ not measured, SA not diagnosed</td>
</tr>
<tr>
<td>Author</td>
<td>Study design/objectives</td>
<td>Participants</td>
<td>Outcomes</td>
<td>Intervention</td>
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| (Yamamoto, et al., 2007) | Case control study of the effects of aerobic exercise | 18 stable NYHA II-III, systolic HF patients (EF<45%) with SDB (AHI>10)     | 1) Sleep (polygraph)   
2) Exercise capacity (CPET) | **Study group (n=10):** 6 months @ 3/week 1 hour cycling/ walking    | **Study group:**  
BNP decreased significantly (p<0.05)  
BMI did not change  
AHI significantly decreased (p<0.01)  
CSA decreased (p<0.01)  
OSA unchanged  
Significant improvement in arterial oxygen saturation (p<0.05)  
Increased peak V02 (p<0.05)  
Decrease in the VEVC02 slope (p<0.01)  | First study to show aerobic exercise improved exercise capacity & ameliorated breathing abnormalities in HF patients. | Majority male  
No control group  
Small sample  
No specialised exercise staff |
| (Ueno et al., 2009)   | Cross over case control study to test effects of exercise on sleep + neurovascular control | 24 stable, systolic HF patients (EF<45%), 9 healthy age matched controls | 1) Sleep (PSG)  
2) Micro-neurography  
3) Forearm blood flow  
4) Peak V02  
5) QOL (MLWHF) | **Healthy age matched control group (n=9):** 4 months @ 3/week 60 min aerobic/ resistance exercise | **Study group:**  
Increased functional class  
Improved peak V02  
Reduced MSNA (higher in HF + OSA/CSA)  
Patients with HF + OSA  
Increased stage 3-4 sleep + oxygen saturation  
Decreased arousals + AHI | Excluded DM + high BMI patients  
Finapres not reliable |
<table>
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<tr>
<th>Author (year)</th>
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<th>Strengths</th>
<th>Weaknesses</th>
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| Servantes et al., 2012 | RCT to test effectiveness of home based exercise | 50 chronic HF patients with sleep apnoea | 1) CPET  
2) Isokinetic strength + endurance  
3) MLHF  
4) PSG | Study group 1 (n=18): 3 months daily recommended home aerobic training  
Study group 2 (n=18): 3 months daily recommended home aerobic + strength training  
Study group 3 (n=14): untrained | Decreased AHI (group 1+2). Group 1 decrease in hypopnoea. Group 2 decrease apnoea and hypopnoea. Both groups exhibited decreased number of nocturnal arousals and increased sleep efficiency. | | Generalisability of sample – many patients not able to safely exercise at home  
Reliance on self monitoring - ? compliance |
| P. Duarte Freitas et al., 2011 | Cohort study to evaluate impact of card rehabilitation program on physical parameters & QOL of cardiac patients. | 101 cardiac patients | 1) Anthropometry  
2) QOL  
3) SF-36  
4) HADS  
5) PSQI | 1 month @ 5/week @ 3 hours per day cardiac rehabilitation program | 25% improvement in sleep quality  
29% decrease in anxiety  
32% decrease in depression  
Weight loss associated with decreased anxiety  
Improved SQ related to mental health state | | Short duration of intervention  
Multi-factorial program =? effect of other parts of program on sleep (medications, nutrition, psychological support) |
Effect of Exercise on Subjective Measures of Sleep

One article which met review criteria examined the relationship between exercise and subjective (self-reported) sleep variables. In this recent study by Duarte Freitas et al (P. Duarte Freitas, et al., 2011) a 25% improvement in global sleep quality (p<0.001) was identified following an intensive four-week, in-patient cardiac rehabilitation program (P Duarte Freitas et al., 2011). These findings are consistent with previous investigations regarding the effect of exercise on sleep quality in other populations (Afshar, et al., 2011; Arcos-Carmona, et al., 2011; Caldwell, Harrison, Adams, & Triplett, 2009; K. M. Chen et al., 2009; K. M. Chen et al., 2010; M. C. Chen, Liu, Huang, & Chiou, 2012; de Castro Toledo Guimaraes, et al., 2008; King, et al., 1997; King et al., 2008; Kline et al., 2011; Li et al., 2004; Reid et al., 2010; Richards et al., 2011; Sprod, et al., 2010; Tang, et al., 2010; Tworoger et al., 2003). In this cohort study of 101 patients referred for cardiac rehabilitation at Clinique Saint-Orens France, participants completed daily aerobic exercise of 2-3 hours duration including 45 minutes of ergo cycle or treadmill, 1 hour of walking outside plus a variety of sessions including fitness, gymnastics, relaxation, Qi Gong and aquatic training. Further to improvements in sleep quality the study identified significant improvements in quality of life, anxiety and depression after the rehabilitation program. While this study lacked a control group it provided a much larger sample size than any other investigation on the topic in this population group. It is difficult to ascertain however, which component of this comprehensive program produced improvements in sleep, as a variety of exercise interventions were offered. Furthermore, this program which was offered to patients with a number of different cardiac conditions involved optimising medical therapy, controlling cardiovascular risk factors, diet monitoring, education and psychological support. The improvements in sleep quality, depression and QOL identified may have been attributable to the other interventions described above. While this study produced significant improvements in sleep, replication of the study would be difficult in our current health care system given the costs associated with an intensive in-patient treatment over a four week period.
Effect of Exercise on Objective Measures of Sleep

The majority of studies included in the review examined the effect of exercise on objective measures of sleep. These studies were undertaken in stable systolic HF patients with existing sleep complaints, with one investigation completed in women with diastolic HF. Study interventions included bicycle ergometer, walking, strength training and Tai Chi. Study durations ranged from 3 to 6 months. The majority of interventions were conducted three times a week. Study designs also differed; two studies used a case control design, two were randomised controlled trials and the last involved a retrospective review of data collected in a randomised controlled trail (RCT).

Evidence from these studies suggests objective measures of sleep are also optimised following exercise programs in persons with HF. Yamamoto and colleagues (Yamamoto, et al., 2007) enrolled 18 stable systolic HF patients with demonstrated SDB on cardiorespiratory polygraphy. Of the 18 participants recruited to the study, 10 agreed to participate in an exercise intervention and the remaining 8 served as controls. The exercise intervention consisted of 6 months of aerobic exercise in the form of walking or cycling 3 times per week. The number of quantified respiratory events per hour of sleep time, commonly known as the apnoea hypopnoea index (AHI), was significantly decreased in the exercise group (p<0.01), with reduction in central but not obstructive apnoea events. Exercise was also shown to increase oxygen levels during sleep (p<0.05). This study was limited by its small sample size, case control design and lack of specialist exercise supervision.

In contrast to the findings of Yamamoto, Ueno and colleagues found that exercise reduced the AHI and improved oxygen saturation during sleep only in the subgroup with co-existing OSA (Ueno, et al., 2009). This prospective cohort study examined 24 stable HF patients before and after a 4 month exercise intervention (3 times per week aerobic and resistance exercise), compared to 9 subjects without HF. Heart failure participants were further grouped according to results of PSG into OSA, or no sleep apnoea. Those with OSA also tended to have increased levels of deep, stage 3-4 sleep following exercise. This study was also limited by its small
sample size and lack of randomised controlled design. Furthermore, Ueno and colleagues excluded patients with diabetes mellitus and overweight individuals (Ueno, et al., 2009). As 30% of patients with HF also suffer from diabetes and many are overweight, it is difficult to apply these results to the usual HF population (Ueno, et al., 2009).

 Likewise to the findings of Ueno and colleagues, Yeh et al identified an increase in stable sleep (p=0.04) in their retrospective analysis of ECG-based sleep spectography. This trial involved 12 weeks of Tai Chi exercise in 18 patients with stable systolic HF (Yeh, Mietus, et al., 2008; Yeh, Wayne, & Phillips, 2008). This study is limited by its use of retrospective analysis of data and the use of 24 hour continuous ECG data to measure sleep rather than polysomnography which would have allowed deeper review of sleep stages. The sample size of this study was small and like other studies, was unable to clarify which part of the exercise intervention was responsible for improvements in sleep.

 In an examination of the effect of home-based exercise for patients with HF and sleep apnoea, a significant decrease in AHI was identified following exercise (Servantes, et al., 2012). In this study, the 50 participants were randomly allocated to one of three groups; aerobic training (n=18), aerobic with strength training (n=18) and untrained (n=14). Participants were provided with three supervised sessions then were instructed to exercise in their homes for three months and were monitored weekly by telephone. Aerobic exercise was found to decrease hypopnoea events while aerobic exercise with the addition of strength training decreased both apnoea and hypopnoea events. Nocturnal arousals decreased in both groups and this was associated with a significant increase in sleep efficiency. Limitations of this study relate to sample generalisability with almost 85% of patients screened for inclusion, not eligible for study inclusion. Another study limitation involves the use of self-report for exercise adherence therefore it is not possible to confirm the extent to which the individual complied with the exercise regime.
Gary and Lee (Gary & Lee, 2007) randomly allocated 23 women with stable diastolic HF to a 12 week program of thrice weekly, self-monitored graded outdoor walking or an attention control group of weekly home-based education (Gary & Lee, 2007). While these investigators were unable to identify a significant difference in study outcomes between women in the walking group and education group, increased sleep duration documented by actigraphy by observed in exercise participants (p<0.01) following intervention. This study was limited by its small sample size and lack of an objective measure of sleep thus investigators were unable to confirm whether existing sleep disturbance contributed to results. Further limitations involve the use of an un-standardized questionnaire to measure sleep quality and a lack of measurement of potential confounding factors such as the effect of light exposure.

Potential Mediators of Improvement in Sleep

These investigations highlight several potential moderators of sleep enhancement. Improvements in sleep appeared to be associated with reductions in anxiety and depression (P. Duarte Freitas, et al., 2011), improved quality of life (Gary & Lee, 2007; Yeh, Mietus, et al., 2008) and increased exercise capacity (Servantes, et al., 2012; Yeh, Mietus, et al., 2008).

Effect of Exercise Frequency, Intensity, Time and Type

This review of the literature highlights a lack of clarity regarding the most effective form of exercise intervention for improvement in sleep quality and many questions remain regarding the optimal frequency, intensity, timing and type of exercise required to elucidate improvements in sleep. Previous investigators have suggested that a u-shaped association exists between exercise and sleep with insufficient exercise and very high amounts of exercise appearing to have unfavourable effects on sleep (S. D. Youngstedt, 2005). This theory however is refuted by Kline and colleagues who later report that even low doses of exercise significantly decrease the odds of sleep disturbance (Kline et al., 2012). While an acute episode of exercise has been found to have a favourable effect on sleep there is greater support of the effects of habitual exercise in improving sleep (Uchida et al.,
This may be because chronic exercise is needed to bring about changes in body composition, basic metabolic rate, cardiac function, glycaemic control, and immune function (Pedersen, 2006).

A team of researchers in Finland have proposed that there is no relationship between exercise intensity or duration and sleep quality (Myllymaki et al., 2012). In another study however, moderate intensity exercise was suggested to be the most effective in improving symptoms associated with poor sleep (Uchida, et al., 2012; S. D. Youngstedt, 2005). Question also remains regarding the most effective form of exercise for sleep improvement however it appears that the greatest evidence lies with aerobic exercise interventions. More recent studies have examined the effects of yoga, Tai Chi and resistance exercise and appear to show favorable results, although greater evidence is required to confirm these findings.

### 1.3 SUMMARY AND IMPLICATIONS

This review of the literature suggests that there may be a role of exercise in improving a range of sleep disturbances in HF. This theory is supported by the positive effect of exercise on measures of sleep identified in other populations. Although these studies are small, they report favourable effects of exercise on several sleep parameters. Exercise training in HF patients appears to lead to an increased proportion of stable, deep sleep (Ueno, et al., 2009; Yeh, Mietus, et al., 2008) and may reduce the severity of sleep apnoea independent of body weight changes (Ueno, et al., 2009; Yamamoto, et al., 2007).

While existing literature is promising, interpretation and synthesis of the results is limited by methodological issues. This may explain the lack of comment regarding the beneficial effects of exercise on sleep quality in current heart failure guidelines ("Australia's health 2012," 2012). Studies used a range of exercise interventions (varying by type, timing, frequency, intensity and duration) and few reported adherence levels. Many of the studies were not randomised and few of the controlled studies used an attention control. Studies also employed a range of
outcomes and measures, and the relationship between objective measures of sleep (sleep architecture, sleep disordered breathing), subjective sleep quality and sleepiness, and objective measures of daytime functional impairment remains unclear. Finally, the way in which exercise influences its sleep enhancing effects was not confirmed and many confounding factors or alternative explanations are evident.

Further investigation is therefore required to confirm the beneficial effect of exercise in this population. To ensure the success of these investigations several important design aspects need to be met. Firstly, future studies should be adequately powered and use a randomised controlled design. It is equally important the population enrolled adequately reflects that population to which the intervention applies. Studies should also examine subjective sleep measures because poor sleep quality may be an important symptom of an underlying sleep or medical disorder (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Furthermore, an outcome of improved sleep carries a real meaning for patients and is likely to improve compliance with exercise regimes. While difficult, it is also important that efforts be made to clarify the mechanism by which exercise exerts its sleep promoting effects. Lastly, studies should also examine the best form of exercise intervention in terms of frequency, intensity, time and type of exercise.

In conclusion these findings suggest that exercise has the potential to improve several objective and subjective measures of sleep in patients with HF. Evidence suggests that improvements in sleep quality coincide with improvements in sleep pattern and breathing, quality of life, anxiety and depression, exercise performance and body composition. This information may be valuable for patients and their healthcare providers in motivating exercise participation. Further well-conducted studies are also required to further elucidate mechanisms of sleep improvement and interrelationships between physiological, subjective and functional sleep variables.
1.4 STUDY AIM

An examination of the literature highlighted a number of issues with treatment for sleep disorders in patients with HF. Exercise programs were identified as a potential solution given their role in good sleep hygiene in other populations and in light of the positive research evidence identified in small studies of patients with HF (Driver & Taylor, 2000; Paparrigopoulos, Tzavara, Theleritis, Soldatos, & Tountas, 2010). A study of the effect of exercise on sleep quality in HF was important because the effect of such programs on sleep quality in HF was not known (Flynn, et al., 2009; O'Connor, et al., 2009). An outcome of subjective sleep quality was chosen because it is often the individual’s perception of their sleep state which motivates them to seek treatment. This outcome was also selected in light of the high costs and access issues associated with polysomnography.

The primary aim of this study was therefore to examine the effect of a supervised, hospital-based aerobic and resistance exercise program in addition to a standard HF DMP on (1) clinical change (≥3 points) in global Pittsburgh Sleep Quality Index (PSQI) score; (2) change in component and global PSQI score and; (3) change in sleep category (good/poor).

Secondary aims were to examine;

- The effect of dose of exercise on clinical change (≥3 points) in global Pittsburgh Sleep Quality Index (PSQI) score;
- The effect of potential mediators of improvement in sleep including depression, exercise performance and body mass index (BMI) and;
- The effects of baseline sleep quality on exercise adherence.

1.5 STUDY HYPOTHESIS

1.5.1 Primary Hypothesis

The primary hypothesis of the study was that a 3 month program of supervised, hospital-based exercise training will produce greater clinically significant improvement in subjective sleep quality when compared to a standard HF DMP.
1.5.2 Secondary Hypothesis

1. Increased dose of exercise is related with greater clinical improvement in sleep quality.

2. Improvements in sleep quality as measured by change in global PSQI score are mediated by improvements in depression as measured by the change in Geriatric Depression Scale (GDS) between Baseline and Month 3.

3. Improvements in sleep quality as measured by change in global PSQI score are mediated by improvements in exercise performance as measured by change in six minute walk test (6MWT) distance between Baseline and Month 3.

4. Improvements in sleep quality as measured by change in global PSQI score are mediated by a reduction in BMI between Baseline and Month 3.

5. Poor baseline sleep quality is related with reduced adherence to intervention and reduced adherence to physical activity (PA) guidelines.
Chapter 2: Research Design

2.1 METHODOLOGY

This is a sub-study of the EJECTION-HF trial. Methods for the full study have been published in the European Journal of Heart Failure (Mudge et al., 2011). The primary objective of the EJECTION study is to measure the impact of supervised exercise training on death and readmission in heart failure patients enrolled in a post-hospital disease management programme. While conducting this study investigators identified difficulty sleeping as a common and debilitating complaint of study participants. Literature review revealed a paucity of studies in heart failure patients, but some evidence that exercise improves sleep quality in other populations. The addition of a sleep quality questionnaire to the existing protocol would permit exploring the potential role of exercise training on sleep quality, adding important patient-centred data to the main study.

