UNIVERSITY OF SOUTHAMPTON FACULTY OF HEALTH SCIENCES

A Feasibility Study of a Nordic Walking Intervention for Women Experiencing Aromatase Inhibitor Associated Arthralgia

By Jo Fields

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ABSTRACT

FACULTY OF HEALTH SCIENCES

Doctorate in Clinical Practice

A FEASIBILITY STUDY OF A NORDIC WALKING INTERVENTION FOR WOMEN WITH AROMATASE INHIBITOR ASSOCIATED ARTHRALGIA

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Abstract

Background: Women taking AIs (Aromatase Inhibitors) as treatment for breast cancer commonly experience joint pain and stiffness (aromatase inhibitor associated arthralgia; AIAA) which can lead to early discontinuation of treatment. Exercise is often recommended and there is preliminary evidence it might prove helpful. Nordic Walking is a popular form of exercise in women with breast cancer, and based on a biopsychosocial model, could provide additional benefits over normal walking alone. There is a need to find interventions for this problem; therefore a study was designed to determine the acceptability and safety of a Nordic walking intervention in women with AIAA, and to test the feasibility of a proposed randomised controlled trial in terms of recruitment, methods and measures.

Methods: A feasibility study was carried out in a sample of women with AIAA using a randomised control design, with a waiting list control. Forty women were recruited and randomised to either intervention (six weeks of supervised group Nordic walking training followed by six weeks of 4 x 30min/week self managed Nordic walking) or enhanced usual care. Data were collected on feasibility outcomes including recruitment, acceptability (attrition and adherence), safety, and research design issues. Outcome data (pain, depression, quality of life & self-efficacy) were collected at baseline, T1 (following supervised group Nordic walking training) and T2 (following self managed Nordic walking).

Findings: The recruitment rate (25%) was comparable to other breast cancer exercise studies, suggesting that there was interest in this type of intervention despite joint pain. Attrition was low (10%) and safety demonstrated. In the intervention group, adherence was high for weekly supervised Nordic walking sessions (>90%) but low for self managed sessions (average of two sessions per week, with most (70%) only managing one), although higher exercise frequencies were attained when all aerobic activity was considered together. Participants in the control group also reported increased physical activity, mainly through normal walking. Most of the outcome measures used appeared suitable for use, demonstrated responsiveness to change and gave support for using a biopsychosocial model of pain. Improvements in pain and other outcomes were demonstrated in both the intervention and control groups, possibly as both increased their physical activity.

Conclusions: Our findings indicate that women with AIAA may not adhere to an intensive programme of self-managed NW; however, increasing physical activity is feasible in this population, and may improve symptoms. A future trial should test a physical activity intervention including a supervised component throughout to maximise adherence.

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Academic Thesis: Declaration of Authorship

I, Jo Fields

declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

A Feasibility Study of a Nordic Walking Intervention for Women Experiencing Aromatase Inhibitor Associated Arthralgia

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

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5. I have acknowledged all main sources of help;

6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

7. None of this work has been published before submission

Signed:

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Date: 01.03.2015

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Abbreviations

AI	Aromatase inhibitor
AIAA	Aromatase inhibitor associated arthralgia
Arthralgia	Pain or stiffness in the joint
BPI-SF	Brief Pain Inventory - Short Form
CES-D	Center for Epidemiological Studies Depression Scale
CI	Confidence interval
FIQ	Fibromyalgia impact questionnaire
GP	General Practitioner
HR	Hazard ratio
LBPRS	Low back pain rating scale
MDT	Multidisciplinary team
MRI	Magnetic Resonance Imaging
Ng/ml	Nanograms per millilitre
NHSE	National Health Service Executive
NICE	National Institute for Health and Clinical Excellence
PHFT	Poole Hospital NHS Foundation Trust
PIS	Participant Information Sheet
PSEQ	Pain self efficacy questionnaire
RCT	Randomised controlled trial
SF-36	Short Form 36 (quality of life outcome measure)

Chapter 1: Introduction

Almost 50,000 women are diagnosed with breast cancer in the United Kingdom each year, and of these 85% will survive for five years or more (Cancer Research UK, 2011). Whilst this figure has improved by 33% over the past 30 years (Cancer Research UK, 2011), and can be considered progress in the management of breast cancer, it also means that more people are living with the consequences breast cancer and its treatment. The National Cancer Survivorship Initiative (NCSI) was formed with the aim of ensuring that those living with and beyond cancer get the care and support they need to lead as healthy and active a life as possible, for as long as possible (NCSI, 2014). One of the five areas of priority for the NCSI is effectively managing the long term consequences of treatment. A recent report by Macmillan Cancer Support has outlined key recommendations for this emerging issue, and includes a call to the research community to extend, build on, and ratify the evidence base for effective interventions (Macmillan Cancer Support, 2013).

As a specialist nurse practitioner running follow up clinics for women diagnosed with breast cancer, I am acutely aware of the long term consequences of treatment and the impact these can have on women's lives. Part of my role in these clinics is to identify and manage the side effects experienced by women on endocrine therapy, which is an oral treatment usually given for five years following primary treatment to reduce the risk of cancer recurrence. One of the most commonly reported side effects of endocrine therapy is joint pain and stiffness, commonly referred to as aromatase inhibitor associated arthralgia (AIAA) (Cella and Fallowfield, 2008). This symptom is reported predominantly by women taking one of the aromatase inhibitors (AIs), a hormonal therapy which lowers oestradiol to undetectable levels. The clinical significance of this symptom is that many women consider discontinuing their treatment due to the discomfort they experience whilst taking it (Presant *et al.*, 2007; Fontaine *et al.*, 2008), leading to an increased risk of disease recurrence. Currently there are few well tested evidence-based strategies to manage this symptom in this population.

The overarching aim of this study was to test an intervention which could be used to reduce joint pain in women with AIAA, with the ultimate purpose that this might improve adherence to aromatase inhibitor therapy.

Joint pain and stiffness in other chronic musculoskeletal populations such as osteoarthritis, rheumatoid arthritis and fibromyalgia has been shown to be reduced with aerobic exercise (Busch *et al.*, 2007; Fransen and McConnell, 2008; Hurkmans *et al.*, 2009). Nordic walking, a form of walking with the addition of handheld poles used in opposition to lower limb locomotion (Fritschi *et al.*, 2012), has been found to be popular with breast cancer survivors at my workplace. This led

to my interest in studying the effectiveness of this type of exercise in women with AIAA. Research in this area is timely and relevant as exercise is being recommended in guidance directed at managing this side effect (Coleman *et al.*, 2008). Furthermore exercise is a recommended component of self-management to improve overall well-being in cancer survivors (Department of Health, 2011a),

However, there was no prior literature describing how exercise such as Nordic walking might target pain mechanisms in AIAA, nor previous research testing Nordic walking in women with breast cancer and joint pain. Therefore, this thesis describes the development of a theoretical framework to underpin a Nordic walking intervention for AIAA and the conduct of a subsequent feasibility study in this population.