Both studies used a RCT design with blinded end-point analysis. Participants were randomly assigned to a 3 month DMP of education and self-management support including standard exercise advice (Control) or to the same DMP as the control group with the addition of a tailored exercise programme designed and supervised by a physiotherapist and/or clinical exercise physiologist (Intervention). A paper based randomisation procedure was co-ordinated centrally. Randomisation was undertaken in blocks of 10 to allow consistent referral rates to the exercise programme and was stratified across hospital sites.

2.2 PARTICIPANTS

Study recruitment was carried out between June 2009 and August 2011. Participants were 112 patients referred to hospital heart failure services (HFS) at three hospitals in South East QLD, Australia including the Royal Brisbane and Women’s Hospital, The Prince Charles Hospital and Logan Hospital. In order to be safe to exercise and to ensure a representative HF population, participants were
required to meet a number of inclusion criteria. Participants were required to (1) have been admitted to hospital with symptomatic congestive HF as a dominant clinical diagnosis, with documented symptoms and signs of HF combined with either chest x-ray changes or echocardiography evidence of left ventricular dysfunction within the past 6 week period; (2) currently on medical therapy for HF\(^1\); and (3) able to regularly attend the program and follow-ups. (Mudge, et al., 2011).

Exclusion criteria included the following: (1) a terminal diagnosis; (2) serious cognitive impairment; (3) other serious physical impairment which would prevent program attendance and participation; (4) Implantable Cardiac Defibrillator (ICD) insertion within 4 weeks of programme commencement; (5) Cardiac Resynchronisation Therapy (CRT) within 6 months of programme commencement\(^2\); (6) awaiting cardiovascular procedure (revascularisation or hospitalisation for surgery); (7) completed a full 12 week regime of formal exercise rehabilitation in the past 12 month period; or (8) did not satisfy study safety criteria listed below in Figure 1.

1. Refractory chest pain.
2. Uncontrolled cardiac arrhythmias causing symptoms of haemodynamic compromise.
3. High-degree AV block.
4. Pacemakers which do not permit adequate heart rate response to exercise.
5. Heart failure secondary to significant uncorrected primary valvular disease (except for mitral regurgitation secondary to LV dysfunction).
6. Isolated pulmonary hypertension.
7. Poorly controlled symptomatic postural hypotension.
8. Obstructive cardiomyopathy.

Figure 2. Study safety criteria.

Participants were recruited through active screening by hospital HF service staff of emergency department, medical and cardiology ward admission lists, as well as active screening of patients actively engaging in hospital HF service activities. However, this approach may have limited the recruitment of those with the most difficult or refractory symptoms. It is possible that more patients with refractory symptoms were excluded than needed. Therefore, the sample may not be representative of the population with HF (Zaske, 2012).

\(^1\) Heart failure medication optimisation was not a pre-requisite for study entry therefore it is likely that certain medications may have been titrated during the study.

\(^2\) CRT is known for its positive influence on cardiac output (CO) making interpretation of the effect of exercise difficult. A decision was made to exclude patients with recent CRT to exclude this as a potential confounder of study results.
as by physician and ward nursing referral. The program physiotherapist or exercise physiologist assessed all potential participants for eligibility to exercise according to the established study safety criteria (*Figure 2. Study safety criteria*). The study project officer was subsequently notified regarding eligible patients who were then invited to participate in the research study. A written informed consent was obtained from each patient prior to the patient’s entrance into the study. Before recruitment and enrolment, each prospective participant was given a full explanation of the study in plain English and was allowed to read the approved informed consent form at their own discretion. Project staff informed the prospective participant of the purpose of the study, randomisation of study groups and the follow-up schedule. They discussed any foreseeable risks involved, as well as potential benefits that may result from the new treatment, and informed the participant that their medical records will be subject to review. The prospective participant was informed that they were free to refuse participation in the study and, if they chose to participate, that they may withdraw from the study at any time without compromising further medical care.

Once project staff were assured that the individual understood the implications of participating in the study, the participant was asked to give consent to participate in the study by signing the informed consent form. A copy of the signed consent was provided to the patient and the original form was maintained with the participants’ records at the site (*Appendix A Patient Information and Consent Form*).

The study was approved by human research ethics committees (HREC) at participating institutions and all patients gave written informed consent prior to participation.

### 2.3 INSTRUMENTS

Questionnaires were administered at Baseline and 3 months post commencement of intervention (*Appendix B Pittsburgh Sleep Quality Index, Appendix C Geriatric Depression Scale, Appendix D Six Minute Walk Test Case Report Form, and Appendix E Study Case Report Forms*).
2.3.1 Measurement of Primary Outcome

Sleep Quality

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) (see Appendix B). This self-rated 19-item index takes five to ten minutes to complete and assesses sleep quality during the previous month. The PSQI offers a concise, clinically useful review of a number of sleep disturbances (M. T. Smith & Wegener, 2003).

The first four questions of the PSQI examine usual bed time, time it takes to fall asleep, wake time and amount of actual sleep per night. Questions 5, 7, 8, 9 and 10 examine how often particular issues disturb sleep. These questions are rated on a scale between 0-3, with 0 indicating the issue affected sleep “not during the past month” and 3 “3 or more times a week”. Question 6 asks the participant to rate their sleep quality with 0 indicating “very good” sleep quality and 3 “very bad”.

The survey assesses several components of sleep quality including 1) subjective sleep quality (1 item); 2) sleep latency (2 items); 3) sleep duration (1 item); 4) habitual sleep efficiency (3 items); 5) sleep disturbances (9 items); 6) use of sleeping medication (1 item); and 7) daytime dysfunction (2 items). Specific problems the tool examines which contribute to poor sleep include; pain, urinary frequency, breathing difficulty, snoring, dreams and temperature. Global PSQI score is calculated by grouping the 19-items into seven component scores. Each component score is weighted equally on a 0-3 scale. The seven component scores are summed to give a global PSQI score. The global PSQI score has a range of 0-21 with higher scores indicating worse sleep quality (Smyth, 2007). A global PSQI of >5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa =0.75, p<0.001) in distinguishing good and poor sleepers (Buysse, et al., 1989). The tool has established acceptable measures of internal homogeneity, consistency and validity (Buysse, et al., 1989) (see Appendix F PSQI Scoring).
2.3.2 Measurement of Potential Mediating Variables

Depression

Depressive symptoms were measured using the Geriatric Depression Scale (GDS) see Appendix C and Appendix G (D. L. Hare & Davis, 1996; Wise, Harris, & Carter, 2006). This validated 15-item questionnaire was specifically developed for use with older people, aged 60 years and above. The GDS is easy to use in a more unwell, elderly population who may feel easily fatigued. Its ease of administration and scoring is due to its simple yes/no format, making comprehension easier than instruments that present four-choice answers. It has been extensively used in community, acute and long-term care settings.

Exercise Performance

A 6 minute walk test (6MWT) on a 25 metre walking track was used to measure exercise capacity. This test measures the distance an individual is able to walk at a comfortable pace in 6 minutes. It has been used extensively to examine functional capacity in HF drug trials because of its simplicity, safety and low-cost (Yeh, Mietus, et al., 2008; Zugck et al., 2000). The 6MWT was performed twice at Baseline to account for any learning effect and to ensure the validity and reliability of results. The higher of the two results was used in study analysis. Prior to testing, rate of perceived exertion (RPE) using a modified Borg scale (Borg, 1982), heart rate (HR) and pulse oximetry were recorded. Standard instructions were given to the patient at the start of the test ("ATS statement: guidelines for the six-minute walk test," 2002). Patients were able to stop and rest during the test, with the timer still running. On completion of the 6 minutes, RPE, HR and pulse oximetry were repeated and the total distance was recorded. See Appendix D for details.

Anthropometry

Body weight (kg) and height (metres) were assessed using standard procedures at each visit to obtain BMI (kg/m²).
2.3.3 Measurement of Dose of Exercise

Adherence to Intervention: Attendance Logs

Exercise specialists at each of the participating institutions recorded individual participation in exercise and education classes across the 3 month period.

Adherence to Physical Activity Guidelines

Self-reported activity was examined at the Baseline and Month 3 visits. Patients were asked at these times whether they met national physical activity guidelines of 30 minutes or more of moderate intensity activity daily.

2.4 PROCEDURE AND TIMELINE

All eligible patients were screened for study eligibility and a Baseline assessment was undertaken (see Appendix E). The eligibility review examined details of the patients’ most recent hospital stay as well as review of recent echocardiography and chest x-ray results. At Baseline and at the end of the 3 Month Intervention period participants returned to the hospital for an assessment which involved completion of questionnaires, physiological examination and exercise performance testing (6MWT). Sub maximal exercise testing using a 6MWT was performed on all participants at Baseline to determine exercise capacity and to tailor the exercise program to each participant. Participants were randomised to a 3 month disease management programme (DMP) of education and self-management support including standard exercise advice (Control) or to the same DMP as the Control group with the addition of a tailored exercise programme designed and supervised by a physiotherapist and/or clinical exercise physiologist (Intervention).

2.5 INTERVENTIONS

2.5.1 DMP plus standard exercise advice (Control)

Participants randomised to the Control arm received a comprehensive DMP including (1) education on the physiology, medications and management of HF; (2) education on the role of exercise training in HF and provision of a home-based
graduated exercise programme; (3) telephone follow-up to monitor symptoms and response to therapy; (4) medication titration (if appropriate) according to protocols and in consultation with physician; (5) written materials to support education; and (6) a patient diary for recording weight, medications and symptoms. The sessions reinforced the patient’s physiological understanding of HF through education on diet, medications, energy conservation and psychological aspects of this chronic disease. The programme also included education and written support for a home exercise programme in accordance with National Heart Foundation (NHF) guidelines (Briffa T, 2006). The home programme was prescribed at week one, and reviewed weekly for the duration of the intervention, to optimise participant safety and confidence. The home programme included aerobic and resistance exercises using minimal equipment (see Appendix G). An exercise goal of a minimum of four sessions per week of 30 minutes duration was encouraged; however this program was modified on a case-by-case basis to ensure exercise safety and adherence for individual participants. Participants were requested to record their exercise on the provided exercise activity sheet.

2.5.2  DMP plus supervised exercise programme (Intervention)

Those randomised to the Intervention arm received the same DMP as patients in the control group. Participants were also offered twice weekly hospital based supervised group exercise classes of approximately 1.5 hours duration for 3 months. Classes consisted of a 10-15 minute warm-up followed by a 1 hour period which included 30 minutes of aerobic exercise and 30 minutes of concentric and eccentric resistance exercise, balance and stretching. Exercises were tailored to the participant’s capabilities. At the completion of these exercises there was a 10-15 minute cool down period. Exercise prescription followed the FITT guidelines for best practice prescription and progression according to ACSM guidelines (American College of Sports Medicine, 2005).

Aerobic exercise intensity was measured using heart rate monitors and reports of perceived exertion using a modified Borg scale. Heart rate limits were calculated using age and risk factor stratification based on modified American Association of
Cardiovascular and Pulmonary Rehabilitation (AACVPR) (American Association of Cardiovascular and Pulmonary Rehabilitation, 2004). As HF patients are considered high risk, heart rate limits were initially set at 50-60% of heart rate reserve (Karnoven method)(Karvonen, Kentala, & Mustala, 1957). Exercise intensity was alternatively measured using the Borg rating of perceived exertion (RPE) 20 point scale, utilising an RPE of 9-13 where 9 was considered fairly light and 13 was considered somewhat hard. This correlates with the talk test zone where an individual is able to carry out a conversation without significant shortness of breath.

Initial workloads for the resistance exercises were determined by the prescribing exercise specialist based on Baseline test results. When an individual was able to achieve 3 sets of 10 repetitions within heart rate (HR) limits and with an RPE of 9-13, intensity was progressed. The minimum work to rest ratio was 1:2. Complete details on the exercise protocol are described in Appendix H.

Intervention group participants were also provided with specific advice and support for a graded home exercise programme, in order to facilitate the transition to an ongoing home exercise programme.

2.6 ANALYSIS

Effect sizes from other studies (Lewith, Godfrey, & Prescott, 2005; Morgan, Dixon, Mathers, Thompson, & Tomeny, 2003) were examined for the power calculations. These studies identified a difference of 3 on PSQI to be clinically significant in patients with sleep disturbance (Lewith, et al., 2005). Therefore in order to demonstrate a mean difference on 3 points on the PSQI, with baseline scores between 9.0 and 6.0, it was estimated that a sample size of 28 patients in each group would provide more than 80% power. Assuming a 20% drop out rate by Month 3, this would require enrolment of 34 patients per group.

Case report forms (CRFs) were developed and coded for entry into a Microsoft Access database. Subsequent analysis of this data was performed in SPSS for
Windows Release 20.0 (SPSS Inc, Chicago 11). Frequency distributions and histograms of all variables were examined with SPSS to check for missing and invalid data. All variables were checked to ensure they were within appropriate range. Outliers were checked against raw data to ensure accuracy.

Primary analyses were conducted on an intention-to-treat (ITT) basis, where patients were examined according to their original randomisation result regardless of adherence to the treatment regime.

Categorical data were summarised as frequencies and percentages. Continuous data were summarised as means and standard deviations where assumptions of normality were met and medians and inter-quartile ranges when data was skewed. Patient characteristics of groups were compared using Fisher’s exact Chi Squared Tests for categorical variables and one way analysis of variance (ANOVA) for continuous variables.

Sleep quality subscales and global scale were calculated according to scoring methods as defined by Buysse and colleagues (Buysse, et al., 1989) (see Appendix B). The primary outcome variable of clinical change in global sleep quality as measured using the Pittsburgh Sleep Quality Index was analysed using Chi Squared Tests which was used to compare pre and post intervention clinical change between the study groups. A one way analysis of variance (ANOVA) was also used to compare the difference in change in the seven subscales and global score of the Pittsburgh Sleep Quality Index. Pre and post intervention change scores on the primary outcome variables and their 95% confidence intervals were computed to determine the intervention effects. To enhance clinical meaning, changes was also categorised into improved, unchanged or worse sleep at 12 weeks compared to baseline, based on the proposed minimal clinically important difference of 3 points, and differences between groups compared using chi squared testing (Lewith, et al., 2005).
Per protocol analyses involving those who were considered adherent to intervention (attendance of 67% or more of scheduled exercise classes) and adherent to physical activity guidelines (≥30min/day of moderate intensity exercise) were also completed. A Chi Squared Test was also used to compare pre and post intervention clinical change between those who were adherent and non-adherent with the intervention and physical activity guidelines.

The relationship between the primary outcome of sleep quality and potential mediating factors including depression, exercise performance and BMI was examined using a general linear model (GLM). Analysis of covariance (ANCOVA) was then used to assess whether the intervention was an independent modifier of sleep quality after adjusting for a single covariate (either changes in depression, exercise performance or BMI).

The relationship between Baseline sleep quality and sleep quality at Month 3 (good/poor) was examined using a McNemar test.

An alpha level of less than 0.05 was considered to indicate statistical significance in all analyses.

2.7 ETHICS

This study was conducted in keeping with the ethical principles of The Belmont Report, the Declaration of Helsinki, and with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines.

A copy of the protocol, informed consent forms, and other information to be completed by participants, such as survey instruments or questionnaires, and any proposed advertising / recruitment materials were submitted to the participating institution Human Research Ethics Committees (HREC) prior to study
commencement for written approval. See Appendix I for ethics approval documentation.
973 patients were examined for study inclusion. Eighty-eight percent of these were not recruited because screening criteria were not met (n=712), or patients were unable to commit to the length of the study (n=139). Ten patients were not able to participate for other reasons (history of non-compliance, completed exercise program within past 12 month period, discharged to non-participating HF service). Six patients did not complete a Baseline PSQI and were therefore not included in the study. One hundred and six individuals (11%) met the inclusion criteria and were randomised: 54 to Intervention and 52 to Control. No participants officially withdrew from the study during the intervention period. Twenty-six participants (10 Intervention, 16 Control) were lost to follow-up. Four participants (4%) died, 1 (1%) was unable to attend due to illness, 2 (2%) returned to work and 19 (18%) did not attend due to time commitments or inconvenience. There were no differences in characteristics of patients who completed the study and those that were lost to follow-up (see Appendix J). A summary of randomisation, patient flow and retention through the course of the trial is shown in Figure 2.
3.1 BASELINE PARTICIPANT CHARACTERISTICS

The mean age of study participants was 62 years. Eighty-one percent of patients were male. The mean left ventricular ejection fraction (LVEF) was $32 \pm 16$, and approximately half of the participants recruited had been newly diagnosed with HF on their recent admission. In many cases HF aetiology was ischemic (43%). Forty-four percent of participants had co-morbid hypertension and almost all patients were prescribed beta blockers, angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and diuretic therapy at Baseline.
Comparison of characteristics of patients in the Control and Intervention groups are shown in Table 3.1. There were no differences in intervention groups at Baseline.