Chapter 2: Background

2.1 Introduction to Aromatase Inhibitor Associated Arthralgia (AIAA)

Treatment for breast cancer is an individualised process, and usually includes a combination of treatments including surgery, chemotherapy, radiotherapy, endocrine therapy, and/or herceptin. Approximately 75% of women with breast cancer will have hormone sensitive (oestrogen receptor positive; ER+) tumours, i.e. tumours which are stimulated by the female hormone, oestrogen (Dunnwald *et al.*, 2007). Guidelines produced by the National Institute for Health and Clinical Excellence (NICE) for the treatment of women with hormone sensitive early breast cancer in the UK include treatment with endocrine therapy (National Institiute for Health and Clinical Excellence, 2009a). Most endocrine therapies work by depriving the cell of oestrogen or by blocking its receptor (Goldhirsch *et al.*, 2002). NICE guidelines further recommend that postmenopausal women with hormone sensitive breast cancer are treated with a group of drugs called aromatase inhibitors (AIs), for a duration of five years. This is because large randomised controlled trials have shown clinical superiority in terms of disease free survival in those receiving AIs compared to the previous gold standard in endocrine therapy, tamoxifen (Dowsett *et al.*, 2010). The three AIs recommended for use in clinical practice are anastrozole, letrozole, and exemestane. All AIs have the same mechanism of action, which is to inhibit aromatase, an enzyme found mainly in peripheral tissues and the liver. This enzyme is responsible for the conversion of androstenedione to oestrone, and is the main pathway of oestrogen production in postmenopausal women. Consequently, aromatase inhibitors decrease levels of circulating oestrogen to virtually undetectable levels in the plasma and peripheral tissues and reduce the oestrogen supply for hormone dependant breast cancers. This is important as oestrogen may increase the risk of recurrent disease (Rock *et al.*, 2008). Although the tolerability profile of aromatase inhibitors is considered acceptable in comparison to other treatments such as chemotherapy (Coates *et al.*, 2007), side effects can include menopausal like symptoms, reductions in bone density, and joint pains and stiffness (aromatase inhibitor associated arthralgia; AIAA) (Burstein, 2007) all of which are thought to be related to oestrogen deprivation (Coleman *et al.*, 2008).

In order to better understand AIAA, and to consider suitable interventions, this chapter will go on to explore the clinical presentation of aromatase inhibitor associated arthralgia, prevalence, and adherence, as these factors serve to highlight the clinical significance of this symptom. Following on from this, evidence for the link between oestrogen deprivation and arthralgia will be presented, followed by a critique of the research exploring the possible mechanisms by which this occurs. These will be compared to findings in osteoarthritis and rheumatoid arthritis, as ultimately, if similarities are found, it may follow that interventions which are effective at reducing pain resulting from these diseases may prove to be effective in improving joint pain in AIAA.

2.2 Clinical presentation

Although symptoms of AIAA vary, the typical picture described in the literature which concurs with observations in clinical practice, is that of bilateral joint pain, together with early morning stiffness (Burstein, 2007). The results of cross sectional studies investigating the features of AIAA have revealed the joints most commonly affected to be the hands/wrists, feet, knees and back (Presant *et al.*, 2007; Henry *et al.*, 2008b; Dizdar *et al.*, 2009; Mao *et al.*, 2009; Helzlsouer *et al.*, 2012). See table 2.1 for a summary of their findings. This has similarities with the joints most commonly affected in osteoarthritis (Dieppe, 2005). However, there is considerable variation in prevalence between studies which may reflect the methods used to collect data. In addition, the cross sectional design of the majority of these studies means that it is difficult to say with any certainty that these symptoms are solely related to AI use and may reflect pre-existing musculoskeletal conditions, such as osteoarthritis, which are likely to be common in this age group. However, Helzlsouer et al (2012) used a longitudinal design and compared women taking AIs (n=100) with a control group (n=200) and found that there was a significant increase in hand/wrist pain in those treated with AIs compared to controls at six months from treatment initiation.

Table 2.1: Joints most commonly affected in AIAA.

Author/ Date	Sample size	Study Design	Joints affected (%)							
			Hands /wrist	Feet/ ankle	Knees	Back	Hips	Neck	Shoulder	Elbow
Mao et al (2009)	139	Cross sectional	60.4	51.8	59.7	54	42.5	34.5	29.5	20.1
Presant et al (2007)	34	Cross sectional	44	44	59	32	26	-	26	59
Dizdar et al (2009)	30	Cross sectional	63/70	-	70	-	-	-	-	-
Helzlsouer et al (2012)	100	Longitudinal (at 6months)	63	33.3	59.3			42.6		29.6
Henry et al (2008b)	38	Cross sectional	39	24	30	18	16	32		-

2.3 Onset and resolution

In term of onset, a cross sectional study of 300 postmenopausal women with breast cancer taking adjuvant AIs found 74% those reporting arthralgia did so within the first three months of therapy, although the most prevalent time for onset was within the first month (Mao *et al.*, 2009). More specifically, a prospective longitudinal study of 100 women (Henry *et al.*, 2008a) found that the median time to onset of arthralgia was 1.6 months (range 0.4-10 months), which may be a more accurate estimate, as a prospective design does not rely on participant recall. The implication of these findings are that women are often faced with coping with the sudden onset of symptoms, and indicates that clinicians should be alert to the development of this side effect within the first three

months of treatment, and target support accordingly. Although there is little in the way of longitudinal evidence, observations in clinical practice suggest these symptoms may continue for the duration of their hormone therapy. A small cohort study reported resolution of side effects on discontinuation of treatment (Donnellan *et al.*, 2001), a pattern also observed in clinical practice.

2.4 Prevalence

A review of the literature on the prevalence of arthralgia highlights the scale of the problem in postmenopausal breast cancer populations, the majority of whom will be taking an AI for five years following initial treatment.

Although a review of previous research suggests that levels of joint pain are also raised during the peri-menopausal transition in non breast cancer populations, (Magliano, 2010), a cross sectional study comparing frequency of joint aches, muscle pain and stiffness in 247 women with breast cancer to 274 aged matched controls concluded prevalence was higher in women who had received chemotherapy or hormone therapy for breast cancer (Fenlon *et al.*, 2008). In particular, use of AIs increased risk, (OR 2.41 95% CI, 1.06 to 5.48); although tamoxifen also increased the risk of joint pain in this study. However, it has previously been reported in large treatment effectiveness RCTs that there is a higher incidence of joint pain in women on anastrozole compared with those on tamoxifen (949 of 2698 women [35·2%] *vs* 829 of 2735 women [30·3%]; OR 1·25 [1·11–1·40]) (Sestak *et al.*, 2008).

In randomised controlled trials investigating the effectiveness of AIs (Breast International Group (BIG) 1-98; Intergroup Exemestane Study (IES);Arimidex, Tamoxifen Alone or in Combination (ATAC); and MA-17), prevalence of arthralgia was reported to be between 20-36% (Goss *et al.*, 2003; Howell *et al.*, 2005; Coates *et al.*, 2007; Coombes *et al.*, 2007). See table 2.2.

However, more recent cross sectional studies specifically investigating the prevalence of AIAA demonstrate a higher incidence of joint pain in non trial populations of somewhere between 32.6 and 72% (table 2.3). These findings correlate more closely with observations in clinical practice. For example, findings from a cross sectional survey of 200 women taking AIs were that 47% of women reported associated joint pain and 44% reported stiffness (Crew *et al.*, 2007b). Furthermore, in this study, nearly a quarter of participants reporting arthralgia rated their symptoms as severe. Although cross sectional designs can lead to selection bias, in this study this is unlikely as only two percent declined participation. In addition, as women who had already discontinued AI due to severe side effects were not included this study, it possibly under-estimates the true incidence of arthralgia in this population.

Table 2.2: Prevalence of musculoskeletal symptoms in women treated with AIs vs tamoxifen in phase III RCTs, and discontinuation rates (where given)

Study	Treatment arms	Symptom	AI (%)	Tam (%)	p-value	Stopped due to toxicity
ATAC (Howell *et al.*, 2005)	Anastrozole 5y	Arthralgia	35.6	29.4	<0.001	11.1% anastrozole vs 14.3% (tamoxifen)
	Tamoxifen 5y	CTS*	3%	1	<0.001	
BIG 1-98 (Coates *et al.*, 2007)	Letrozole 5y	Arthralgia	20.0	13.5	<0.001	
	Tamoxifen 5y	Myalgia	7.1	6.1	0.19	
IES (Coombes *et al.*, 2007)	Tamoxifen 2-3y switched to exemestane 2-3y	Arthritis	14.1	12.0	<0.001	5.8 % (*n*=138) exemestane vs 5.1% (*n*=121) tamoxifen
		Arthralgia	18.6	11.8	<0.001	
		CTS	2.8	0.3	<0.001	
	Tamoxifen 5y	MSK* pain	21	16.1	<0.001	
		Cramps	2.3	4.2	<0.002	
		Joints stiff	1.9	1.0	<0.009	
MA-17 (Goss *et al.*, 2005)	Tamoxifen 5y switched to letrozole 5y	Arthritis	6	5	0.07	4.9% (letrozole) vs 3.6% (tamoxifen)
		Arthralgia	25	21	<0.001	
		Myalgia	15	12	0.004	
	Letrozole 5y switched to tamoxifen 5y	Bone pain	5	6	0.67	

*CTS = carpal tunnel syndrome; MSK = musculoskeletal

The disparity in prevalence between phase III RCTs and cohort studies may be due to several factors. These include how arthralgia and bone pain are defined. In addition, it is likely that people participating in clinical trials will be healthier, younger, less likely to complain of problems with study drugs, or less likely to acknowledge symptoms for fear of having to stop the study medicine. Furthermore, there is a difference between clinician reporting adverse events that occur in clinical trials and studies which use patient reported outcomes to collect data (Din *et al.*, 2010). Given the importance of clinical trials in the development of clinical guidelines, limitations regarding reporting of treatment toxicity should be acknowledged (Oberguggenberger *et al.*, 2011).

In conclusion, there is wide variety in the reported prevalence of AIAA, of between 20 and 72%. However, even at the lower end of prevalence, it is still common enough a reported problem to be a significant issue for AI users.

Table 2.3: Prevalence of AIAA in non trial populations

Author And Year	Study Design	N=	Primary Outcome	Onset	Associated predictors	prevalence
Crew et al 2007b	Cross sectional survey	200	Prevalence of pain/stiffness	-	↓ Being overweight BMI (0.33, CI 0.14-0.74) ↓ Prior tamoxifen (0.4, CI 0.19-0.87) ↑ Prior taxanes (OR 4.08 (CI 1.58-10.57)	47% joint pain 43 % stiffness
Mao et al 2009	Cross sectional survey	300	Prevalence of joint pain (self devised questionnaire)	74% within 3mths	↑ LMP within 5 years (OR 3.39(95% CI 1.21-9.44, p=0.02)	47% joint pain
Henry 2008a	Prospective longitudinal	97	Joint pain (VAS)	1.6mths	-	45.4% (Pain Visual analogue score >5)
Obergugg-enberger et al 2011	Cross sectional survey	280	Side effects (FACT-B + ES) compared to pivotal trials	-	-	59.6% joint pain (95%CI = 54-65)
Presant et al 2007	Cross sectional	56	Joint pain	-	-	61% new or worsening joint pain
Quy and Neda (2010)	Cross sectional	57	Prevalence joint pain and stiffness	'most' within first six months	-	72% joint pain 63% stiffness
Dizdar et al 2009	Cross sectional study	92	Prevalence of AIAA and physiological assessment	-	-	32.6%

VAS=visual analogue score; FACT-B= Functional Assessment of Cancer Therapy-Breast; ES=endocrine symptoms; OR=odds ratio

2.5 Adherence issues

The clinical significance of arthralgia is that in addition to affecting quality of life (Fenlon *et al.*, 2013), this symptom has been found to increase non adherence. Again, although Phase III RCTs investigating the efficacy of AIs reported low withdrawal rates due to adverse events for participants taking AIs (table 2.2); subsequent studies report that arthralgia leads to higher numbers of women discontinuing their hormone therapy. For example, a retrospective analysis of 185 women on letrozole (Fontaine *et al.*, 2008) found 12% of women discontinued therapy due to arthralgic symptoms. Similarly, a cross sectional study of 57 women commencing AIs (Presant *et al.*, 2007) found 20% discontinued treatment due to joint pain, all within the first three months of

therapy. In addition, longitudinal data from three public health databases on AI use found that mean adherence (defined as medication use of 80%) over the first twelve months of therapy ranged from 82% to 88% in the three data sets, dropping to 62-79% adherence by end of year three (Partridge *et al.*, 2008). However, a retrospective analysis of 325 women who had taken an AI for five years (Guth *et al.*, 2008), found that although only 66.6% of their cohort completed five years treatment, only 10% of the total sample was intentionally non adherent, with other causes for discontinuation including disease recurrence, never starting treatment, or serious medical reasons.

Nevertheless, this high level of treatment discontinuation has the potential to adversely affect prognosis, as it has been demonstrated that longer duration of endocrine treatment is associated with lower recurrence rates (Sacco *et al.*, 2003). More specifically, although there are no studies which examine the relationship of adherence to AIs and mortality, a retrospective cohort study examining tamoxifen adherence and its relationship to mortality in 2080 women with breast cancer (McCowan *et al.*, 2008), found that adherence of less than 80% was associated with poorer survival (HR 1.10, 95% CI 1.001–1.2).

2.6 Experience of AIAA and self management strategies

Although there is some evidence that women coping with menopausal symptoms after a diagnosis of breast cancer prefer non-medical strategies (Hunter *et al.*, 2004), there is very little in the literature describing how women with AIAA specifically experience and manage this symptom. A cross sectional study of 200 women taking AIs found that of those reporting arthralgia, 67% reported moderate to severe symptoms (Crew *et al.*, 2007b). Just over half of those with AIAA took oral medication for symptom relief (56/106), with half of these using non steroidal anti-inflammatory medications, a third taking paracetamol, and a quarter using supplements including glucosamine, chondroitin or omega 3 fish oil. Seventy eight percent reported moderate relief of symptoms from medication. Nearly half also used exercise for symptom management. A further cross sectional study reported similar self-management strategies (Presant *et al.*, 2007), although twenty percent of women in this study went on to discontinue AIs, suggesting that oral medication is not always an effective or acceptable strategy for women experiencing this symptom. Indeed, in clinical practice, many women are reluctant to take analgesia for symptom relief due to the long duration of AI therapy (five years).