Comparison of primary outcome measures between groups at Baseline is presented in Table 3.4. No differences in primary outcome measures were identified between study groups at Baseline.
Table 3.1

Baseline Characteristics of Study Participants by Intervention Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n=52)</th>
<th>Intervention (n=54)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>62 ± 13</td>
<td>61 ± 15</td>
<td>0.55</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>36 (69%)</td>
<td>46 (85%)</td>
<td>0.064</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>46 (89%)</td>
<td>46 (85%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Aboriginal/TSI/PI</td>
<td>5 (10%)</td>
<td>7 (13%)</td>
<td></td>
</tr>
<tr>
<td>Clinical Factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%), mean ± SD</td>
<td>31 ± 15</td>
<td>32 ± 16</td>
<td>0.78</td>
</tr>
<tr>
<td>De novo heart failure, n (%)</td>
<td>26 (50%)</td>
<td>29 (54%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Aetiology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>25 (48%)</td>
<td>19 (36%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>8 (15%)</td>
<td>8 (15%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>19 (37%)</td>
<td>26 (49%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>19 (37%)</td>
<td>28 (52%)</td>
<td>0.12</td>
</tr>
<tr>
<td>NYHA Class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>0.65</td>
</tr>
<tr>
<td>2</td>
<td>39 (75%)</td>
<td>36 (67%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 (15%)</td>
<td>8 (15%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (8%)</td>
<td>8 (15%)</td>
<td></td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>51 (98%)</td>
<td>49 (91%)</td>
<td>0.21</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>50 (96%)</td>
<td>46 (85%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diuretic</td>
<td>45 (87%)</td>
<td>48 (89%)</td>
<td>0.77</td>
</tr>
<tr>
<td>PSQI, mean ± SD</td>
<td>5.7 ± 4</td>
<td>6.7 ± 4.3</td>
<td>0.26</td>
</tr>
<tr>
<td>GDS, mean ± SD</td>
<td>4.8 ± 3.7</td>
<td>4.6 ± 3.6</td>
<td>0.72</td>
</tr>
<tr>
<td>6min walk distance (m), mean (SD)</td>
<td>364 ± 119</td>
<td>392 ± 124</td>
<td>0.24</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>30 ± 6</td>
<td>30 ± 6</td>
<td>0.69</td>
</tr>
<tr>
<td>Meets PA guidelines, n (%)</td>
<td>30 (59%)</td>
<td>25 (46%)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

* Significant at p<0.05

3.2 ATTRITION

A measure of adherence with the intervention protocol was attendance at the 24 scheduled exercise training sessions. Patients were considered adherent with group sessions if 67% or more of classes were attended. Figure 4 shows the proportion of scheduled exercise classes attended by Intervention group participants. The median attendance at scheduled exercise classes was 16 (IQR 10-21). Older participants were significantly more likely to be adherent with 67% or more of the Intervention (see Table 3.2). No exercise related adverse events were experienced by any participants during the study.
Figure 4. Proportion of scheduled exercise classes attended.
Table 3.2

Baseline Characteristics of Participants in the Intervention Group Who Were Adherent versus Non-Adherent with Exercise Classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;67% Attendance (n=26)</th>
<th>≥67% Attendance (n=28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>55 ± 15</td>
<td>66 ± 14</td>
<td>0.011*</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>22 (85%)</td>
<td>24 (86%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>21 (81%)</td>
<td>25 (89%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Aboriginal/TSI/PI</td>
<td>4 (15%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Clinical Factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%), mean ± SD</td>
<td>28 ± 15</td>
<td>36 ± 16</td>
<td>0.08</td>
</tr>
<tr>
<td>De novo heart failure, n (%)</td>
<td>15 (58%)</td>
<td>14 (50%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Aetiology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>8 (32%)</td>
<td>11 (39%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>3 (12%)</td>
<td>5 (18%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (56%)</td>
<td>12 (43%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>12 (46%)</td>
<td>16 (57%)</td>
<td>0.59</td>
</tr>
<tr>
<td>NYHA Class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0.67</td>
</tr>
<tr>
<td>2</td>
<td>2 (8%)</td>
<td>6 (21%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (15%)</td>
<td>4 (14%)</td>
<td></td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>25 (96%)</td>
<td>24 (86%)</td>
<td>0.35</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>24 (92%)</td>
<td>23 (79%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diuretic</td>
<td>(89%)</td>
<td>25 (89%)</td>
<td>1.0</td>
</tr>
<tr>
<td>PSQI, mean ± SD</td>
<td>7.7 ± 4.4</td>
<td>5.7 ± 4.1</td>
<td>0.1</td>
</tr>
<tr>
<td>GDS, mean ± SD</td>
<td>4.6 ± 3.6</td>
<td>4.6 ± 3.8</td>
<td>0.95</td>
</tr>
<tr>
<td>6min walk distance (m), mean (SD)</td>
<td>420 ± 127</td>
<td>365 ± 116</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>30 ± 6</td>
<td>31 ± 6</td>
<td>0.58</td>
</tr>
<tr>
<td>Meets PA guidelines, n (%)</td>
<td>12 (46%)</td>
<td>13 (46%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
3.3 INTERVENTION EFFECTS ON SLEEP QUALITY

Intervention effects on component and global sleep quality scores are shown in Table 3.4. Reductions in component PSQI scores and a lower overall global PSQI score are indicative of improvements in subjective sleep quality. Patients who were randomly allocated to Intervention showed significantly greater reductions in their component sleep quality (p=0.015), component sleep disturbance (p=0.004), and global sleep quality scores (p=0.032) after 3 months in comparison to the Control group. Standard deviations for change were high indicating either a large variability within the study group in change in sleep quality or instrument weaknesses with the PSQI.

Analysis also showed a statistically significant difference between study groups in the proportion of patients with a clinically significant (>3 points) change in global sleep quality score following Intervention (p=0.016). A greater proportion of participants in the Intervention reported a significant improvement (a reduction of 3 or more points) in global sleep quality between Baseline and Month 3 (Table 3.3).

Ceiling and floor effects are suggested to play a role in sleep research (S. D. Youngstedt, 2001). This means that Baseline levels of sleep quality may limit the amount of change possible. For example, patients with the highest levels of sleep at Baseline may have little or no room for improvement and the reverse for those with the lowest levels of sleep. McNemar’s test was used to test the probability of changing from poor to good sleep after intervention. Using McNemar’s test, a significant tendency was found for subjects in the Control group with good Baseline sleep quality to report poor sleep at 3 months (p=0.039) with 42% of participants with “good” Baseline sleep quality reporting “poor” sleep at Month 3. In contrast, Intervention subjects were very likely to continue to have good sleep at 3 months (p=0.08) with 50% of patients with “poor” Baseline sleep quality reporting “good” sleep at Month 3. See Appendix K and L.
Table 3.3
*Proportion of Patients with a Clinically Significant Change in Sleep Quality According to Intervention Group*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (n=36)</th>
<th>Intervention (n=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No clinically significant change</td>
<td>20 (56%)</td>
<td>20 (46%)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Significant improvement (≥3 points)</td>
<td>5 (14%)</td>
<td>18 (41%)</td>
<td></td>
</tr>
<tr>
<td>Significant deterioration (≤3 points)</td>
<td>11 (31%)</td>
<td>6 (14%)</td>
<td></td>
</tr>
</tbody>
</table>

*significant at p<0.05
Table 3.4
*Change in Sleep Quality by Intervention Group*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (n=36)</th>
<th>Intervention (n=44)</th>
<th>P-value of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Mean ± SD Week 12</td>
<td>Change</td>
</tr>
<tr>
<td><strong>Pittsburgh Sleep Quality Index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep duration (range 0-3)</td>
<td>0.8 ± 1.0</td>
<td>0.7 ± 1.0</td>
<td>0.0 ± 1.0</td>
</tr>
<tr>
<td>Sleep disturbances (range 0-3)</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.7</td>
<td>0.1 ± 0.8</td>
</tr>
<tr>
<td>Sleep latency (range 0-3)</td>
<td>0.9 ± 1.0</td>
<td>0.9 ± 0.9</td>
<td>0.3 ± 0.8</td>
</tr>
<tr>
<td>Daytime dysfunction (range 0-3)</td>
<td>0.8 ± 0.8</td>
<td>0.8 ± 0.8</td>
<td>0.0 ± 0.9</td>
</tr>
<tr>
<td>Habitual sleep efficiency (range 0-3)</td>
<td>0.8 ± 1.2</td>
<td>0.8 ± 1.0</td>
<td>-0.1 ± 0.2</td>
</tr>
<tr>
<td>Subjective sleep quality (range 0-3)</td>
<td>0.9 ± 0.9</td>
<td>0.9 ± 0.7</td>
<td>0.2 ± 0.8</td>
</tr>
<tr>
<td>Use of sleep medication (range 0-3)</td>
<td>0.2 ± 0.6</td>
<td>0.3 ± 0.6</td>
<td>0.0 ± 0.8</td>
</tr>
<tr>
<td>Global score (range 0-21)</td>
<td>5.7 ± 4.0</td>
<td>5.8 ± 3.4</td>
<td>0.4 ± 3.8</td>
</tr>
</tbody>
</table>

*significant at p<0.05
3.4 EFFECT OF EXERCISE DOSE ON SLEEP QUALITY

3.4.1 Adherence to Intervention

Per protocol analysis was undertaken to identify whether increased dose of exercise was related with more pronounced effects on primary outcomes. The first of these analysis involved splitting Intervention group participants into two categories: (1) Non-adherent with Intervention (<67% prescribed classes attended); and (2) Adherent with Intervention (≥67% prescribed classes attended). No statistically significant difference was identified regarding adherence to intervention and achievement of clinically significant change in global sleep quality score (see Appendix M).

3.4.2 Adherence to Physical Activity Guidelines

Per protocol analysis was also undertaken to identify whether increased dose of exercise as measured by adherence to national physical activity guidelines (30 minutes or more of moderate intensity exercise per day (Department of Health and Ageing, 1999)) at Month 3 affected change in global and component sleep quality scores. Participants were split into four categories: (1) Control - non adherent with Guidelines; (2) Control - adherent with guidelines; (3) Intervention - non-adherent with guidelines; and (4) Intervention - adherent with Guidelines.

Following intervention, a significant difference was identified in achievement of clinically significant change in global PSQI score between groups who were adherent and non-adherent with physical activity guidelines (see Table 3.5). Significantly less of the Intervention group that were adherent with physical activity guidelines at this time reported deterioration in sleep quality and more reported improvement (p=0.016).
Table 3.5

Proportion of Patients with a Clinically Significant Change in Sleep Quality by Adherence with Physical activity guidelines

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control Non-adherent with Physical Activity Guidelines (n=9)</th>
<th>Control Adherent with Physical Activity Guidelines (n=23)</th>
<th>Intervention Non-adherent with Physical Activity Guidelines (n=6)</th>
<th>Intervention Adherent with Physical Activity Guidelines (n=34)</th>
<th>P-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in global PSQI score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No clinically significant change</td>
<td>3 (33%)</td>
<td>16 (70%)</td>
<td>3 (50%)</td>
<td>16 (47%)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Clinical improvement (≥3 points)</td>
<td>3 (33%)</td>
<td>2 (9%)</td>
<td>2 (33%)</td>
<td>16 (47%)</td>
<td></td>
</tr>
<tr>
<td>Clinical deterioration (≤3 points)</td>
<td>3 (33%)</td>
<td>5 (22%)</td>
<td>1 (17%)</td>
<td>2 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

*significant at p<0.05

¹ Significance value of difference between groups in clinically significant change in global sleep quality following Intervention.
3.5 EFFECT OF POTENTIAL MEDIATORS OF CHANGE IN SLEEP

No significant differences were identified between study groups in change in any of the potential mediating variables following intervention (BMI, GDS, 6MWD) (see Table 3.6). Analysis was completed to examine whether there was a significant difference between Intervention groups in the proportion change in 6MWD. This analysis was completed in light of the variability in distances walked between study participants. For example, an improvement of 5 meters may have been more significant to a patient who initially walked 50 meters than a patient who walked 600 meters. No significant differences were identified between Intervention groups in proportion change in 6MWD (see Appendix N).

Improvements in sleep quality, as measured by change in global PSQI score between Baseline and Week 12 correlated with change in geriatric depression score ($p<0.001$) and six minute walk distance ($p=0.04$). There was no significant correlation between sleep quality and BMI (see Figures 4-6).

Figure 5. Correlation between change in sleep quality and change in depression following Intervention
Figure 6. Correlation between change in sleep quality and change in BMI following Intervention

Figure 7. Correlation between change in sleep quality and change in 6 minute walk distance following Intervention

General linear models were used to examine whether the changes in sleep quality following intervention occurred independently of changes in depression and six minute walk distance as these items were found to correlate with sleep quality. Results suggest that for every 1 point improvement in depression there was a 0.4 point improvement in global sleep quality score (p<0.001). For every 1 meter change in walk distance there was a 0.02 point improvement in sleep quality (p=0.009). After adjustment for change in depression and change in distance walked
the intervention had a 2.0 unit improvement in sleep quality (p=0.016) (See Table 3.7).

Table 3.6
Change in Potential Mediating Variables According To Intervention Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control Mean ± SD</th>
<th>Intervention Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS, mean ± SD</td>
<td>-1.0 ± 4.2</td>
<td>-1.2 ± 2.5</td>
<td>0.79</td>
</tr>
<tr>
<td>6MWD (m), mean ± SD</td>
<td>26 ± 41</td>
<td>11 ± 66</td>
<td>0.29</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>0.4 ± 1.5</td>
<td>-0.1 ± 1.4</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Table 3.7
General Linear Models of Change in Global PSQI from Baseline to Month 3 to Compare Control with Intervention with Adjustment for Covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Effect Size (B)</th>
<th>Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>2.02</td>
<td>0.39, 3.65</td>
<td>0.016*</td>
</tr>
<tr>
<td>Depression</td>
<td>0.44</td>
<td>0.20, 0.69</td>
<td>0.001*</td>
</tr>
<tr>
<td>Six minute walk distance</td>
<td>-0.02</td>
<td>-0.03, -0.005</td>
<td>0.009*</td>
</tr>
</tbody>
</table>

* Significant at p<0.05
3.6 **EFFECT OF BASELINE SLEEP QUALITY ON EXERCISE ADHERENCE**

Further investigation was completed to examine the effect of Baseline sleep quality. At Baseline, “good” sleep was more common in males (p=0.005), those with low depression scores (p=0.01) and more mild (NYHA class I or II) HF (p=0.001) (Table 3.8).

Analysis was also undertaken to review the effect of Baseline sleep quality on adherence to intervention as it is hypothesised that lower Baseline levels of sleep are related with lower adherence to exercise. No significant difference was identified in adherence to the Intervention (attendance ≥ 67% scheduled exercise classes) according to Baseline sleep quality (Table 3.9).
Table 3.8  
*Baseline Characteristics of Participants with Good (Global PSQI < 5) or Poor (Global PSQI ≥ 5) Sleep Quality at Baseline*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Good PSQI &lt; 5 (n=58)</th>
<th>Poor PSQI ≥ 5 (n=48)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>63 ± 14</td>
<td>60 ± 14</td>
<td>0.28</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>51 (88%)</td>
<td>31 (65%)</td>
<td>0.005*</td>
</tr>
<tr>
<td><strong>Ethnicity</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>52 (90%)</td>
<td>40 (83%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Aboriginal/TSI/PI</td>
<td>5 (9%)</td>
<td>7 (15%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%), mean ± SD</td>
<td>31 ± 16</td>
<td>33 ± 15</td>
<td>0.59</td>
</tr>
<tr>
<td>De novo heart failure, n (%)</td>
<td>32 (55%)</td>
<td>23 (48%)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Aetiology</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>23 (40%)</td>
<td>21 (44%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>11 (19%)</td>
<td>5 (10%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>23 (40%)</td>
<td>22 (46%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>24 (41%)</td>
<td>23 (48%)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>NYHA Class</strong>, n (%)</td>
<td></td>
<td></td>
<td>0.001*</td>
</tr>
<tr>
<td>1</td>
<td>3 (5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>43 (74%)</td>
<td>32 (67%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11 (19%)</td>
<td>5 (10%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (2%)</td>
<td>11 (23%)</td>
<td></td>
</tr>
<tr>
<td><strong>Medications</strong>, n (%)</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>55 (95%)</td>
<td>45 (94%)</td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>52 (90%)</td>
<td>44 (92%)</td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>51 (88%)</td>
<td>42 (88%)</td>
<td></td>
</tr>
<tr>
<td><strong>GDS</strong>, mean ± SD</td>
<td>3.6 ± 3.1</td>
<td>6.1 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6min walk distance (m), mean (SD)</td>
<td>376 ± 120</td>
<td>379 ± 124</td>
<td>0.91</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>30 ± 6</td>
<td>31 ± 6</td>
<td>0.66</td>
</tr>
<tr>
<td>Meets PA guidelines, n (%)</td>
<td>32 (56%)</td>
<td>23 (48%)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Significant p<0.05

Table 3.9  
*Adherence to Intervention (≥67% classes) According to Baseline Sleep Quality*

<table>
<thead>
<tr>
<th>Baseline Sleep Quality</th>
<th>Intervention (non-adherent) n=26</th>
<th>Intervention (adherent) n=28</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good (PSQI &lt; 5)</td>
<td>10 (39%)</td>
<td>15 (54%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Poor (PSQI ≥ 5)</td>
<td>16 (62%)</td>
<td>13 (46%)</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 4: Discussion

This study examined the effect of a 3 month program of supervised, aerobic and resistance exercise training on sleep quality in HF patients. The major findings of the study are that a hospital-based exercise training program produces significantly higher rates of clinical improvement in global sleep quality (≥3 points) than usual care (Table 3.3). These programs also deliver greater improvement in component sleep quality, component sleep disturbance and global sleep quality scores (Table 3.4). Intervention group participants that adhered to physical activity guidelines were significantly more likely to report clinical improvement and less likely to report clinical deterioration in global sleep quality at Month 3 (Table 3.5). Control group participants who reported “good” sleep at Baseline were significantly more likely to report “poor” sleep at Month 3. Improvements in sleep quality were found to relate to improvements in depression and exercise performance, however not with changes in BMI (Figures 4-6). Sleep disturbance was common in study participants with 55% of patients reporting poor sleep at Baseline. Patients with poor sleep at this time were significantly more likely to be sicker and depressed (Table 3.8). Baseline sleep quality was not found to affect attendance at scheduled exercise sessions (Table 3.9).