In summary, AIAA is a significant problem in clinical practice, with high prevalence, and which leads to poor adherence, due to its impact on quality of life. Although half of women use analgesia or supplements; in practice, many do not want to take additional medication to control symptoms. Consequently, if non pharmacological interventions can be found to help women manage AIAA, this may encourage them to adhere to treatment for the recommended duration, which is usually five years (National Instituite for Health and Clinical Excellence, 2009a)..

2.7 Physiological mechanisms underlying AIAA.

In order to develop interventions that may help to reduce AIAA, it is necessary to have an understanding of the likely aetiology, in order that efforts can be targeted appropriately. Although it is suggested that oestrogen deficiency leads to AIAA (Coleman *et al.*, 2008), the underlying aetiology is not well understood. There are several prevailing theories including a local and /or systemic inflammatory response, Vitamin D deficiency, and alterations in pain processing.

2.7.1 Oestrogen deficiency and joint pain (arthralgia)

Observational studies of women with differing hormonal environments provide evidence for the modulating effect of oestrogens on pain perception. For example, cross sectional studies have demonstrated that women entering the menopause when oestrogen levels drop have elevated levels of joint pain compared to pre menopausal women (Ho *et al.*, 1999; Sievert and Goode-Null, 2005; OlaOlorun and Lawoyin, 2009a; Olaolorun and Lawoyin, 2009b). In addition, a longitudinal study of arthralgia in the menopausal transition found that the incidence of joint aches in 438 Australian premenopausal women aged 45-55 increased from 53.6% at baseline to 58.7% at the end of the study, and that this correlated with biochemical menopausal status (Szoeke *et al.*, 2008). Furthermore, various interventional studies of hormone replacement therapy (HRT) use in postmenopausal women provide evidence for the protective effect of oestrogen against joint pain. Although not all research shows this association, the largest of these studies , the Women's Health Initiative Study, (a randomised, double-blind, placebo-controlled trial of 16,608 postmenopausal women), found that at 1 year, more women taking HRT reported a relief in the symptom of joint pain or stiffness than those taking placebo (47% vs 38%; OR 1.43; 1.24-1.64), and were less likely to report new onset of joint pain and stiffness (10.1 vs 4.1% OR 0.68; 0.61-0.76, $p<0.001$) (Barnabei *et al.*, 2005). The robust design of this interventional study reduces the chance of bias and supports the role of hormone replacement in reduction of joint pain.

2.7.2 Pathophysiological change in joints: clinical and radiological evidence

The possible mechanisms underlying AIAA have been investigated using clinical and radiological evidence.

A prospective longitudinal cohort study of 100 consecutive women taking either letrozole or exemestane aimed to characterise the musculoskeletal symptoms that develop in women taking AIs (Henry *et al.*, 2008a). The authors found that 45.4% of the sample met the criteria for rheumatologic referral, with the most common clinical diagnoses being non inflammatory musculoskeletal syndrome, or inflammation localised to tenosynovial structures. More specifically, 14% of those referred were diagnosed with tenosynovitis, 28.9% with osteoarthritis, and 21.1% with carpal tunnel syndrome. Indeed, the results of the ATAC trial, a large RCT comparing the effectiveness of five years of anastrozole to tamoxifen, indicated a higher incidence of carpal

tunnel syndrome in women taking anastrozole compared with tamoxifen after 100 months follow up (2.6% vs 0.7)(Sestak *et al.*, 2009). However, the difference in prevalence of carpal tunnel syndrome between these two studies may be related to lack of specialist assessment by a rheumatologist in the ATAC trial and thus many cases of carpal tunnel syndrome may have gone undiagnosed.

Preliminary studies using ultrasound and magnetic resonance imaging (MRI) to assess affected joints also provide evidence of a local inflammatory response in tenosynovial structures, including increased incidence of tendon sheath thickening, joint effusions, and carpal tunnel syndrome (Morales *et al.*, 2007; Morales *et al.*, 2008; Dizdar *et al.*, 2009).

A cross sectional study of twelve women taking either letrozole or exemestane reporting severe musculoskeletal pain underwent clinical, ultrasound and MRI examination (Morales *et al.*, 2007). The most commonly reported symptom was severe early morning stiffness and hand/wrist pain. Clinical examination revealed limited flexion and extension of the fingers with trigger finger and carpal tunnel syndrome being the commonly reported clinical signs. Ultrasound was performed in five participants and all showed fluid in the tendon sheath surrounding the digital flexor tendon. MRI found enhancement and thickening of the tendon sheath in all twelve participants. This study has methodological limitations including a cross sectional design, small numbers, incomplete data collection, and lack of comparison group which means that although abnormalities were present, without a comparison group one cannot guarantee that AIs are responsible for the symptom of joint pain and stiffness. However, the same authors undertook a further longitudinal study of seventeen consecutive women with early stage breast cancer, twelve of whom commenced an AI and five tamoxifen. At both baseline and 6 months patient underwent blinded clinical examination by a rheumatologist to include hand grip strength, and MRI of both hands and wrists. At six months, women on AI had a decrease in grip strength (p=0.0049) and an increase in tenosynovial changes on MRI (p=0.001). However, the correlation between MRI findings and grip strength were not significant (p=0.07), and numbers were small for this study, therefore findings should still be interpreted with caution. Evidence of increases in tendon thickness and joint effusion in women on AIs has been supported in a larger case control study of 92 women on adjuvant AIs compared with 32 controls assessed with ultrasound, electromyography and self report of pain (Dizdar *et al.*, 2009). This study, which assessed the knee joint as well as the hand/wrist, found that women on an AI reporting new or worsening joint pain had significantly higher rates of joint effusion than those without this symptom (69% vs 42%; $p<0.05$) and more frequent electrophysiological findings of carpal tunnel syndrome (46% vs 20%; $p<0.05$). Women taking AIs had thicker tendons than those not on AIs ($p<0.001$) but there was no difference in tendon thickness between those with or without arthralgia. However, of note, a third of women in this study with AI related joint pain had no detected morphological abnormalities.

These studies suggest that increased tendon thickness in women on AIs may reflect tendinopathy, with further damage to tendons and synovium resulting in effusions in tendon sheaths and joints in a subgroup of women, which translates into the symptom of arthralgia. Further prospective longitudinal studies are required to clarify whether these findings are the cause of arthralgia or simply related to AI use. In addition, as noted above, a significant percentage of women with no tenosynovial, joint or electrophysiological changes still have symptoms of arthralgia which indicates that other mechanisms also play a role in the pathogenesis of these symptoms. Altered pain processing may be one of these.

2.7.3 Altered pain processing

Three observational phenomena give strong support for the hypothesis that altered pain processing may be implicated in AIAA. The first is the fact that joint pain and stiffness tends to be distributed in a symmetrical pattern rather than unilaterally, which implies that changes in central modulation of nociceptive (nerve generated) input contribute to symptoms (Kidd, 2006). The second observation is that symptoms usually rapidly decrease on discontinuation of treatment (Donnellan *et al.*, 2001), suggesting that pathophysiological processes within the joint do not provide a complete explanation for these symptoms. The third is the evidence provided by Dizdar's (2009) study that a third of women had arthralgia in the absence of any observed pathophysiological joint changes on MRI and ultrasound.

Normal physiological joint pain arises from stimulation of peripheral nociceptive neurons due to intense pressure or painful stimuli. These fibres can be found in joint capsule, synovium, periosteal bone, ligament and periarticular structures (Felson and Cummings, 2005). In arthralgic conditions, it is thought that there is heightened sensitivity, either peripherally and/or in the central nervous system, to nociceptive input, which leads to an exaggerated pain response to normal stimuli (Coleman *et al.*, 2008).