4.1 RELATIONSHIP WITH PREVIOUS STUDIES

The findings from this study make several contributions to the current literature. This is the first study to evaluate the effects of a supervised, aerobic and resistance exercise training program on sleep quality in recently hospitalised HF patients. This study also enrolled a population that was two to three-fold larger than the majority of intervention studies of sleep undertaken in HF patients. Of the six studies to examine the effect of exercise on sleep in HF, the majority were undertaken in stable, NYHA class II to III, systolic HF patients who had been medically optimised for at least 3 months prior to recruitment. Sleep disturbance is also extremely common in patients with diastolic HF (Chan et al., 1997) therefore
our study provides important information regarding the effect of exercise on a broader HF population through our inclusion of patients with diastolic HF.

The majority of previous studies review the relationship between exercise and sleep disordered breathing and fail to report on the relationship between exercise and sleep quality (Brostrom & Johansson, 2005; Erickson, et al., 2003; Parker & Dunbar, 2002). These studies rely on assessment of sleep disturbance through objective measures such as PSG. Reliance on such measures to identify sleep disturbance may not be practical in this population given that these types of examination are expensive, labour intensive and can be limited in availability (Ferrier, et al., 2005; Rao & Gray, 2005). Because it is often the individual’s perception of their sleep state which motivates them to seek treatment, subjective sleep quality may be a more practical and cost-effective outcome measure. The examination of the effect of exercise on sleep quality is also important as an outcome of improved sleep is one which carries a real meaning for patients and demonstrate that exercise improves sleep may provide a valuable incentive to patients to continue exercise, which is crucial for maintenance of other health benefits.

4.1.1 Exercise Effects on Subjective Measures of Sleep

Our study showed that in recently hospitalised HF patients, participation in a 3 month DMP including exercise was associated with improvement in sleep quality. These patients reported significantly greater clinical improvement in global sleep quality as well as improvement in sleep disturbance and sleep quality component scores following exercise intervention. These results are in keeping with the findings of Duarte Freitas et al (P. Duarte Freitas, et al., 2011) who report an improvement in sleep quality following exercise intervention in cardiac patients. Our findings are also consistent with studies in older persons which show an improvement in sleep quality following a variety of exercise interventions (K. M. Chen, et al., 2010; M. C. Chen, et al., 2012; King, et al., 1997; Singh, et al., 1997; Vitiello, Larsen, & Moe, 2004; Yang, Ho, Chen, & Chien, 2012).
While only a 16% improvement in global sleep quality was identified in our study, in comparison to a 25% increase in the Duarte Freitas study, these investigators conducted a far more intense intervention in patients with a variety of cardiac conditions exercising as in-patients for two to three hours daily over a 4 week period. This study also utilised an aerobic exercise intervention where we provided a combination of aerobic and resistance exercises. Perhaps because of this more intense intervention, these investigators were able to identify a significant reduction in body weight and improvement in depression score which was not replicated in our study.

4.1.2 Potential Mediators of Improvement in Sleep

Various alternative mechanisms for improvements in sleep following exercise have been postulated including reductions in depression and anxiety, weight loss, increases in exercise performance, social interaction, stabilisation of sympathetic nervous activity, thermoregulation, energy conservation, circadian rhythm shifting through exposure to bright light and modulation of inflammatory responses or neurotransmitters (Driver & Taylor, 2000; Guilleminault et al., 1995).

We were unable to quantify the effects of many potential mediators of sleep quality, however we can report upon the relationship between improved sleep quality and depression, exercise performance and weight loss or BMI.

**Depression**

Depression is very common and under-recognized in HF (Gnanasekaran, 2011). This was evident in our finding that while 38% of patients reported mild to severe depression at Baseline only one was prescribed antidepressant therapy at this time. Depression is thought to be one of the largest contributors to insomnia (D. Hayes, Jr., et al., 2009; Johansson, et al., 2010). The improvements in depression which are suggested to occur as a result of exercise are thought to produce corresponding improvements in sleep. Exercise may improve depression in a number of different ways. Firstly, exercise is suggested to increase serotonin, a neurotransmitter linked with depression that is involved in mood, sleep, libido and
appetite (Arcos-Carmona, et al., 2011; Basta, et al., 2008; S. D. Youngstedt, 2005). Exercise may also increase endorphins, chemicals in the brain with ‘mood lifting’ properties (S. D. Youngstedt, 2005). Other ways in which exercise may improve depression include increasing energy levels, providing a distraction from worries, providing social support, reducing loneliness and increasing an individual’s sense of control by giving them an opportunity to take an active role in their recovery (Gill, Womack, & Safranek, 2010). In our study, we identified a modest but statistically significant correlation between improvements in sleep quality and improvements in depression following exercise. These results confirm the findings of Duarte Freitas et al and Saleh and colleagues who demonstrated a significant association between quality of sleep and anxiety and depression symptoms (P. Duarte Freitas, et al., 2011; Saleh et al., 2008).

Similar findings have been reported in studies of the elderly and patients with insomnia whereby improvements in depression were found to be significant predictors of improvements in sleep quality (K. M. Chen, et al., 2010; Lavie & Milani, 2001; Passos et al., 2011; Singh, et al., 1997).

Exercise performance

Improved physical fitness is also suggested to influence sleep quality (Tworoger, et al., 2003). This has been shown in a number of studies in patients with HF and other conditions (Muller, Christov, Schreiber, Hess, & Hager, 2009; Niebauer, Clark, Webb-Peploe, & Coats, 2005; Sakkas, et al., 2008; Servantes, et al., 2012; Ueno, et al., 2009; Yamamoto, et al., 2007; Yeh, Mietus, et al., 2008). For example, in a study by King et al of healthy, sedentary older adults reporting moderate sleep complaints, treadmill duration during a VO₂ max test was associated with increased sleep duration, decreased napping during the day, and reduced sleep latency (King, et al., 1997). In a study of 10 elderly men, increases in maximal aerobic capacity following a 3-month fitness program were associated with improvements in sleep pattern (Van Someren, Lijzenga, Mirmiran, & Swaab, 1997). Improved physical fitness is suggested to be linked with improvements in total sleep
time and sleep-onset latency (SOL) according to the results of cross-sectional and prospective studies (Driver & Taylor, 2000).

A recent Swiss study however counteracts these suggestions and proposes that benefits of exercise on sleep are predominantly mental (Gerber, Brand, Holsboer-Trachslr, & Puhse, 2010). In this study, 862 young adult students responded to a series of questionnaires regarding their perceived physical fitness, physical activity, insomnia and quality of sleep. They found that high perceived physical fitness, but not exercise, was associated with better sleep related scores. They also showed that perceived lack of physical activity was associated with poor sleep. Perceived physical fitness and physical activity levels were only moderately correlated (Gerber, et al., 2010).

In our study, improvements in sleep quality following exercise correlated with improvement in exercise performance. No differences were identified however between study groups in change in exercise performance (6 minute walk distance) between Baseline and Month 3. These results may support the conclusion that improvements in sleep following exercise are cognitive, however they may also suggest that our training strategy was not sufficient. A lack of difference between the Control and Intervention group in change in exercise performance following intervention may also be because the Control group were also exercising. These patients were prescribed an individualised home exercise program at Baseline and 74% reported they met national physical activity guidelines at Month 3.

A lack of difference between study groups in exercise capacity following intervention may also because of the higher rate of drop-out in the Control group, with the likelihood of those with poorer walk results to not return for follow-up. In addition, our use of sub-maximal exercise testing (six minute walk test), while potentially more clinically appropriate, may not have picked up on subtle differences in exercise performance as well as a VO₂ max test would have. The six minute walk test is self-motivated and results may fluctuate according to mood and morale (Opasich et al., 2001).
Body Mass Index

Another way in which exercise is thought to improve sleep is via weight reduction. Obesity is a major risk factor for obstructive sleep apnoea and reductions in weight which coincide with increased exercise are thought to have the potential to reduce obstructive sleep apnoea. Our study was not able to report a correlation between sleep quality and BMI. These results concur with the findings of many other researchers who were also unable to attribute improvements in sleep following exercise to weight change (Kline, et al., 2011; Norman, et al., 2000; Sengul, et al., 2011; Servantes, et al., 2012; Ueno, et al., 2009; Yamamoto, et al., 2007). Weight and BMI may be poor measures of body composition in this group given their propensity for frequent change in weight related to medications and disease acuity. This is because when the heart is not pumping as efficiently due to this condition, fluid retention can result and cause sudden weight gain. Diuretic therapy is prescribed to deal with symptoms such as fluid retention and can result in rapid diuresis or weight loss (Bucca, et al., 2007).

4.1.3 Other Mediators of Change

Our results could also be explained by a number of other study related factors. Firstly, the group classes offered to Intervention patients exposed participants to greater social interaction and interaction with specialised HF clinicians. Increased social interaction may be particularly important in this patient group who may have limited social contact given their debilitating condition. This may also explain the greater improvement in depression identified in this group.

The final explanation for the improvements in sleep quality seen in the Intervention group relates to sleep hygiene. Good sleep hygiene includes the maintenance of a regular routine. Participation in exercise classes necessitates the maintenance of a more disciplined routine and therefore may improve sleep hygiene and overall sleep.
4.2 IMPLICATIONS FOR CLINICAL PRACTICE

The findings of this study have a number of important implications for clinical practice. Firstly, this study confirms the magnitude of sleep disturbance in HF with 55% of participants reporting poor sleep at Baseline. Patients with poor sleep at Baseline were significantly more likely to be sicker and depressed. These patients may benefit the most from targeted exercise programs and thought needs to be placed upon how to better engage these individuals in programs.

In patients with heart failure exercise has been established to improve QOL and reduce physical de-conditioning (Flynn, et al., 2009). It has also been shown to improve functional capacity, heart failure symptoms and neurohormonal imbalance (Keteyian 2011). This study adds to the established literature and suggests improvement in sleep quality as an additional positive effect of supervised, hospital based exercise programs. This adds weight to recommendations that exercise programs be offered as part of the standard disease management program in this patient group.

Effective management of HF involves empowering patients to take an active role in their health care through adherence to established HF therapies such as medications, fluid restriction and exercise. Exercise initiation and adherence however remain a major challenge for HF clinicians. This could be because both heart failure and disorders of sleep are conditions associated with high levels of fatigue and cognitive impairment making it difficult for patients to self-manage. Improvements in sleep quality which were found to accompany exercise may reduce fatigue and subsequently improve adherence to vital heart failure therapy. The information acquired in this investigation could be used to encourage greater participation in exercise programs and may encourage increased investment in hospital and community-based exercise programs for this vulnerable patient group.
4.3 STUDY LIMITATIONS AND STRENGTHS

A number of important limitations need to be considered. Firstly, the project enrolled a sample of patients with a recent heart failure related admission. These patients may be sicker and have higher levels of sleep disturbance related to their recent admission. In addition, a large proportion of patients screened for inclusion were excluded either because they did not meet study inclusion criteria or because they declined participation, putting the generalisability of study results further into question. Our study group may also be compromised by compliance bias with a higher proportion of the Control group not completing the study. This may explain the lack of difference in change in exercise performance between study groups with an increased likelihood that patients with poorer walk results to not return for reassessment. All four deaths in study participants were identified in the Control group. This group may have experienced a higher rate of adverse events throughout the study. Furthermore, adherence to the Intervention was less than predicted and some participants may not have received a sufficient dose of Intervention to enable change.

Given the strong evidence supporting exercise therapy in the rehabilitation of HF patients, it would have been unethical to include a sedentary group. Participants in the Control group were therefore provided with an individualised home exercise program and were encouraged to meet national physical activity guidelines. Home exercise has been found in other studies to improve measures of sleep (Coleman et al., 2003; Sprod, et al., 2010; Tang, et al., 2010). These patients appear to have been exercising more than predicted at home, with 74% reporting they met national physical activity guidelines at Month 3 (Table 3.5). Participants in the Control group also had regular contact with HF clinicians at weekly education sessions reinforcing the importance of exercise and they could have felt more empowered to exercise in a home environment than the intervention group who may not have felt comfortable exercising outside of a “safe” hospital environment. The Control group may have also had more flexibility in implementing their exercise regime as Intervention sessions were offered only at set times during regular business hours making participation of those who had returned to work difficult.
Our results suggest that neither meeting national physical activity guidelines alone nor regular attendance at exercise classes alone is sufficient to induce significant improvements in sleep in most patients. Participation in a supervised exercise program combined with meeting exercise guidelines appeared to produce the greatest improvement in sleep quality. This may be related to exercise volume, with greatest improvements in sleep quality seen in those who both exercise at home and attend exercise classes. This is confirmed in a recent re-analysis of the HF:ACTION study data, where exercise volume was found to influence clinical events (Keteyian et al., 2012). This study was not able to clarify the amount of exercise required to elucidate improvements in sleep or which component of the supervised classes caused improvements in sleep quality.

The third source of weakness in this study was the reliance on self-report. While this outcome may be of significance to patients, information cannot be verified and results can be linked with increased risk of reporting or recall bias. It is well established that HF patients report less daytime dysfunction using the Epworth Sleepiness Scale (Brostrom, Stromberg, Dahlstrom, & Fridlund, 2004). This could be because of the similarities between HF and sleep disturbance symptoms. Self-reported activity levels may also be unreliable. Actual activity levels will be verified in a larger study which is currently being completed.

The absence of objective data regarding sleep may be another limitation. It is also possible that some participants had a pre-existing sleep disorder which may have influenced results, particularly given the propensity for ceiling and floor effects in sleep research. There is also a need for future studies to examine the effect of exercise on a range of differing sleep disorders in order to identify which benefits the most from exercise intervention so that future interventions can be aimed at suitable target groups.

Another issue that was not addressed in this study was differences between study groups in morbidity levels during the Intervention period. This will be measured in a larger study.
Other potential explanations for the improvement in sleep quality identified in this study also exist. These factors are known as confounders. For example, components of the multi-disciplinary disease management program such as the optimisation of HF medications, increased social interaction and other treatment effects may have played a role in improving sleep quality. Strong evidence suggests that certain heart failure medications not only prolong life but improve symptoms in systolic heart failure in trials that involved forced up titration to specified target doses \cite{Hjalmarson2000,LeJemtel1999,Packer1996,Packer2001}. In our study, like that of Webb-Peploe at al \cite{Webb-Peploe2000} medication optimisation was not a prerequisite of study entry and it is possible that continuing optimisation of important heart failure medications may have been a source of confounding. However, evidence suggests that many patients do not achieve optimal doses of medications post discharge and the extent of this potential bias is probably small \cite{Fonarow2008,NHS2010}. In addition the high level of medication prescription at Baseline that was identified in both study groups may guard against this as a confounder.

### 4.4 DIRECTIONS FOR FUTURE RESEARCH

This research has identified other issues in need of further investigation. It is recommended that future studies be conducted in a more representative patient group as this study was only able to recruit 12% of patients identified due to eligibility considerations. Large, randomised controlled trials which assess both objective and subjective measures need to be undertaken. Such investigations need to examine the effect of exercise interventions on the different types of sleep disorders possible in this population and clarify the relationship between objective and subjective measures of sleep. Assessment of the effect of exercise on sleep using a number of different screening methods may also be useful to establish which measure is the most reliable, practical method for examining this increasingly well-recognised issue in HF patients.
More information regarding the effect of confounding factors such as exposure to bright light, increased social interaction, adverse events and the effects of other components of the HF disease management program would also assist in the understanding of how exercise improves sleep.