There is evidence that oestrogen suppression may contribute to this heightened sensitivity in the following ways. Firstly, oestrogen may modulate pain centrally by reducing the release of pro-inflammatory mediators such as nitric oxide and prostaglandin E2 from microglia (immune cells) in the central nervous system (Vegeto *et al.*, 2001). These mediators have a role in promoting peripheral nociception (the afferent process of signalling potential or actual tissue damage), thus a lack of oestrogen may increase pain perception through this method. Oestrogen also has an anti-nociceptive influence through opioid pain fibres which express oestrogen receptors in the brain and spinal cord (Eckersell *et al.*, 1998; Flores *et al.*, 2003) .

Peripherally, alpha and beta oestrogen receptors have been identified in human synoviocytes (the cells of the synovial membrane) and articular chondrocytes (bone cells) which provides a possible mechanism by which joints may be sensitive to oestrogens (Ushiyama *et al.*, 1999). In addition, the aromatase enzyme is known to be expressed in human bone tissue including synoviocytes. (Sasano *et al.*, 1997; Le Bail *et al.*, 2001). Therefore, a lack of oestrogen may directly affect these tissues. Various animal and in vitro studies suggest that oestrogen may play a role in the regulation of cartilage turnover and development of joint disease by modulating the synthesis of chondrocyte matrix proteins and decreasing subchondral bone remodelling (Richette *et al.*, 2003) . For example, in an experimental model of postmenopausal osteoarthritis with ovariectomised rats, oestrogen deficiency accelerated cartilage turnover and increased cartilage surface erosion, whereas administration of oestrogen or selective oestrogen receptor modulators suppressed cartilage degradation significantly (da Silva *et al.*, 1993). In summary, the evidence suggests that AIs may affect pain processing due to direct and indirect effects of oestrogen suppression within the nervous system both peripherally and centrally.

2.7.4 Auto-immune/systemic inflammatory response

A further proposed mechanism underlying AIAA involves a link between AI therapy and autoimmunity. This is built from evidence acquired through preclinical studies of an association between oestrogen deficiency and increased secretion of pro inflammatory cytokines (Vural *et al.*, 2006), and that oestrogen has the ability to repress the transcription of pro-inflammatory genes through the oestrogen receptor (Cvoro *et al.*, 2008). Thus AIs could lead to increases in inflammation due to their ability to suppress oestrogen. Small cohort studies and case reports have previously suggested that AI therapy may lead to autoimmune diseases such as rheumatoid or Sjogrens syndrome (Laroche *et al.*, 2007; Morel *et al.*, 2007). However, more robustly designed studies which include control groups have shown no evidence of a correlation between raised inflammatory markers and AIAA. For example, a cross sectional study of 105 women taking AIs, both with and without arthralgia, compared to control, found that inflammatory markers including erythrocyte sedimentation rate (ESR), creatinine reactive protein (CRP), rheumatoid factor and anti-nuclear antibodies were not significantly elevated (Dizdar *et al.*, 2009). Furthermore, a prospective longitudinal study comparing 30 cases of AIAA with controls who were taking an AI but without arthralgia, found no increase in pro-inflammatory cytokines between groups (Henry *et al.*, 2010). A limitation of this study was the multiple significance testing and small sample size. In addition, it is also possible that inflammatory markers other than those tested by the above studies may be involved in AIAA. Consequently, the evidence to date suggests the mechanism underlying AIAA is unlikely to be related to a systemic inflammatory reaction. However, further longitudinal research using larger samples is required to confirm these preliminary findings.

2.7.5 Vitamin D deficiency

Various authors have suggested a possible role for Vitamin D deficiency in AIAA. Vitamin D is necessary for the 'expression' of CYP3A4 within the liver. CYP3A4 is an enzyme which is used by aromatase inhibitors in the process of metabolism. As a result, aromatase inhibitors increase the body's requirements for Vitamin D (Drocourt *et al.*, 2002; Waltman *et al.*, 2009).

Although studies in both non breast cancer (Chlebowski *et al.*, 2011) and breast cancer populations (Waltman *et al.*, 2009; Napoli *et al.*, 2010), have shown a correlation between low vitamin D and joint pain, to date this effect has not been observed in women taking AIs. Two prospective longitudinal studies have tested whether AI use lowers vitamin D levels. Helzlsouer (2012) compared 100 women initiating AIs to a no treatment group (n=200) and found that although pain scores had increased significantly at 6 months in the AI group, this was not associated with 25(OH) levels (a marker for Vitamin D). A further longitudinal study of 416 women taking AIs found that Vitamin D levels did not show correlation with musculoskeletal symptoms either at baseline or over time (Singh *et al.*, 2012). Although a limitation of this study was that no standardised questionnaire was used to assess musculoskeletal symptoms in this study, the evidence to date fails to show an association between vitamin D deficiency and AIAA.

2.7.6 Summary of proposed mechanisms underlying AIAA

In summary, the evidence above suggests that the underlying mechanisms responsible for the symptom of joint pain and stiffness (arthralgia) in women taking AIs are most likely to be local inflammation within the joints, in particular surrounding and within tendons; and alterations in pain processing peripherally and in the central nervous system; with both mechanisms related to oestrogen suppression. Longitudinal assessment of joints with MRI/ultrasound after discontinuation of treatment when symptoms resolve may provide further evidence as to whether arthralgia is related to pathophysiological change (if changes resolve), alterations in pain processing (if changes are still seen), or a combination of both. To date there does not appear to be a role for a systemic inflammatory component or vitamin D deficiency.

2.8 Comparison to other chronic musculoskeletal conditions.

The pathophysiology and pain pathways of rheumatoid arthritis, osteoarthritis and fibromyalgia are now briefly described. This is because if AIAA has similar mechanisms, it is possible that treatments for these conditions may be transferrable. As AIAA is a musculoskeletal condition which appears to principally cause joint pain and stiffness, a comparison to osteoarthritis and rheumatoid arthritis seems rational. However, as some women with AIAA describe muscle soreness/pain (see table 2), fibromyalgia is also considered.

2.8.1 Osteoarthritis

Osteoarthritis (OA) is a disease affecting the synovial joints characterised by focal areas of damage to the articular cartilage, associated with new bone formation at the joint margin (osteophytes), changes in the subchondral bone, mild synovitis, and thickening of the joint capsule. Clinical presentation of this disease usually involves joint pain related to use, and short lasting inactivity stiffness. Joints most commonly affected include the hip, knee and hand (Huskisson, 2010). Prevalence of OA is more common in women than men in most joints, and increases dramatically after the age of 50 (Felson *et al.*, 2000).

2.8.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an inflammatory disease which exerts its greatest effect on synovial lined joints. It most commonly presents as pain and early morning stiffness affecting the small joints of the hands and feet, usually with symmetrical distribution, but can affect any synovial lined joint (National Institute for Health and Clinical Excellence, 2009b). Underlying pathophysiology includes proliferation of the synovial membrane with an increase in synovial fluid (swelling), and pain (due to stretching of pain receptors in the soft tissues around, and the bone on either side of the joint). These features result in rapid loss of muscle around an affected joint, and this, along with pain and swelling lead to loss of joint function. RA can also affect the synovium lining tendon sheaths and thus cause progressive damage in these structures. However, RA also exerts systemic effects and commonly involves other organs, and is progressive, often leading to long term tissue damage. It is associated with raised inflammatory markers including erythrocyte sedimentation rate and creatinine reactive protein.

As described for AIAA in section 2.7.3, pain pathways in both rheumatoid and osteoarthritis are thought to involve peripheral and central sensitisation (Dieppe, 2005; Kidd, 2006). At a local level, mediators released from synovium, bone or other tissues will induce the sensitisation of articular pain receptors. In chronic conditions such as RA and OA there is also evidence of increased excitability of spinal neurons leading to enhanced pain perception at the site of injury, as well as to the development of pain and tenderness in normal tissues both adjacent to and removed from the primary site. This is called central sensitisation and occurs as a result of repeated or prolonged activity in primary afferent neurons leading to an increased response in the secondary sensory neurons in the spinal cord (Woolf *et al.*, 2004). Spinal nociceptive processing in people with arthritis is also under the influence of inhibitory controls both within the spinal cord and also descending from the brainstem. Psychological and social factors are also believed to modulate nociceptive processing at a supraspinal or cortical level, enhancing pain perception, pain reporting and behavioural change, including disability (Kidd, 2006). When central sensitisation at the cortical level occurs, reliance on therapies which act at peripheral or spinal level are unlikely to prove successful, and therefore non pharmacological strategies may also need to be employed.

2.8.3 Fibromyalgia

Fibromyalgia (FM) is characterised by long-lasting, widespread pain which is reported as muscle, rather than joint pain. This is accompanied by generalised allodynia (pain caused by a stimulus that does not normally evoke pain) and often fatigue (Wolfe *et al.*, 1990). The prevalence of FM ranges from 10-11% in the general population, and the condition is more common among females than males (Clauw and Crofford, 2003).There is evidence that the primary pathology for fibromyalgia lies within the central nervous system and is due to the process of central sensitisation (Gracely *et al.*, 2003), i.e. pain or sensory amplification within the brain and spinal cord. This appears to be partly due to imbalances in levels of neurotransmitters that affect pain and sensory transmission. These, together with multiple psychological and environmental factors are thought to interact in the development and maintenance of FM (Clauw, 2014).

2.8.4. Summary

When comparing AIAA to other chronic musculoskeletal pain it appears to be most comparable to arthritis pain as it presents in synovial lined joints, and its predominant symptoms are joint pain and stiffness, as is the case with OA and RA. Some of its pathological features are comparable to RA; in that the most common presentation is symmetrical small joint pain, although to date there is no evidence of irreversible damage to articular bone and joint structures in AIAA. In addition tenosynovial changes have been observed as with RA. However, in view of the absence of elevated inflammatory markers and systemic features, this syndrome is markedly different to RA. There are similarities to OA, again, in terms of joints most commonly affected, and also in that prevalence increases markedly at the menopausal transition in both conditions. However there are clearly pathophysiological differences in the disease process as evidence to date suggests AIAA involves tenosynovial structures rather than cartilage and bone as in OA. Comparison to fibromyalgia shows very few similarities. Although pain is widespread in fibromyalgia as in AIAA, fibromyalgia appears to cause pain and originate in muscle rather than joints, although pathophysiological processes are not yet fully understood. However, pain pathways in fibromyalgia are believed to involve central sensitisation which may also be a feature of AIAA.

Therefore, it appears that pathophysiological processes are different in AIAA when compared to OA, RA and fibromyalgia. However, pain mechanisms may be similar, involving peripheral and central sensitisation. Consequently, interventions which target physiological joint changes in OA and RA may not be transferrable from arthritis to AIAA, but interventions which target the pain pathways in OA/RA and fibromyalgia may also be effective in AIAA.

The next section will therefore briefly review the evidence on interventions which have previously been tested in OA/RA/fibromyalgia. This is to identify effective, evidence based interventions for other chronic musculoskeletal conditions which merit testing in women with AIAA. This will be

followed by a review of interventions tested to date in AIAA to determine whether there are any gaps in the research between interventions tested for chronic musculoskeletal conditions and AIAA.

2.9 Management of chronic musculoskeletal pain.

In order to determine which interventions which have been shown to be most effective for pain reduction in OA, RA and fibromyalgia and thus would merit testing in women with AIAA, a literature search was undertaken for systematic reviews in this area. This was because individual studies would be too numerous to fully review within this thesis, and furthermore, the findings of individual research studies are rarely sufficient to justify new treatments. In contrast, systematic reviews can identify, evaluate, combine and summarise the findings of all relevant individual studies, and also give a more reliable estimate of an intervention's effectiveness (National Institute for Health Research, 2012). However, in the field of OA, RA and fibromyalgia, even systematic reviews are numerous. As Cochrane systematic reviews are considered to be the leading producer of high quality systematic reviews (as judged by the World Health Organisation, (The Cochrane Collaboration, 2011), this review was limited to Cochrane systematic reviews only.

Although it is acknowledged that pharmacological therapy is one of the mainstays of management of musculoskeletal conditions such as OA, RA and fibromyalgia, only reviews of non-pharmacological interventions were considered for the purpose of this thesis. This was because observations in clinical practice are that most women do not wish to take additional medication in the form of analgesia to control their symptoms of joint pain, particularly due to the long term nature of AI therapy and therefore likely prolonged nature of accompanying side effects.

An exploration of the Cochrane database for reviews of non pharmacological interventions for OA, RA and fibromyalgia revealed sixteen reviews in total: six examining the effect of exercise (Brosseau *et al.*, 2003a; Han *et al.*, 2004; Bartels Else *et al.*, 2007; Fransen and McConnell, 2008; Fransen and McConnell, 2009; Hurkmans *et al.*, 2009), two reviews of the effect of therapeutic ultrasound (Casimiro *et al.*, 2002; Rutjes *et al.*, 2010) and two reviews of acupuncture (Casimiro *et al.*, 2005; Manheimer *et al.*, 2010). Other treatment modalities reviewed included thermotherapy (Brosseau *et al.*, 2003b) and balneotherapy (Verhagen *et al.*, 2008) for OA, the role of occupational therapy interventions (Steultjens *et al.*, 2004), splints/orthoses (Egan *et al.*, 2003) electrical stimulation (Brosseau *et al.*, 2002), and low level laser therapy (Brosseau *et al.*, 2005) for RA; and multidisciplinary rehabilitation for Fibromyalgia (Karjalainen *et al.*, 2000).

The results of these reviews are summarised in tables 2.4, 2.5 and 2.6. Overall the quality of the evidence available for each review (as assessed by authors) was low to moderate, except for one high quality review for exercise interventions in OA.