Finally, further investigation and experimentation into the best form of exercise intervention in terms of frequency, intensity, time and type of exercise is strongly recommended. This is important because much debate still exists regarding which form of exercise is beneficial and the duration and intensity which produces the best results.
Chapter 5: Conclusions

Heart failure is a clinical condition associated with high levels of sleep disturbance. Sleep disturbances exacerbate HF symptoms and lead to increases in morbidity and mortality in this disease. This study has shown that the addition of a 3 month program of aerobic and resistance exercise to the usual HF DMP produces significantly greater rates of clinical improvement in sleep quality.

In summary, in a sample of recently hospitalised HF patients, the addition of 3 months of supervised exercise training to usual care significantly improves sleep quality. These improvements were independent of the effects of exercise training on BMI. Improvements were related with improvements in depression and exercise performance highlighting the antidepressant effects of exercise training and the modulating effect of depression on sleep quality. Additional research with more comprehensive measurement of sleep is warranted, but exercise training appears to significantly improve sleep quality in HF patients. We anticipate that these findings will stimulate further study.


during, and after hospitalization for heart failure (from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). *Am J Cardiol*, 102(11), 1524-1529


Paparrigopoulos, T., Tzavara, C., Theleritis, C., Soldatos, C., & Tountas, Y. (2010). Physical activity may promote sleep in cardiac patients suffering from insomnia. *Int J Cardiol, 143*(2), 209-211


stretching intervention on sleep quality in postmenopausal women. *Sleep, 26*(7), 830-836

Uchida, S., Shioda, K., Morita, Y., Kubota, C., Ganeko, M., & Takeda, N. (2012). Exercise effects on sleep physiology. *Front Neurol, 3*, 48


Appendices

Appendix A

Patient Information and Consent Form

Participant Information Sheet

EC No: 2008/001

Project Title: A supervised exercise programme following hospitalisation for heart failure: does it add to disease management?

Name of Researchers: Dr Alison Mudge, Dr Charles Demare, Dr John Atherton, Dr Adam Scott, Dr Deborah Meyers, Dr George Jaworsky, Prof Tom Marwick, Prof Paul Schaffham, Dr Peter O'Rourke

You are invited to take part in a study looking at the best design of a group programme for patients who have been admitted to hospital because of heart failure, like yourself.

Background

Our hospital physiotherapist and/or nurses have identified you as a suitable participant for our Hospital to Home Heart Failure Outreach Programme, a new service offered at the Royal Brisbane and Women’s Hospital since May 2006. This service was set up because research shows patients who have been hospitalised with heart failure are healthier and less likely to need another hospital stay if they participate in a programme of education, regular health checks and self-management. These programmes are being set up all over the world.

However, research has not clearly shown which parts of this programme do the most good. Exercise, dietary advice, medication management and advice, and managing tiredness and other symptoms may all have a place, but different programmes may place more emphasis on one aspect than another. This research project is to identify whether group programmes with more emphasis on exercise have better results for patients and for hospitals.

The research has been funded by the National Health and Medical Research Council of Australia and will be conducted at three hospitals in Brisbane. The researchers are specialists involved in the treatment of patients with heart failure as well as experts in evaluating the benefits of health programmes. The study has been reviewed and approved by the Human Research Ethics Committees of the Royal Brisbane and Women’s Hospital, The Prince Charles Hospital, and the Princess Alexandra Hospital.

What will it involve?

We will enrol 360 patients with a recent hospital admission with heart failure in our project over a three year period. If you agree to participate, you will be randomly selected for one of two different group programmes. You will be asked to attend the groups at least once a week for 12-24 weeks. Both groups will be offered a programme of education, support and telephone follow-up, but one will also include more intensive, supervised exercise. Your specialist medical and nursing management will not be affected by which group you are enrolled in. We will let your specialist team and general practitioner know that you are involved in our study.

We will collect a range of information to assess the programmes. We will invite you for an assessment at the beginning, 3 months and 6 months into the project. At this time, we will provide you with questionnaires for completion either in the clinic or at home, and a pre-paid envelope to return completed questionnaires to us. We will also assess you fitness with a simple walking test. A small amount of blood about 45 ml (3 tablespoons) will be collected for routine testing. We will also seek information from your medical record about any admissions to hospital over this time. At twelve months, we will request information from the Queensland Government Health Information Centre, which keeps a record of all hospital admissions and deaths in Queensland, to find out whether you have needed any more admissions to hospital. We will also use hospital records to find out whether you have needed to attend the emergency department or outpatients.

Benefits

Until quite recently, it was thought that exercise could be dangerous in people with heart failure. However, small research studies all over the world have shown that supervised exercise is safe in the right people, and
Participant Information Sheet

that patients undertaking exercise are fitter and feel better. However, there are not enough studies to tell us whether exercise can reduce the likelihood of death, admission to hospital or depression, or whether the increased fitness we measure in an exercise test makes day-to-day activity easier. This study will help to answer these questions.

All people in this study will be offered our beneficial new Hospital-to-Home Heart Failure Outreach Service, with a carefully designed education programme to help you manage better at home. If we can show that supervised group exercise is a useful addition to this programme, we will be able to offer it to patients with heart failure in years to come; if we do not show any benefit, we can use more resources for the other parts of the programme such as home visits and telephone calls.

Risks and Side Effects

Hundreds of patients with heart failure have been in research projects looking at the impact of exercise on the heart and muscles, and there have been very few reports of side effects. However, people with heart disease carry a higher risk of heart attack or sudden death with strenuous exercise. Therefore our programme is supervised by trained exercise professionals, within the hospital environment. We will carefully assess every patient before commencing the programme, and each patient will have a programme that is tailored to their fitness. In research trials to date, there have been no more deaths or hospital admissions during the periods of supervised exercise or home exercise, suggesting there is not a significantly increased risk in a supervised programme with carefully chosen patients.

The main inconvenience will be attending the hospital once or twice per week, where a safe, supervised programme can be offered. We have designed our programme to minimise this inconvenience. If you are required to attend more than once per week we can assist with your transport costs. We will also provide assistance with transport costs (e.g., taxis or parking vouchers) to attend the 3 month and 6 month assessments. Regular telephone calls will help support your progress in the group. Possible side effects from having a blood sample taken include fainting (fear) and pain, swelling, bruising, or bleeding where the needle is inserted. There is also a slight possibility of infection where the needle is inserted.

Confidentiality and Privacy

All information that the research team collects about you is confidential. The information is stored in a secure location, and only the researchers will have access to the information. Information will be kept in a secure location for at least 15 years, so that we can reliably answer questions that other researchers might ask about our findings.

When we have completed collecting information about you, we will remove identifying information (your name, address, etc) from the database. We do need these details to obtain the information about hospital readmissions and deaths from the Health Information Centre, but all correspondence with them is strictly confidential, and any information exchanged with them is protected and relies only to this research study. Any publications or conference presentations or other public documents relating to the study will only contain grouped information, and no individual patient will be able to be identified.

Withdrawal from the study

You are able to withdraw from the study at any time, and you will continue to receive usual care from your heart failure team. The researchers recognise that some people will become too unwell or tired to continue the programme. It is still useful for us to continue to collect information even if you are not able to come to all the sessions, however participation in the 3 month and 6 months follow-up visits is voluntary.
Participant Information Sheet

Further Information
Please discuss any questions you might have with the research staff when they come to ask consent.
For further information at any time through the study, you can contact the Project Manager who will help you directly or help you to contact one of the principal researchers.

Project manager: Jessica Mayrseidl
Phone: 07 3636 5769
Email: Jessica_Mayrseidl@health.qld.gov.au

Principal researcher: Dr Alison Mudge, Royal Brisbane and Women's Hospitals
Phone: 07 3636 8111

If at any time you have concerns about the study, wish to make an independent complaint, or wish to discuss your involvement with someone not connected with the study, you may contact the Coordinator, Human Research and Ethics Committee on 07 3636 5460 who will forward concerns to the Chair, Human Research Ethics Committee.
Consent Form

EC No: 2008/001

Project Title: A supervised exercise programme following hospitalisation for heart failure: does it add to disease management?

Name of Researchers: Dr Alison Mudge, Dr Charles Denaro, Dr Adam Scott, Dr John Atherton, Dr Deborah Meyers, Dr George Javorky, Prof Tom Marwick, Prof Paul Schuffham, Dr Peter O’Rourke

I agree to participate in the above named project and in so doing acknowledge that:

- I have been informed as to the nature and extent of any risk to my health or well-being.
- I am aware that, although the project is directed to the expansion of medical knowledge generally, it may not result in any direct benefit to me.
- I have been informed that my refusal to consent to participate in the study will not affect in any way the quality of treatment provided to me.
- I have been informed that I may withdraw from the project at any time and that this decision will not affect in any way the quality of treatment.
- I have been advised that this project has been approved by the hospital Human Research Ethics Committee.
- I am aware that I may request further information about the project as it proceeds.
- I am aware that my GP and specialist may be informed that I am taking part in the project.
- I understand that, in respect of any information (which may consist of records outside of this hospital) confidentiality will be maintained to the same extent as for my Hospital medical records. In the event of any results of the project being published, I will not be identified in any way.
- I agree that, if necessary, my medical records (in respect of my involvement in this project) may be inspected by a Research Assessor. This assessor may be external to but approved by the Hospital, provided that the Assessor does not identify me or my hospital’s medical records in any way to a third party.

Patient’s name: …………………………… Signature: …………………….. Date: __/__/____

Name of Witness: …………………………… Signature: …………………….. Date: __/__/____

I confirm that, to the best of my knowledge, the participant has understood the information provided to him/her, and the implications of this information. The participant will be provided with a copy of this document.

Name of Research staff: …………………………… Signature: …………………….. Date: __/__/____
**Appendix B**  
**Pittsburgh Sleep Quality Index**

THE PITTSBURGH SLEEP QUALITY INDEX (PSQI)

**INSTRUCTIONS:**
The following questions relate to your usual sleep habits during the past month only. Your answer should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

**During the past month,**
1. What time have you usually gone to bed at night? ________________________________
2. How long (in minutes) has it usually taken for you to fall asleep each night? __________
3. What time have you usually gotten up in the morning? ____________________________
4. How many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed) ____________________________

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

   | Not during the past month (0) | Less than once a week (1) | Once or twice a week (2) | Three or more times a week (3) |
---|-------------------------------|--------------------------|--------------------------|--------------------------------|
   a. Cannot get to sleep within 30 minutes    |                            |                          |                            |
   b. Wake up in the middle of the night or early morning |                            |                          |                            |
   c. Have to get up to use the bathroom       |                            |                          |                            |
   d. Cannot breathe comfortably               |                            |                          |                            |
   e. Cough or snore loudly                   |                            |                          |                            |
   f. Feel too cold                            |                            |                          |                            |
   g. Feel too hot                             |                            |                          |                            |
   h. Have bad dreams                          |                            |                          |                            |
   i. Have pain                                |                            |                          |                            |
   j. Other reason(s), please describe,       |                            |                          |                            |

How often during the past month have you had trouble sleeping because of this?

| Very good (0) | Fairly good (1) | Fairly bad (2) | Very bad (3) |
---|----------------|----------------|---------------|--------------|

6. During the past month, how would you rate your sleep quality overall?

---
EJCTION-HF Trail

<table>
<thead>
<tr>
<th></th>
<th>Not during the past month (0)</th>
<th>Less than once a week (1)</th>
<th>Once or twice a week (2)</th>
<th>Three or more times a week (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. During the past month, how often have you taken medicine (prescribed or &quot;over the counter&quot;) to help you sleep?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?</td>
<td>No problem at all (0)</td>
<td>Only a very slight problem (1)</td>
<td>Somewhat of a problem (2)</td>
<td>A very big problem (3)</td>
</tr>
<tr>
<td>9. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10. Do you have a bed partner or room mate?</td>
<td>No bed partner or room mate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partner/room mate in other room</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partner in same room, but not same bed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partner in same bed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you have a room mate or bed partner, ask him/her how often in the past month you have had

<table>
<thead>
<tr>
<th></th>
<th>Not during the past month (0)</th>
<th>Less than once a week (1)</th>
<th>Once or twice a week (2)</th>
<th>Three or more times a week (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Loud snoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Long pauses between breaths while asleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Legs twitching or jerking while you sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Episodes of disorientation or confusion during sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Other restlessness while you sleep, please describe,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How often during the past month have you had trouble sleeping because of this?
# Appendix C

## Geriatric Depression Scale

Please choose the best answer for how you have felt over the PAST WEEK, indicate ✓ where applicable.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are you basically satisfied with your life?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Have you dropped many of your activities and interests?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you feel that your life is empty?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you often get bored?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Are you in good spirits most of the time?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Are you afraid that something bad is going to happen to you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you feel happy most of the time?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you often feel helpless?</td>
<td></td>
<td></td>
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<tr>
<td>9. Do you prefer to stay at home, rather than going out and doing new things?</td>
<td></td>
<td></td>
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<tr>
<td>10. Do you feel you have more problems with memory than most?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Do you think it is wonderful to be alive now?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Do you feel pretty worthless the way you are now?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Do you feel full of energy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Do you feel that your situation is hopeless?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Do you think that most people are better off than you are?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Appendix D

## Six Minute Walk Test Case Report Form

<table>
<thead>
<tr>
<th>TIME</th>
<th>BP</th>
<th>HR</th>
<th>SPO2</th>
<th>BORG</th>
<th>DISTANCE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 min</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1-2 min</td>
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<td></td>
<td></td>
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<tr>
<td>2-3 min</td>
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<tr>
<td>3-4 min</td>
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<tr>
<td>4-5 min</td>
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<td></td>
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<tr>
<td>5-6 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TIME TO RECOVERY:** 【 minutes 】 seconds

**MAX RPE:** 【 】

**TOTAL DISTANCE ACHIEVED:** 【 meters 】

---

**Notes:**
- Please note that tests are only required at the baseline visit.
- The following section is to be completed by the Project Officer.
- OXYGEN: (0) Nil  (1) Supplemental C2, please specify: 【 】
- AIDS: (0) Nil  (1) Walking aid, please specify: 【 】

---

**Test 2 Start Time:** 【 hours (24-hour format) 】

<table>
<thead>
<tr>
<th>TIME</th>
<th>BP</th>
<th>HR</th>
<th>SPO2</th>
<th>BORG</th>
<th>DISTANCE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2-3 min</td>
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<tr>
<td>3-4 min</td>
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<td></td>
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<tr>
<td>4-5 min</td>
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<td></td>
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<tr>
<td>5-6 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TIME TO RECOVERY:** 【 minutes 】 seconds

**MAX RPE:** 【 】

**TOTAL DISTANCE ACHIEVED:** 【 meters 】

---

EMWIT Version 3 dated 17 November 2011

---

90 Appendices
### EJECTION-HF TRIAL

#### TIMED UP AND GO

<table>
<thead>
<tr>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 10M WALK SPEED (BASELINE AND MONTH 3 VISITS ONLY)

<table>
<thead>
<tr>
<th>Speed</th>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comfortable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Speed</th>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comfortable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### GRIP STRENGTH

<table>
<thead>
<tr>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Hand</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Hand</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Project Officer: [FIRST NAME] [SURNAME]  
Signature: ________________________________  
Date: ____________  
Time: ____________

When complete please forward signed form to the Project Manager (07) 8626 8943 for entry into the study database.

---

Data Entered into Database: [ ]

Note: Version 3 dated 17 November 2011
EJECTION-HF TRIAL

COMPLETION GUIDELINES

Please refer to the following definitions for assistance with item completion.

6 MINUTE WALK TEST
The 6MWT measures the distance a patient can walk on a flat, straight, hard surface, in an area that is seldom travelled, in a period of 6 minutes. The turnaround points should be marked with a cone (such as an orange traffic cone) and the area marked at metre intervals to 25 metres in length.

Required equipment
1. Countdown timer or stopwatch
2. Small cones to mark the turnaround points
3. Chairs that can be moved along the walking course
4. Worksheets on a clipboard
5. Source of oxygen (as required)
6. Sphygmomanometer
7. Telephone
8. Pulse oximeter

Patient preparation
1. Comfortable clothing should be worn & appropriate walking shoes.
2. Patients should use their usual walking aids during the test.
3. Patient's usual medical regimen should be continued.
4. Patients should not exercise on the day of the test.
5. If oxygen supplementation is usually required during walking, then during all walks the patient should have oxygen delivered in the same way with the same flow. Record the flow used.