Table 2.4: Cochrane systematic reviews of non-pharmacological interventions for OA

Author/date	Sample size	Intervention/ population	Quality of evidence	SMD* (effect size)	Conclusion
(Fransen and McConnell, 2008)	3616 (32 RCTS)	Land based Exercise/knee OA	High	Pain: SMD 0.40 (95%CI 0.30-0.50) Function: SMD 0.37 (95% CI 0.25-0.49)	Land based exercise has benefit in reducing knee pain and improving physical function in knee OA
Bartels et al 2007	800 (6 RCTS)	Aquatic exercise /OA	Moderate	Pain: 3% absolute reduction (6.6% relative reduction) from baseline Function: SMD 0.26 95% (CI 0.11-0.42)	Some beneficial short term effects for people with hip and or knee OA
Fransen et al 2009	204 (5 RCTS)	Exercise/hip OA	Low	Pain: SMD -0.33 (95%CI-.84-0.17) -	Not statistically significant due to small sample sizes
(Brosseau *et al.*, 2003b)	179 (3 RCTS)	Thermotherapy	Low	Pain not measured	Beneficial effect on ROM*, function and knee strength.
(Rutjes *et al.*, 2010)	341 (5 RCTS)	Therapeutic ultrasound knee OA	Low	Pain: -1.2 (95% CI -1.9—0.6) Function: -1.3 95% CI -3.0 to 0.3)	May be beneficial for knee OA
(Verhagen *et al.*, 2008)	498 (7 trials	Balneotherapy	Low	1.82-0.34	
(Manheimer *et al.*, 2010)	3498 (16 RCTs)	Acupuncture	Not given	Short term effect on pain: SMD -0.28, 95%CI -0.45to – 0.11);	Sham controlled trials showed small, statistically significant benefits that are unlikely to be clinically relevant

ROM=range of motion; SMD= standardised mean difference.

2.9.1 Therapeutic ultrasound

A systematic review of therapeutic ultrasound in RA (Casimiro *et al.*, 2002) revealed two studies (n=80) that met the inclusion criteria. Findings were that ultrasound significantly increased hand

grip strength compared to control. Improvements in other outcomes including wrist dorsal flexion, duration of morning stiffness, number of swollen joints and number of painful joints were also statistically significant. Limitations of the papers reviewed included poor methodological quality, small number of studies and small sample sizes. Furthermore, both included studies were carried out over twenty years ago, and there was a lack of long term follow up.

The role of therapeutic ultrasound for knee OA was evaluated in a systematic review of five RCTs (Rutjes *et al.*, 2010). Ultrasound was compared to sham ultrasound or usual care. There was an effect in favour of ultrasound therapy compared to control for improvement in pain (difference of 1 on a pain scale of 0-10), although again, methodological quality was poor in included studies.

In summary, the reviews suggest there may be a beneficial effect from ultrasound in reducing pain in OA and RA, but contemporary research, of better methodological quality would strengthen the findings of these reviews.

Table 2.5. Cochrane systematic reviews of non-pharmacological interventions for RA

Author/date	Sample	Intervention	Quality of evidence	Result	Conclusion
Hurkmans et al 2009	(8 studies)	Dynamic exercise (aerobic +/- strength training)	Moderate	Pain VAS: -0.53 (-1.09 to 0.04)	Aerobic training combined with muscle strength training is recommended as routine practice in people with RA.
(Steultjens *et al.*, 2004)	>1700 (38 studies)	OT interventions (various)	Moderate	Splints reduced pain by 1.0	Evidence for the efficacy of instruction on joint protection.
(Han *et al.*, 2004)	206 (4 RCTS)	Tai chi	Low	Joint tenderness -0.83 [-3.30, 1.64]	Low quality evidence for improving ROM. No effect on joint tenderness
(Brosseau *et al.*, 2005)	222 (5 RCTS)	Low level laser therapy	Low	Pain reduced by 1.1 (95%CI 1.82-0.39)	Silver level evidence for short term pain relief
(Egan *et al.*, 2003)	2003	Splints and orthoses	Low	No pooled effect given	No benefit of splints in pain or function Extra depth shoes may reduce foot pain
(Casimiro *et al.*, 2005)	84 (2 RCTS)	Acupuncture and electro-acupuncture	Low	Electro acupuncture effect on knee pain (WMD: -2.0; 95% CI -3.6,-4.0	No effect with acupuncture. Small reduction in knee pain with electro acupuncture
(Brosseau *et al.*, 2002)	15 (1 RCT)	Electrical stimulation	Low	Grip strength 458; (95% CI 310 to 606)	Clinically beneficial effect on grip strength and fatigue resistance
(Casimiro *et al.*, 2002)	40 (2 RCTs)	Therapeutic ultrasound	Low	No. painful joints: [WMD 1.20 (95%CI: 0.45 to 1.95)].	Borderline reduction in number of swollen /painful joints

Table 2.6: Cochrane systematic reviews of non-pharmacological interventions for Fibromyalgia

Author/date	Sample	Intervention	Quality of evidence	SMD	Conclusion
(Busch *et al.*, 2007)	2276 (34 trials)	Exercise	Moderate	Pain (SMD 0.65, 95%CI: -0.09-1.39)	Exercise may reduce pain and tender points
(Karjalainen *et al.*, 2000)	1050 (7 RCTS)	Multidisciplinary rehabilitation	Low	No results presented	No conclusions could be drawn due to methodological differences.

2.9.2 Acupuncture

Acupuncture has also been evaluated in both OA and RA populations.

A systematic review of acupuncture and electro-acupuncture for the treatment of RA (Casimiro *et al.*, 2005) revealed two studies involving 84 people. One study compared acupuncture to sham acupuncture and found there was no statistically significant difference between groups (4 points on a 100 point visual analogue scale versus 0). In the second trial which compared electro acupuncture

to acupuncture using incorrect stimulation points, a significant decrease in pain was reported (weighted mean difference of -2.0). However, there were significant methodological weakness including use of a non validated outcome measure for pain, no report of means/standard deviations and a small sample size, limiting the validity of the results.

Manheimer et al (2010) conducted a systematic review of acupuncture in people with knee and/or hip OA and found sixteen RCTs (n=3498) that met inclusion criteria. Comparison groups varied widely between studies reducing the effect pooled results. Overall, when compared with sham acupuncture (ten trials), true acupuncture showed statistically significant, short-term improvements in osteoarthritis pain. (1 point lower in the intervention group on a 0-20 scale). In studies comparing acupuncture with the 'supervised osteoarthritis education' and the 'physician consultation' control groups, acupuncture was associated with short- and long-term improvements in pain and function. However, studies which compared acupuncture to home exercises/advice leaflet and supervised exercise, found that acupuncture was associated with similar treatment effects as the control group. Furthermore, acupuncture as an adjuvant to an exercise based physiotherapy programme did not result in any greater improvements than the exercise programme alone.

In summary, currently, there is no evidence from Cochrane systematic reviews that acupuncture reduces pain in RA; and the evidence presented in OA suggests there may be a small effect on pain when compared to usual care, but that acupuncture is unlikely to be superior to exercise interventions. Further research is required in both conditions using more rigorous methodology.

2.9.3 Exercise

The role of exercise has been assessed in OA, RA and fibromyalgia, all with evidence of a small but significant beneficial effect on pain.