Procedure
1. Patient should sit at rest in a chair located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse, blood pressure & oxygen saturation (SpO2) and ensure that clothing and shoes are appropriate. Record resting observations. If patient is able to carry the pulse oximeter, ensure that their stride is not affected. If the study personnel needs to hold the pulse oximeter they should follow behind the patient so as to not influence the patients walk rate.
2. Have the patient stand and rate their baseline dyspnoea and overall fatigue using the Borg scale.
3. Instruct the patient as follows: The object of the test is to walk as far as possible for 6 minutes. You will walk back and forth around the course. You may get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary, and you may resume walking as soon as you are able.
4. Demonstrate by walking one lap yourself, pointing around the course.
5. Position the patient at the starting line. As soon as the patient starts to walk, start the timer.
6. At the end of each lap, mark on the distance section in the worksheet. Record the SpO2 & heart rate readings and ask the patient to rate themselves on the Borg scale at the minute intervals.
7. When the timer shows only 1 minute remains, tell the patient, “You are doing well, you only have one minute to go.”
8. When the timer reaches 6 minutes ask the patient to stop, walk to the patient and mark the stop point. Reset the stopwatch or timer to record the recovery time. Assist the patient to a chair and record final SpO2, heart rate and Borg scale rating.
9. Count up total distance walked and record.

Reasons for stopping a 6MWT include the following: (1) Chest pain, (2) intolerable dyspnoea, (3) leg cramps, (4) staggering, (5) diaphoresis, and (6) pale or ashen appearance. Record the reason for stopping any 6MWT.

TIMED UP AND GO TEST

Required equipment
1. Stopwatch
2. Standard height chair with arms
3. Marked 3 metre course

Patient preparation
1. Comfortable clothing should be worn & appropriate walking shoes.
2. Patients should use their usual walking aids during the test.

Procedure
1. Patient begins seated in a standard height armchair with their back against the backrest and arms resting on the armrests.
2. A marker (such as an orange traffic cone) is placed on the floor 3 metres from the chair.

EMRC Version 3 dated 17 November 2011
EJECTION-HF TRIAL

3. Instruct the patient "on the word "go" I want you to walk at a comfortable and safe pace to the marker on the floor, turn, walk back to the chair and sit down again"

4. Start the stopwatch on the word "go" and stop when patient is back sitting in the chair

GRIP STRENGTH
The purpose of this test is to measure grip or forearm muscle strength. As a generalisation, people with strong grip strengths tend to be stronger overall body strengths.

Equipment Required: Handgrip dynamometer

Procedure:
The subject to be tested holds the dynamometer in the hand to be tested, with the arm at right angles and the elbow by the side of the body. The handle of the dynamometer is adjusted if required. The base should rest on the first metacarpal (base of palm), with the handle resting on the middle surface of the fourth fingers. The subject squeezes the dynamometer with maximum isometric effort, which is maintained for approximately five seconds. No other body movement is permitted.

RATING OF PERCEIVED EXERTION: BORG SCALE
The rating of perceived exertion (RPE or Borg scale) is subjective measure of exercise intensity and is a good indicator of relative fatigue (see scale below). It can be used in conjunction with the heart rate to determine the consistency of effort from one study to the next in a given patient.

Ask the patient which number best describes the level of exertion they are feeling at the time of questioning. (Print off the page and hold up the score sheet below as patient walks past and then record the number identified by the patient for every minute walked)

<table>
<thead>
<tr>
<th>BORG SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

EPRINT Version 3 dated 17 November 2011
# Appendix E

## Study Case Report Forms

### Visit: Eligibility

**EJECTION-HF TRIAL**

<table>
<thead>
<tr>
<th>Reg Num</th>
<th>\</th>
<th>\</th>
<th>\</th>
<th>\</th>
</tr>
</thead>
</table>

Data of Completion: \ |

Affix patient label

Please print all details and INITIAL, and DATE all corrections, indicate ✓ where applicable. Please only select one answer for each question.

### DEMOGRAPHICS

The following section is to be completed by the Project Officer.

**GENDER:**
- (1) Male
- (2) Female

**ETHNICITY:**
- (1) Caucasian
- (2) European
- (3) Mediterranean
- (4) Asian
- (5) Aboriginal/TSI/Pacific Islander
- (6) Hispanic
- (7) Other, please specify:

### ADMISSION DETAILS

**ADMISSION DATE:** \ | \ | \ | \ | \ |

**DISCHARGE DATE:** \ | \ | \ | \ | \ |

**HOSPITAL PRESENTATION:**
- (1) Emergency admission for heart failure
- (2) Emergency admission for other cardiovascular disease
- (3) Emergency admission for non-cardiovascular disease

**KNOWN PREVIOUS HEART FAILURE DIAGNOSIS:**
- (1) De Novo HF presentation
- (2) Decompensated HF

**UNPLANNED ADMISSIONS IN THE PAST 6 MONTHS:** \ | \ | \ | \ | \ |

**DATE OF MOST RECENT PREVIOUS ADMISSION:** \ | \ | \ | \ | \ |

**TREATING TEAM:**
- (1) Cardiology
- (2) General medicine
- (3) Other, please specify:

**CONSULTANT:**
- (1) Home alone
- (2) Home with others / carers
- (3) Residential care
- (4) Other, please specify:

**DISCHARGE DESTINATION:**

Eligibility Form Version 3.1 dated 30 March 2012

---

94 Appendices
### EJECTION-HF TRIAL

#### Visit: Eligibility

<table>
<thead>
<tr>
<th><strong>HEART FAILURE AETIOLOGY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Ischaemic</td>
</tr>
<tr>
<td>(2) Primary valvular disease</td>
</tr>
<tr>
<td>(3) Contributory valvular disease</td>
</tr>
<tr>
<td>(4) Primary myocardial hypertrophic muscle disease</td>
</tr>
<tr>
<td>(5) Hypertensive</td>
</tr>
<tr>
<td>(6) Alcohol cardiomyopathy</td>
</tr>
<tr>
<td>(7) Toxic</td>
</tr>
<tr>
<td>(8) Pregnancy related</td>
</tr>
<tr>
<td>(9) Thyroid related</td>
</tr>
<tr>
<td>(10) Idiopathic</td>
</tr>
<tr>
<td>(11) Familial</td>
</tr>
<tr>
<td>(12) Other, please specify:</td>
</tr>
</tbody>
</table>

#### CLINICALLY LIKELY CAUSE OF HEART FAILURE

[as per definition of]

#### GP INFORMATION

<table>
<thead>
<tr>
<th>GP NAME</th>
<th>GP NAME</th>
<th>GP SURGERY NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GP ADDRESS</th>
<th>GP ADDRESS</th>
<th>SUBURB</th>
<th>POSTCODE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

---

*Eligibility Form Version 3.1 dated 30 March 2012*
## EJCTION-HF TRIAL

### Visit: Eligibility

#### ELIGIBILITY CHECKLIST

The following section is to be completed by the Project Officer.

### INCLUSION CRITERIA

1. **≥ 6 weeks post acute admission to hospital with symptomatic heart failure as dominant clinical diagnosis.**

   - EVIDENCE ON ADMISSION OF ≥ 2 CLINICALLY SIGNIFICANT CRITERIA:
     - Dyspnea
     - Fatigue
     - Peripheral oedema
     - Elevated JVP
     - Elevated JVP
     - 2D heart sound
     - Capillary refill time
     - Pulmonary venous congestion
     - Pulmonary oedema
     - Constrictive

   **COMBINED WITH chest x-ray changes (please attach report):**

2. **ECHOCARDIOGRAPHY WITHIN 6 MONTHS:**
   - Date of echocardiogram: dd/mm/yyyy
   - Ejection fraction: %
   - Echocardiography modality:
     - (1) Radionuclide ventriculography
     - (2) Echocardiography 2D
     - (3) Echocardiography 3D
     - (4) Contrast ventriculography
     - (5) Techniques myocardial perf imaging
     - (6) Other, please specify:

3. **ON MEDICAL THERAPY FOR HEART FAILURE (refer to pharmacological therapy):**

4. **ABLE TO REGULARLY ATTEND THE DURATION OF THE PROGRAMME AND ALL FOLLOW-UPS:**

5. **SATISFY SAFETY CRITERIA (see next page):**

6. **SIGNED WRITTEN INFORMED CONSENT:** dd/mm/yyyy

7. **AGED 18 YEARS OR OLDER:**

---

Eligibility Form Version 3.1 dated 30 March 2012
### EXCLUSION CRITERIA

<table>
<thead>
<tr>
<th>No.</th>
<th>Criterion</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Life expectancy &lt; 6 months / Terminally ill</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Serious cognitive impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Serious other physical impairment which prevents attendance &amp; participation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>ICD insertion &lt; 4 weeks preceding programme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>CRT &lt; 6 months preceding programme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Waiting cardiovascular procedure or hospitalisation for surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Exercise testing results / clinical judgement by exercise specialist precludes safe exercise training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Completed a full 12 week regime of formal exercise rehabilitation in the past 12 month period</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SAFETY CRITERIA

<table>
<thead>
<tr>
<th>No.</th>
<th>Criterion</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Refractory chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Uncontrolled cardiac arrhythmias causing symptoms of haemodynamic compromise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>High-degree AV block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Pacemakers which do not permit adequate heart rate response to exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Heart failure secondary to significant uncorrected primary valvular disease (except for mitral regurgitation secondary to LV dysfunction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Isolated pulmonary hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Poorly controlled symptomatic postural hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Obstructive cardiomyopathies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Project Officer: ____________________________  Signature: ________________  Date: __________  Affmon YYYY

When complete please fax to the Project Manager (27) 3636 694 for randomisation and entry into the study database.

### RANDOMISATION

The following section is to be completed by the Project Manager

RANDOMISED ALLOCATED TREATMENT:  
- [ ] Control Arm  
- [ ] Intervention Arm

STUDY START DATE: ____________________________  Affmon YYYY

Project Manager: ____________________________  Signature: ________________  Date: __________  Affmon YYYY

Following randomisation please forward signed form with Baseline 6MMT CRFs to study exercise staff for programme development.

Data Entered into Database [ ]
EJECTION-HF TRIAL

Visit: Eligibility

COMPLETION GUIDELINES

Please refer to the following definitions for assistance with completion.

Ethnicity

- Mediterranean: - Europe: Spain, France, Monaco, Malta, Slovenia, Croatia, Bosnia-Herzegovina, Montenegro, Albania, Greece, Turkey. In Asia: Syria, Cyprus, Lebanon, Israel. In Africa: Egypt, Libya, Tunisia, Algeria, Morocco.

Clinically likely cause of heart failure:

- Ischemic - at least 1 major epicardial coronary artery with greater than 70% obstruction by coronary angiography. HR of acute MI associated with wall motion abnormality by echocardiography or gated blood pool imaging. Stress testing (with or without imaging) diagnostic of coronary artery disease.

- Primary valvular disease - moderately severe or severe, 3+ or 4+ aortic insufficiency, moderately severe or severe, 3+ or 4+ mitral insufficiency with echo evidence that mitral insufficiency is a primary abnormality, and not secondary to ventricular dilation. Moderately severe or severe aortic stenosis defined by estimated aortic valve area by catheterization or Doppler echo of less than or equal to 1.0 cm². Moderately severe or severe mitral stenosis defined by estimated mitral valve area by catheterization or echo of less than 1.0 cm².

- Contributory valvular disease - Valve disease that is felt to be significant but does not fulfill the above definitions.

- Primary myocardiial hypertrophic muscle disease - Evidence for symmetric or asymmetric hypertrophy without outflow tract obstruction. Congenital muscular dystrophy.

- Hypertensive - One of the following conditions must be met:
  - Uncontrolled systolic BP > 160 mm Hg or diastolic > 105 mm Hg for at least 3 months.
  - Hypertension requiring at least 2 drugs for control for at least 5 years.
  - Presence of diabetes and hypertension, treated or untreated.
  - Documented left ventricular hypertrophy on echo or MRI.

- Alcoholism: alcohol consumption (75 g/day at least 5 days/week) for at least 5 years.

- Toxic - Temporal relationship to other cardiotoxic substance or drug, evidence of drug or drug-related symptoms and evidence of drug toxicity on echo.

- Pregnancy related - Onset of cardiomyopathy associated with pregnancy. Irreversible, causing permanent damage to the myocardium.

- Thyroid related - Presence of otherwise unexplained cardiomyopathy associated with thyroid disorder.

- Idiopathic - Heart failure and reduced systolic function with evidence for any of the above etiologies or other disease known to cause cardiomyopathy.

- Familial - One of the following conditions must be met:
  - Possible presence of otherwise unexplained cardiomyopathy, diagnosis of heart failure, atrial fibrillation or life threatening ventricular arrhythmias, conduction system disease, or sudden death in first degree relative under 60 years of age.
  - Possible presence of above in two relatives under 60 years of age who are related to each other and the patient.
Visit: Baseline

REG No: 
Date of Completion: 

Please print all details, and INITIAL and DATE all corrections, indicate where applicable. Please only select one answer for each question.

**MEDICAL HISTORY**

The following section is to be completed by the Project Officer.

**HYPERTENSION:**

(As per definition p6)  
(3) No  
(1) Yes

**BASELINE SIGNS AND SYMPTOMS**

**DYSPNOEA AT REST:**

(As per definition p5)  
(3) No  
(1) Yes

(3) No  
(1) Running or other sport, please specify: ____________________________

**DYSPNOEA ON EXERTION:**

(2) Walking up an incline, distance: ____ metres  
(3) Walking on a flat surface, distance: ____ metres  
(4) Performing usual ADLS  
(5) Standing

**PHYSICAL EXAMINATION**

**HEIGHT:** ______ metres  
**WEIGHT:** ______ kilograms

**IN THE LAST 2 WEEKS, ON AVERAGE, HOW MANY MINUTES PER DAY OF MODERATE ACTIVITY FOR THE PURPOSE OF EXERCISE HAVE YOU COMPLETED?**

(1) 15 minutes or more moderate physical activity 5-7 days a week.  
(2) 30 minutes or more moderate physical activity 5-7 days a week.

Project Officer: ________________________________  
Signature: ________________________________  
Date: _______  

When complete please forward with the BMWT, NMBSE and Questionnaire Baseline 1 CRFs along with a copy relevant de-identified source data (ECG, x-ray, chest x-ray) to the Project Manager (07) 363 0943 for entry into the study database.

Date Entered into Database: 

Baseline Form Version 8 dated 26 March 2012

Appendices 99
EJECTION-HF TRIAL

Visit: Baseline

COMPLETION GUIDELINES

Please refer to the following definitions for assistance with completion:

Hypertension – has of HTN diagnosed & treated with meds, diet and/or exercise.
- 140 mmHg systolic or 90 mmHg diastolic on at least 2 occasions
- 130 mmHg systolic or 80 mmHg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease.

Dyspnoea at rest – pt describes uncomfortable awareness of breathing while resting in a sitting position

Dyspnoea on exertion – pt describes uncomfortable awareness of breathing while exerting himself
EJECTION-HF TRIAL

Visit: Month 3

Date of Completion: Date

Reg Num:

Please print all details, and INITIAL and DATE all corrections, indicate X where applicable. Please only select one answer for each question.

PHYSICAL EXAMINATION

The following section is to be completed by the Project Officer.

HEIGHT: __________ meters

WEIGHT: __________ kilograms

IN THE LAST 2 WEEKS, ON AVERAGE HOW MANY MINUTES PER DAY OF MODERATE ACTIVITY FOR THE PURPOSE OF EXERCISE HAVE YOU COMPLETED?

☐ (3) Less than 15 minutes of moderate physical activity 5-7 days a week.

☐ (4) 15 minutes or more moderate physical activity 5-7 days a week.

☐ (5) 30 minutes or more moderate physical activity 5-7 days a week.

Project Officer: __________

Signature: __________

Date: __________

When complete please forward signed form along with BMAT, MMSE and GDS ORUs to the Project Manager (07) 3836 9443 for entry into the study database.

Data Entered into Database: ☐

Month 3 Form Version 1 dated 26 March 2012
Appendix F
PSQI Administration Instructions and Scoring

Form Administration Instructions

The range of values for questions 5 through 10 are all 0 to 3.

Questions 1 through 9 are not allowed to be missing except as noted below. If these questions are missing then any scores calculated using missing questions are also missing. Thus it is important to make sure that all questions 1 through 9 have been answered.

In the event that a range is given for an answer (for example, ‘30 to 60’ is written as the answer to Q2, minutes to fall asleep), split the difference and enter 45.

Reference

Scores – reportable in publications
On May 20, 2005, on the instruction of Dr. Daniel J. Buysse, the scoring of the PSQI was changed to set the score for Q5J to 0 if either the comment or the value was missing. This may reduce the DISTB score by 1 point and the PSQI Total Score by 1 point.

PSQIDURAT  DURATION OF SLEEP
IF Q4 \geq 7, THEN set value to 0
IF Q4 < 7 and \geq 6, THEN set value to 1
IF Q4 < 6 and \geq 5, THEN set value to 2
IF Q4 < 5, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDISTB  SLEEP DISTURBANCE
IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j
(IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) \geq 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j
(IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 1 and \leq 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j
(IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and \leq 18, THEN set value to 2
IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j  
(IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) >  
18, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

**PSQILATEN**  SLEEP LATENCY  
First, recode Q2 into Q2new thusly:  
IF Q2 ≥ 0 and ≤ 15, THEN set value of Q2new to 0  
IF Q2 > 15 and ≤ 30, THEN set value of Q2new to 1  
IF Q2 > 30 and ≤ 60, THEN set value of Q2new to 2  
IF Q2 > 60, THEN set value of Q2new to 3  
Next  
IF Q5a + Q2new = 0, THEN set value to 0  
IF Q5a + Q2new ≥ 1 and ≤ 2, THEN set value to 1  
IF Q5a + Q2new ≥ 3 and ≤ 4, THEN set value to 2  
IF Q5a + Q2new ≥ 5 and ≤ 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

**PSQIDAYDYS**  DAY DYSFUNCTION DUE TO SLEEPINESS  
IF Q8 + Q9 = 0, THEN set value to 0  
IF Q8 + Q9 ≥ 1 and < 2, THEN set value to 1  
IF Q8 + Q9 ≥ 3 and < 4, THEN set value to 2  
IF Q8 + Q9 ≥ 5 and < 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

**PSQIHSE**  SLEEP EFFICIENCY  
Diffsec = Difference in seconds between day and time of day Q1 and day Q3  
Diffhour = Absolute value of diffsec / 3600  
newtib = IF diffhour > 24, then newtib = diffhour – 24  
IF diffhour ≤ 24, THEN newtib = diffhour  
(NOTE, THE ABOVE JUST CALCULATES THE HOURS BETWEEN GNT (Q1) AND GMT (Q3))  
tmphse = (Q4 / newtib) * 100  
IF tmphse ≥ 85, THEN set value to 0  
IF tmphse < 85 and ≥ 75, THEN set value to 1  
IF tmphse < 75 and ≥ 65, THEN set value to 2  
IF tmphse < 65, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

**PSQISLPQUAL**  OVERALL SLEEP QUALITY  
Q6

Minimum Score = 0 (better); Maximum Score = 3 (worse)

**PSQIMEDS**  NEED MEDS TO SLEEP  
Q7

Minimum Score = 0 (better); Maximum Score = 3 (worse)
PSQI  TOTAL
DURAT + DISTB + LATEN + DAYDYS + HSE + SLPQUAL + MEDS
Minimum Score = 0 (better); Maximum Score = 21 (worse)
Interpretation: TOTAL ≤ 5 associated with good sleep quality
TOTAL > 5 associated with poor sleep quality
Geriatric Depression Scale (GDS) Scoring Instructions

**Instructions:** Score 1 point for each bolded answer. A score of 5 or more suggests depression.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are you basically satisfied with your life?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Have you dropped many of your activities and interests?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you feel that your life is empty?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you often get bored?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Are you in good spirits most of the time?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Are you afraid that something bad is going to happen to you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you feel happy most of the time?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you often feel helpless?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Do you prefer to stay at home, rather than going out and doing things?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Do you feel that you have more problems with memory than most?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Do you think it is wonderful to be alive now?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Do you feel worthless the way you are now?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Do you feel full of energy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Do you feel that your situation is hopeless?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Do you think that most people are better off than you are?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_A score of ≥ 5 suggests depression. Total Score_
Instructions for Geriatrics Depression Scale (GDS-S): Scoring The Short Form

Instructions

The GDS-S should be given orally. A clear YES or NO answer is required for each question. If necessary, repeat the question but do not accept a qualified answer from the test taker. Cross off either yes or no for each question. Depressive answers (errors) are circled on the form and are bolded below. Count up 1 for each depressive answer (error). The final score is the tally of the number of depressive answers with the following scores indicating depression.

0-4 No depression
5-10 Suggestive of a mild depression
11+ Suggestive of severe depression

What to do if a patient does not answer a few items.

For example, if 3 of 15 items are not answered then the total score is score on 12 completed PLUS 3/15ths of total score to make-up for omitted items, e.g. if they got a 4 on the 12 they completed or 1/3 positive, add 1/3 of the 3 missing or 1 point for a total of 5.

What if the patient is aphasic?

Use a point-board, or a board with the scale and yes/no next to the items and have patient point out correct answer. If the patient is aphasic due to dementia then other measures should be used to determine the patients level of depression.
**Appendix H**

**Exercise Protocol**

Post acute structured exercise rehabilitation programme

- 12 weeks exercise intervention, hospital based, twice per week (24 sessions). Duration 1.5 hours

**General Structure**

- 10-15 minutes warm up
- 1 hour of exercise session
- 10-15 minutes warm down

Break down – 30 minutes of combined aerobic exercise and 30 minutes of resistance exercises (concentric/eccentric), balance and stretches.

**Exercise Prescription**

Each exercise will follow the F.I.T.T guidelines (frequency, intensity, time & type) for best practice prescription and progression (according to ACSM)

**Measuring Intensity for Exercise Class**

Intensity will be measured by

- Heart Rate (HRR) using heart rate monitors
- RPE – modified BORG scale
- Reported symptoms
- Talk test, which refers to a patient's ability to be able to talk during exercise
Each individual will have heart rate limits calculated using their age and risk stratification based on a modified American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR).

All HF patients are considered High Risk. Therefore HR limits will be set according to 50 – 60% HRR. This is an initial starting level and may change. That is, 50-70% HRR or 60-75% HRR.

Heart rate limits will be calculated using the Heart Rate Reserve method (HRR) alternatively named the Karvonen method.

Heart rate is used as a guide to set exercise intensity because of the relatively linear relationship between HR and % VO2 max.

- Estimate max HR = 220 – age (variance: 1 SD = 10-12bpm)

- **High risk: 50 - 60% HRR**

- Moderate risk: 50 – 70% HRR

- Low risk: 60 – 75% HRR

- Approx 55 to 75% of VO2 max average adult

Prescribing an exercise program with the above formulas has been shown to increase VO2 max and to achieve sufficient improvements in cardio respiratory fitness when combined with an appropriate frequency and duration of training.

**HRR - Heart Rate Reserve method (Karvonen method)**

Target HR range = ([HR max – HR rest] x 0.60 and 0.75) + HR rest

Conversion of a %HR max (or %HRR) value to a %VO2 max value carries with it a standard error of estimated of +/- 6% VO2 max.

Walking = Metabolic Equation:

\[ \text{VO}_2 = (0.1 \times S) + (1.8 \times S \times G) + 3.5 \]
**Rating of Perceived Exertion (RPE) – Modified Borg Scale**

Another method of measuring intensity for the exercise class is the RPE scale.

- When exercising, individuals should aim to stay between an RPE of 9 (very light) and 13 (somewhat hard)

- The Borg Scale Zone of 9 to 13 correlates to the Talk Test Zone where an individual who is exercising in this zone should be able to carry out a conversation without significant shortness of breath. If the individual is too short of breath to carry on a conversation the intensity is too high and they working too hard.

<table>
<thead>
<tr>
<th>RPE</th>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
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</tr>
<tr>
<td>8</td>
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<tr>
<td>11</td>
<td>Fairly light</td>
</tr>
<tr>
<td>12</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>13</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>14</td>
<td>Hard</td>
</tr>
<tr>
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<td>Hard</td>
</tr>
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<tr>
<td>18</td>
<td>Very, very hard</td>
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<tr>
<td>19</td>
<td>Very, very hard</td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>
**Measuring Intensity for Resistance Training**

- Resistance – the initial starting resistance will be determined by the judgment of the exercise prescribing specialist in conjunction with the individuals pre assessment (Physiotherapist/Exercise Physiologist)

- Progression – From the initial starting prescription, progress a patients duration before intensity i.e., increase to 3 sets of 10 reps before increasing the weight

- When an individual can achieve 3 sets of 10 reps comfortably i.e., within their HR limits and with an RPE of 8 to 10, progress the intensity of the exercise by increasing the resistance by a small amount

- Rest period / recovery – Some individuals will require more rest than others. The minimum work : rest ratio will be 1:2

**References**


**Warm-up & Warm-down Prescription**

- Time = 10 minutes for each of WU and WD

  - Marching on spot

  - Walking

  - Skill orientated activities

  - Stretches (3 upper limb and 4 lower limb holding for 20 seconds)
- Some pts may not be able to hold for 20sec therefore begin at a comfortable level e.g., 5 secs and progress when able

- Hamstring
- Hip flexor
- Quadriceps
- Calf
- Triceps
- Posterior shoulder
- Chest (Pectoralis)

**Upper Body Resistance Exercises**

- Aim to achieve 3 sets of 10 reps

- Individuals may need to begin on 2 sets of 7 reps or 3 sets of 5 reps

**Exercise Prescription**

- Bicep curl
- Lateral raises
- Tricep extension
- Seated row
- Chest progression
  - Wall push ups
  - 45 degree push ups
  - Incline chest press with dumbbells
• Modification of individual exercises may need to occur depending on the musculoskeletal limitations of each individual.

• Ensure correct technique at all times

Lower Body Resistance Exercises

Exercise Prescription

• Leg Press

• Leg extensions / knee extensions

• Sit to stand progression
  ◦ Using arms on arm rest
  ◦ Using arms on knees
  ◦ Not using arms (folding arms on chest)

Aerobic Exercises

• Aim to achieve a total of 30 minutes of combined walking/cycling/treadmill/step ups/rowing machine
  ◦ Interval training can be utilised with differing work rest ratios

Special considerations for exercise training

Beta-Blockers

• As patients will be on beta blockers the HRR method of setting HR limits is more appropriate than using %age HR alone. The HRR method takes into consideration the patients resting HR. These limits are a guide with RPE, talk test and patient symptoms being of significant importance when prescribing and progressing exercises.
Angina

- Anginal symptoms can be graded on a scale of 1 to 4, corresponding to perceptible but mild, moderate, moderately severe, and severe, respectively. Ratings of >2 (moderate) should be used as end points for exercise testing and the exercise class with rest and treatment and no more exercise on that day. Ratings of 1 (perceptible but mild) should be used as end point for that particular exercise with rest and monitoring and the option to resume exercise at a lower level of intensity one recovered (ACSM).

- Because symptomatic or silent ischemia may be arrhythmogenic, the target HR for exercise intensity should be set ≥ 10 bpm lower than the heart rate at which the onset of angina or ischemia occurs (ACSM). That is, if angina is reported during any testing procedure (6MWT, EST, or other) or during the exercise class, that heart rate should be noted and the patient should exercise ≥10bpm lower than the onset of the angina.

Adherence

- Record sheet of exercises to be filled out and handed in at end of each session for post acute structured exercise rehabilitation programme.

- Home program with daily record sheet and pictures

- Educational session provided with schedule

- Telephone follow-ups for both exercise and control group.
  - Exercise group for patients who miss sessions or need following up on advice given during the programme. This advice may me physical activity related or nursing related.
  - Control group for patients to receive a similar opportunity for contact with health professionals.

- Motivational interviewing approach throughout with possible specific techniques to be included.
• Record sheet of attendance and if unable to attend, the reason why for documentation

Home Based Exercise Rehabilitation Program **For Exercise Group**

• A home based exercise guide will be given to each patient.

• The home based guide will be in the form of a booklet and will be similar to hospital based exercises. Exercises will be chosen from a list designed to suit the individual’s needs and environment (home and equipment)

**General Structure**

- Warm up
- Aerobic exercise
- Resistance Training – Concentric & Eccentric contractions (upper limb, lower limb)
- Balance
- Stretching
- Warm down

**Exercise Prescription**

- Walking
- Sit to stand
- Wall push ups
- Stairs
- Stationary cycling or rowing machine or treadmill (if own equipment)
Lunges (this is here because some patients may need more advanced exercises to replace machine weighted exercises completed in hospital)

- Bicep curls
- Lateral raises
- Stretches

All of these exercises do not need to be prescribed as the booklet will be sufficient. However there is a need to be flexibly and they are included to provide options for individuals.

- Patients will be instructed to exercise for a total time of 30-40 minutes
  - To be done in conjunction with hospital based exercise programme \( \geq \) 3 days per week
  - To be done in conjunction with hospital based maintenance programme \( \geq \) 4 days per week
  - To be done upon completion of hospital based exercise programme \( \geq \) 5 days per week

- A dedicated education session on exercising in the home will be delivered early on in the 12 week hospital based intervention.

- Safety precautions, limiting factors, do’s and do nots will be included in this session as well as an *Action Plan* for signs and symptoms.

**Education Only Group ‘Usual Care’**

The patients randomised into the education only group will receive a booklet and advice on exercise as an inpatient. This advice will parallel the National Health Activity Guidelines.
This group will receive the same education sessions that the exercise group receive including the dedicated home exercise education session.

Safety precautions, limiting factors, do’s and do nots will be included in this session as well as an *Action Plan* for signs and symptoms.
Appendix I

Ethics Approval Documents

n2747791

Date: Mon, 06 Jul 2009 16:42:55 +1000
From: "Research Ethics" <ethicscontact@qut.edu.au>
Subject: Ethics Application Approval -- 0900060051
To: "Ms Jessica Mayroeidi" <j.mayroeidi@student.qut.edu.au>
Cc: "Ms Janette Lamb" <j.lamb@qut.edu.au>

Dear Ms Jessica Mayroeidi

Project Title:
The effect of exercise on sleep quality in congestive heart failure

Ethics Number: 0900060051
Clearance Until: 6/07/2012
Ethics Category: Human

This email is to advise that your application has been reviewed and confirmed as meeting the requirements of the National Statement on Ethical Conduct in Human Research, and we understand ethics clearance has already been obtained from another institution.

Your QUT ethics approval number is 0900060051. Please quote this number in all future correspondence.

Whilst the data collection of your project has received ethical clearance, the decision to commence and authority to commence may be dependant on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or permissions from other organisations to access staff. Therefore the proposed data collection should not commence until you have satisfied these requirements.

If you require a formal approval certificate, please respond via reply email and one will be issued.

This project has been awarded ethical clearance until 6/07/2012 and a progress report must be submitted for an active ethical clearance at least once every twelve months. Researchers who fail to submit an appropriate progress report may have their ethical clearance revoked and/or the ethical clearances of other projects suspended. When your project has been completed please advise us by email at your earliest convenience.

Regarding variations, please complete and submit an online variation form:
http://www.research.qut.edu.au/ethics/forms/hum/var/var.jsp

Please note that it is your responsibility to contact the unit if you have any queries.

Regards

Research Ethics Unit | Office of Research | Level 4 | #8 Musak Ave | Kelvin Grove
P: +61 7 3138 5123 | F: +61 7 3138 1104 | E: ethicscontact@qut.edu.au

https://mail-mgstore03.qut.edu.au/wm/eml/login.html?sessionid=04bd82869d4146f0f... 8/07/2009

Appendices 117
Dear Ms Lum

Protocol 2608/001: A SUPERVISED EXERCISE PROGRAMME FOLLOWING HOSPITALISATION FOR HEART FAILURE: DOES IT ADD TO DISEASE MANAGEMENT? EC2722

The above Protocol was received by the Office of the Royal Brisbane & Women's Hospital Human Research Ethics Committee on 3 January 2008, and was reviewed by the Expedited Review Process and was given final approval on the 1 February 2008. The Royal Brisbane & Women's Hospital Human Research Ethics Committee is duly constituted, and operates and complies with the National Health and Medical Research Council's 'National Statement on Ethical Conduct in Research Involving Humans' and Supplementary Notes, 2007.

It is advised that on the recommendation of the Human Research Ethics Committee, the Clinical Chief Executive Officer, Royal Brisbane & Women's Hospital has approved your request for ethical approval of the following:

- NEAF dated 6 December 2007
- Patient Information Form Version 2 dated 6 December 2007
- Consent Form Version 1 dated 6 December 2007
- Correspondence – email dated 30 January 2008
- Questionnaires, Instruments and Diaries - OARS ADL/ADL Instrument, MMSE, Geriatric Depression Scale and the Hare – Davis Cardiac Depression Scale, Assessment of Quality of Life (AQOL), Active Australia Questionnaire and Exercise Diary

Other Documents received
- Grant application
- Approval letters from Prince Charles Hospital

During the conduct of the study you are required to adhere to the following conditions:

- If recruitment has not commenced within 12 months, please advise the Coordinator, HREC.
- All forms required when submitting reports to the HREC are accessible on the HREC Intranet. In the first instance, please access the Commencement Form and return to this office when the study commences. Please contact the Coordinator if you do not have access to this site.
- In accordance with RBWH Policy 72025: Clinical Trial Documentation, all medical records of research participants must contain documentation regarding the patient's involvement in the trial.

The Royal Brisbane & Women's Hospital Human Research Ethics Committee is constituted and operates according to the NHMRC's 'National Statement on Ethical Conduct in Research Involving Humans' (2007).

Office
Parnon Rd
Herdin Q 4020
Post Office Herton
Queensland 4020 Australia

Phone
07 3636 5400
07 3636 7800

Fax
07 3636 5490
07 3636 7800
All investigations must be carried out according to the "Declaration of Helsinki 2000" as subsequently modified and the latest statement by the National Health and Medical Research Council on Human Experiments and on Scientific Practice. Should a copy of the "Declaration of Helsinki 2000" as subsequently modified be required, please request a copy from the Coordinator, Human Research Ethics Committee.

Attachment I is a letter listing some matters specified by the National Health and Medical Research Council to which you as the research worker must adhere.

Attachment II gives the Committee composition with specialty and affiliation with the Royal Brisbane & Women's Hospital.

You are required to provide a report on any pilot study and the outcome of the study at the completion of the trial or annually if the trial continues for more than 12 months.

If any subsequent change/amendment is made to the protocol it will be necessary for you to obtain approval from the Human Research Ethics Committee. In addition a summary of the amendments and a comment is required from the Principal Investigator. All amended documents must contain revised version numbers, version dates and page numbers. Changes must be highlighted using Microsoft Word "Track Changes" or similar. Please contact the HREC Coordinator if assistance is required.

Serious Adverse Events must be notified to the Committee as soon as possible. In addition the Investigator must provide a summary of the adverse events, in the specified format, including a comment as to suspected causality and whether changes are required to the Patient Information and Consent Form.

If the results of your protocol are to be published, an appropriate acknowledgment of the Hospital should be contained in the article. Copies of all publications resulting from the study should be submitted to the Human Research Ethics Committee.

Please ensure that a copy of any publication that results from this protocol is also forwarded to the Herston Medical Library for future reference.

The Hospital administration and the Human Research Ethics Committee may inquire into the conduct of any research or purported research, whether approved or not and regardless of the source of funding, being conducted on hospital premises or claiming any association with the Hospital, or which the Committee has approved if conducted outside the Royal Brisbane & Women's Hospital Health Service District. This may include consultation with the Principal Investigator and/or a visit to the research site by a member of the HREC and/or Coordinator of the HREC.

Should you have any problems, please liaison directly with the Administration staff of the Human Research Ethics Committee early in your program.

We wish you every success in undertaking this research.

Yours faithfully

[Signature]

Of Conor Brophy
Chair of Human Research Ethics
Royal Brisbane and Women's Hospital

The Royal Brisbane & Women's Hospital Human Research Ethics Committee is constituted and operates according to the NHMRC's National Statement on Ethical Conduct in Research Involving Humans (2007).

<table>
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<th>Phone</th>
<th>Fax</th>
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<tr>
<td>Herston Rd</td>
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<td>07 3638 5469</td>
<td>67 3638 2800</td>
</tr>
<tr>
<td>Herston Q 4029</td>
<td>Queensland 4029 Australia</td>
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<td>67 3638 2800</td>
</tr>
</tbody>
</table>

Appendices 119
Dr Alison Mudge
Staff Specialist Internal Medicine
IMRU Level 7 Block 7

Dear Dr Mudge,

Re: Ref No: 2008/001 A Supervised Exercise Programme Following Hospitalisation For Heart Failure: Does It Add To Disease Management?

Reference is made to your correspondence dated 25/05/09 & 29/05/09 enclosing amended documents relating to the above protocol. The documentation was reviewed by our Chairperson, Dr Conor Brepley had no scientific or ethical objections and the following are therefore approved:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering letter</td>
<td></td>
<td>25 May 2009</td>
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<tr>
<td>Protocol</td>
<td>5.3</td>
<td>23 April 2009</td>
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<td>Summary Table of Changes dated May 2009</td>
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<td>3</td>
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<tr>
<td>Questionnaire: Participant Questionnaire Booklet 2 Month 3</td>
<td>3</td>
<td>23 April 2009</td>
</tr>
<tr>
<td>Participant Information Sheet &amp; Consent Form</td>
<td>4</td>
<td>23 April 2009</td>
</tr>
</tbody>
</table>

This will be noted by the HREC at its June 2009 meeting.

It should be noted that all requirements of the original approval still apply. Please continue to provide at least annual progress reports until the study has been completed.

Please accept our best wishes for the remainder of the study and should you have any queries, please do not hesitate to contact the Research Ethics Coordinator on 3636 5493.

Yours sincerely,

Odelette Petersen
HREC Coordinator Royal Brisbane & Women’s Hospital
29/05/09

The Royal Brisbane & Women’s Hospital Human Research Ethics Committee is constituted and operates according to the HREC’s National Statement on Ethical Conduct in Human Research (2007).

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<tr>
<td>Butterfield Street</td>
<td>Post Office Herston</td>
<td>07 3636 5493</td>
<td>07 3636 5493</td>
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<tr>
<td>Herston Q 4029</td>
<td>Queensland 4029 Australia</td>
<td>1800 61 7 3636 5499</td>
<td>07 3636 5499</td>
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</table>
Dear Dr Mudge, 

Re: EC2722: A supervised exercise programme following hospitalisation for heart failure; does it add to disease management? A. Mudge; C. Denaro; D. Meyers; J. Atherton; G. Javorsky; A. Scott; A. Hickey

At its meeting of The Prince Charles Hospital Health Service District Human Research Ethics Committee (TPCHHSDHREC) held on the 22 March 2007 the committee reviewed the above protocol. The Prince Charles Hospital and Health Service District Human Research Ethics Committee is duly constituted in accordance with the guidelines of the National Health and Medical Research Council's (NHMRC) "National Statement on Ethical Conduct in Research Involving Humans and Supplementary Notes (1999)", which is accessible on the internet at: http://www.health.gov.au/nhmrc/publications/

I am pleased to advise that on the recommendation of the Committee, the District Manager has approved your human research ethics protocol and the following:

- Participant Information Sheet and Consent form Version 1 dated 26 Feb 07

This is provided that the concerns of the Committee as advised below are addressed and documentation received before the commencement of the research project.

- Protocol - page 11, under Inclusion criteria - potential participants to be recruited from Internal Medicine Inpatient services (RBWH) must have been assessed by a Cardiologist and diagnosed with Congestive Heart Failure (CHF) before being included in the trial.
- Page 11, Exclusion criteria - would patients with AICDs or PM be included or excluded in the trials?

For ease of identification, always quote the EC2722 number allocated to this protocol. In addition, please note that we require 1 Original and 1 copy of all MINOR amendments, 1 Original (for signature by EOR then returned to you) and 4
copies of all Serious Adverse Events summary sheets (not local): 15 copies if on site; and 1 Original and 4 copies of report update to go to the Committee meeting for review/approval.

Patient information collected and distributed as part of the previously approved research has been approved in accordance with Section 62 of the Health Services Act and the recent amendments to the Public Health Act Sections 282 and 284. Any change to the collection and or distribution will need to be reviewed by the HREC.

As a standard requirement of this approval, you are required to provide a report on outcome at the completion of a pilot study or six (6) months after commencement, then annually; and at the completion of an approved research project. E-report templates are available on the Intranet or on request from the Office of Research and Ethics.

When results are to be published, appropriate acknowledgment of the hospital should be included in the article and research subjects are not recognisable in publications or oral presentations. Please forward copies of all publications resulting from the study for inclusion in the Internet website list.

If there is any future change/amendment to the approved protocol, it will be necessary to obtain approval from the Human Research Ethics Committee. A summary of amendments and rationale for changes from the principal investigator would expedite the approval process. For private industry sponsored clinical trials, please note a levy applies for major amendments after Final Approval.

Local Serious Adverse Events must be notified to the Committee as soon as possible. In addition, the Chief Investigator must provide a summary of the adverse events, in the specified format, including a comment as to the suspected causality and whether changes are required to the Patient Information and Consent Form. Please refer to attached table for other timeframes for reporting of other events.

Please advise the Human Research Ethics Committee of the date you intend to commence the research project on the attached form.

If the research does not commence within nine (9) months of this letter, the approval lapses and you will need to reapply before commencing the research. Where no details of commencement have been received after eight (8) months, you will be notified that research approval will lapse in one month. When there are problems with implementing the approved research protocol, investigators will need to discuss the issues with the Chair of the Committee and where appropriate the Executive Director - Medical Services.

On behalf of the Human Research Ethics Committee, I would like to wish you every success with your research endeavors.

Yours sincerely

[Signature]

Philippa Lee, MBA (UQ), BAppSc (QUT), PRCNA, AFAIM
Executive Officer - Research & Ethics
Email: lcep@health.qld.gov.au

29 March 2007
Dr Alison Mudge  
Co-Dept Internal Medicine  
Level 3, James Mayne Building  
Royal Brisbane and Women's Hospital  
Herston QLD 4029

Dear Dr Mudge

HREC Reference number: HREC/07/QPCH/22  
Project title: EC2722: A Supervised Exercise Programme Following Hospitalisation For Heart Failure: Does It Add To Disease Management? A. Mudge; C. Denaro; D. Meyers; G. Javorsky; A. Scott

Protocol number: Protocol Ref N/A  
Amendment number: HREC/07/QPCH/22/AM01  
Amendment Date: 25 May 2009

The above amendment was reviewed at the meeting of the Human Research Ethics Committee meeting held on 18 June 2009.

I am pleased to advise that the amended documents reviewed and approved at the meeting were:

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<td>3</td>
<td>23 April 2009</td>
</tr>
<tr>
<td>Protocol</td>
<td>5.3</td>
<td>23 April 2009</td>
</tr>
<tr>
<td>Patient/Participant Information Sheet and Consent Form</td>
<td>3</td>
<td>23 April 2009</td>
</tr>
</tbody>
</table>

The Northside - The Prince Charles Committee HREC is constituted and operates in accordance with the National Health and Medical Research Council's "National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the "CPMP/ICH Note for Guidance on Good Clinical Practice".
It should be noted that all requirements of the original approval still apply.

Yours faithfully

Philip Lee
Executive Officer
Human Research Ethics Committee
Dear Dr. Mudge,

Research Protocol: 2009/100

A supervised exercise programme following hospitalisation for heart failure: Does it aid to disease management?

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<th>Questionnaire Information Sheet:</th>
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<td>Assessment Quality of Life (AQOL)</td>
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At a meeting of the Princess Alexandra Hospital Human Research Ethics Committee (PAH HREC) held on 5 May 2009, the Committee reviewed the above research Protocol. The Princess Alexandra Hospital Human Research Ethics Committee is duly constituted, operates in accordance and complies with the current National Health and Medical Research Council’s ‘National Statement on Ethical Conduct in Human Research.’

Date: 5 May 2009
On the recommendation of the Human Research Ethics Committee approval is granted for your project to proceed. This approval is subject to researcher(s) compliance throughout the duration of the research with certain requirements as outlined in the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research. Please ensure that you communicate with the PAH HREC on the following:

- **Protocol Changes**: Substantial changes made to the protocol require HREC approval.
- **Problems and SAEs**: The HREC must be informed of any problems that arise during the course of the study which may have ethical implications. Serious Unexpected Adverse Events must be notified to the HREC as soon as possible in accordance with Good Clinical Practice (CPMP/ICH-135/96).
- **Lapsed Approval**: If the study has not commenced within twelve months approval will lapse requiring resubmission of the study to the HREC.
- **Annual Reviews**: All studies are required by the NHMRC to be reviewed annually. To assist with reporting obligations an Annual Report template is available on the PAH HREC website. This form is required to be completed and returned to the HREC within the 12 month reviewing period.

All conditions and requirements regarding confidentiality of public information and patient privacy apply to this study. You are required to comply at all times with all applicable requirements of Australian law including the Health Services Act, the Privacy Act and other relevant legislation as well as all ethical obligations and guidelines, which may be applicable to your organisation from time to time including, without limitation, any requirements for the maintenance, preservation or destruction of patient records.

When the study involves patient contact, it is your responsibility as the principal investigator to notify the relevant consultant and request their approval.

The letter with a copy of the protocol (if not already submitted) must be given to your District Manager for approval before the study can commence.

A copy of this letter should be presented when required as official confirmation of the approval of the Princess Alexandra Hospital Human Research Ethics Committee.

Should you have any problems, please do not hesitate to contact me.

We wish you every success in undertaking this research.

Yours sincerely

[Signature]

Jennifer Fleming

Chair

Human Research Ethics Committee

PRINCESS ALEXANDRA HOSPITAL HEALTH SERVICE DISTRICT
Dr Allison Mudge
Department of Internal Medicine
Royal Brisbane and Women's Hospital
Post Office
Royal Brisbane Hospital 4029

Dear Dr Mudge

Re: 2009/160
A supervised exercise programme following hospitalization for heart failure; Does it add to disease management?

On the 16 June 2009 the Chair of the Princess Alexandra Hospital Human Research Ethics Committee reviewed, noted and approved the following:

- Protocol Version 5.3 dated 23 April 2009 and summary of changes
- Participant questionnaire booklet 1 & 2, version 3 dated 23 April 2009.
- Patient Information and Consent form, version 2 dated 23 April 2009.

If you have any queries please do not hesitate to contact the Human Research Ethics Committee on 3240 7672.

Yours sincerely

Kristina Harej
Acting Ethics Manager
Human Research Ethics Committee
Princess Alexandra Hospital Health Service District
Appendix J

Baseline Characteristics of Patients Lost to Follow-up and Included in Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included (n=80)</th>
<th>Lost to Follow-Up (n=26)</th>
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<tr>
<td><strong>Demographic factors</strong></td>
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<tr>
<td>Age (years), mean ± SD</td>
<td>62 ± 15</td>
<td>59 ± 14</td>
<td>0.22</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>65 (81%)</td>
<td>17 (65%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Ethnicity</strong>, n (%)</td>
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<tr>
<td>Caucasian</td>
<td>72 (90%)</td>
<td>20 (77%)</td>
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</tr>
<tr>
<td>Aboriginal/TSI/PI</td>
<td>6 (8%)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td><strong>Clinical Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%), mean ± SD</td>
<td>32 ± 16</td>
<td>30 ± 15</td>
<td>0.57</td>
</tr>
<tr>
<td>De novo heart failure, n (%)</td>
<td>39 (49%)</td>
<td>16 (62%)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Aetiology</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>34 (43%)</td>
<td>10 (39%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>11 (14%)</td>
<td>5 (19%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>34 (43%)</td>
<td>11 (42%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>35 (44%)</td>
<td>12 (46%)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>NYHA class</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (1%)</td>
<td>2 (8%)</td>
<td>0.35</td>
</tr>
<tr>
<td>2</td>
<td>57 (71%)</td>
<td>18 (69%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12 (15%)</td>
<td>4 (15%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10 (13%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Medications</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>75 (94%)</td>
<td>25 (96%)</td>
<td>1.0</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>72 (90%)</td>
<td>24 (92%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diuretic</td>
<td>70 (88%)</td>
<td>23 (89%)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>PSQI, mean ± SD</strong></td>
<td>6.1 ± 1.3</td>
<td>6.4 ± 3.8</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>GDS, mean ± SD</strong></td>
<td>4.7 ± 3.8</td>
<td>4.6 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>6 min walk distance (m), mean (SD)</td>
<td>374 ± 120</td>
<td>390 ± 128</td>
<td>0.57</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>30 ± 6</td>
<td>31 ± 6</td>
<td>0.27</td>
</tr>
<tr>
<td>Meets PA guidelines, n (%)</td>
<td>39 (49%)</td>
<td>16 (64%)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*Significant p<0.05
Appendix K
Change in Sleep Quality Group Baseline to Week 12 - Control Group

<table>
<thead>
<tr>
<th>Baseline Sleep Quality</th>
<th>Week 12 PSQI group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good (PSQI &lt;5)</td>
</tr>
<tr>
<td>Good (PSQI &lt;5)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>Poor (PSQI ≥5)</td>
<td>2 (17%)</td>
</tr>
</tbody>
</table>

McNemar Test p=0.039*
### Appendix L

**Change in Sleep Quality Group Baseline to Week 12 – Intervention Group**

<table>
<thead>
<tr>
<th>Baseline Sleep Quality</th>
<th>Week 12 PSQI group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good (PSQI &lt;5)</td>
<td>Poor (PSQI ≥5)</td>
<td></td>
</tr>
<tr>
<td>Good (PSQI &lt;5)</td>
<td>16 (80%)</td>
<td>4 (20%)</td>
<td></td>
</tr>
<tr>
<td>Poor (PSQI ≥5)</td>
<td>12 (50%)</td>
<td>12 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

McNemar Test $p=0.08$
### Appendix M

**Proportion of Patients with a Clinically Significant Change in Sleep Quality According to Adherence to Intervention**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>&lt;67% Attendance (n=19)</th>
<th>≥67 Attendance (n=25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in global PSQI score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No clinically significant change</td>
<td>8 (42%)</td>
<td>12 (48%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Significant improvement (≥3 points)</td>
<td>8 (42%)</td>
<td>10 (40%)</td>
<td></td>
</tr>
<tr>
<td>Significant deterioration (≤3 points)</td>
<td>3 (16%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
</tbody>
</table>
**Appendix N**

*Proportion Change in Six Minute Walk Distance According to Intervention Group*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control Mean ± SD</th>
<th>Intervention Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD change %, mean ± SD</td>
<td>-5.5 ± 10.6</td>
<td>-1.5 ± 13.0</td>
<td>0.17</td>
</tr>
</tbody>
</table>