A systematic review of land based exercise interventions for knee osteoarthritis examined 32 studies, with data on 3616 participants (Fransen and McConnell, 2008). The quality of included studies was judged to be high. A meta-analysis revealed a small but significant treatment effect (an estimated reduction in pain of 1 point on a scale of 1-20). However, many participants with very early OA were included in studies, which may have resulted in smaller differences between groups. The authors concluded there is platinum based evidence for exercise, with effects comparable to that provided by non steroidal anti inflammatory drug therapy (Fransen and McConnell, 2008). Similarly, albeit with smaller treatment effects, positive results have also been observed in those with hip osteoarthritis (Fransen *et al.*, 2009). A further systematic review of aquatic exercise for knee and hip osteoarthritis involving six trials and 800 participants found a 3% absolute reduction in pain (0.6 fewer points on a 0 to 20 scale) (Bartels Else *et al.*, 2007). From this it can be concluded that land based exercise may have slight superiority to aquatic exercise. In terms of the effects of differing intensities of exercise on pain, research is limited. A systematic review of exercise intensity for OA (Brosseau *et al.*, 2003a) found only one study exploring this variable and concluded that both low and high intensity appeared equally effective in improving outcomes including pain.

A review examining the effect of dynamic exercise (aerobic and/or strength training) in eight RCTs involving 575 people with rheumatoid arthritis (Hurkmans *et al.*, 2009) demonstrated that exercise reduced pain by on average 0.5 compared to control. There has also been a systematic review of Tai Chi interventions in people with RA (Han *et al.*, 2004). This found that although Tai Chi may improve range of movement, there is no evidence of an effect on RA symptoms including joint tenderness. The quality of evidence in this review was also considered low (silver level).

Exercise for fibromyalgia has been evaluated in a systematic review of 34 studies involving 2276 participants (Busch *et al.*, 2007). Effects were summarised using standardised mean differences. There was moderate quality evidence that aerobic only exercise training had a beneficial effect on pain (SMD 0.65, 95% CI -0.09 to 1.39) and tender points (SMD 0.23, 95% CI 0.18 to 0.65).

In summary, there appears to be evidence from high quality studies that exercise in general has small but significant effect on pain in OA, and also evidence supporting a small beneficial effect in RA and fibromyalgia, although of variable quality. The evidence for different types and intensities of exercise however, is limited.

2.9.4 Other interventions

A review of the value of wrist splints /orthoses in the management of RA (Egan *et al.*, 2003) included ten studies including RCTs, case control and cohort studies. The authors concluded there was insufficient evidence to support the use of wrist splints in decreasing pain or increasing function for people with RA. In contrast, a more recent review examined the role of a variety of occupational therapy (OT) interventions including joint protection, and included six controlled trials judged to be of high quality and nine uncontrolled trials judged to be of low methodological quality (Steultjens *et al.*, 2004). Although the authors stated that the findings were indicative of a benefit from splints on pain, pooled effect sizes were not provided, and the thirteen studies testing splints had mixed results, and none of the high quality studies demonstrated a significant benefit.

A systematic review of thermotherapy for OA (Brosseau *et al.*, 2003b) identified three studies, and found that ice packs/massage had a statistically significant beneficial effect on range of movement, function and knee strength, but no significant effect on pain. However, the small number of studies and small samples limit the conclusions that can be drawn regarding the effect of thermotherapy for OA.

A review of balneotherapy interventions (bathing in warm mineral water) for OA concluded that participants having mineral and sulphur baths had less pain than those receiving usual care immediately after the intervention (Verhagen *et al.*, 2008). However, any effect observed was lost at three months' follow up, and all seven studies were of low methodological quality, with allocation concealment not reported, and most not performing intent to treat analyses.

Brosseau et al (2005) conducted a systematic review of studies comparing the effect of low level laser therapy in people with RA. This review included five RCTs comparing this therapy to a placebo control. The authors found that pain and stiffness reduced in those receiving the intervention. However, methodological quality of included studies was low (silver level), and effects were short lived.

The review of multidisciplinary rehabilitation in fibromyalgia and chronic widespread pain identified seven RCTs suitable for inclusion in the review. However, the authors reported that these were all of low quality, and due to the nature of the review, even qualitative analysis was difficult therefore no conclusion could be drawn regarding the effect

2.9.5 Summary of evidence on interventions for OA, RA and fibromyalgia

While there is limited evidence to support the use of a variety of non pharmacological interventions for RA, OA and fibromyalgia, there is considerable support for the role of exercise in improving pain in all three conditions.

The evidence for balneotherapy and thermotherapy in OA, and low level laser therapy and OT interventions including wrist splints in people with RA, and multidisciplinary rehabilitation in fibromyalgia, is limited by the level of methodological quality and number of reviewed studies. There is some evidence for the role of ultrasound and acupuncture in managing pain in OA and RA. Exercise, however, appears to be the most widely tested intervention and currently has the strongest evidence of benefit in people with OA, RA and fibromyalgia.

As discussed in section 2.8.4, although pathophysiological mechanisms differ; RA, OA and fibromyalgia may share common pain mechanisms and consequently, exercise may also be a suitable intervention for AIAA. The next section provides discussion on the limited research that has been carried out to date on interventions for AIAA. This includes two preliminary studies examining the role of exercise and AIAA.

2.10 Review of tested interventions for AIAA

A review of the literature on interventional studies for AIAA initially revealed little research to date, with areas of particular interest including the role of acupuncture (Crew *et al.*, 2007a; Crew *et al.*, 2010; Mao *et al.*, 2014); and Vitamin D supplementation (Khan *et al.*, 2010; Prieto-Alhambra *et al.*, 2011). However, since my study was first developed in 2010, two studies have been undertaken which look at the effect of exercise in women with AIAA (Irwin *et al.*, 2013; Nyrop *et al.*, 2013). A summary of studies to date is provided in table 2.7, and evidence will be briefly reviewed below.

2.10.1 Exercise

A cohort study aimed to establish the feasibility and promise of a six week self managed walking programme in older women (>65 years) with AIAA, based on the 'walk with ease' self management programme designed for people with arthritis pain and disability (Nyrop *et al.*, 2013). The findings in this study, which recruited 21 participants, were that the proportion of women walking the target of 150 minutes per week increased significantly from 21% at baseline to 50% at six weeks, and also that joint pain and stiffness reduced from baseline to the end of the intervention by 10% and 32% respectively, although this figure was not statistically significant. As this was a feasibility study, there was no comparison group, a small sample size, and limited testing of outcomes. However, the findings suggest that walking as an exercise intervention is acceptable and walking activity can be increased in women with AIAA. Therefore these findings suggest that further research is warranted to test the effect of walking in women with AIAA.

The Hormones and Physical Exercise (HOPE) study is a randomised controlled trial to determine the effect of exercise in women with AIAA (Irwin *et al.*, 2013). A sample of 121 women taking an AI for at least six months, and with a pain score of at least three as measured by the Brief Pain Inventory worst pain item, were randomised to either a twelve month exercise programme

consisting of 150 minutes of aerobic exercise per week and twice weekly muscle strengthening, or usual care. Inclusion criteria included that women had to have gym membership. Outcome questionnaires were completed at baseline, six months and twelve months, with the primary outcome being the difference in worst pain scores between the intervention and control group at twelve months. Findings were that that worst pain scores reduced by twenty percent at twelve months in the exercise group compared to a two percent decrease in the usual care group (p= 0.017), suggesting that exercise may be effective in reducing joint pain in women with AIAA. These results have been presented at conference but are yet to be published; therefore no more detail is available at the current time.

2.10.2 Acupuncture

Three studies have investigated the effect of twice weekly acupuncture for six weeks on AIAA (Crew *et al.*, 2007a; Crew *et al.*, 2010; Mao *et al.*, 2014). A pilot study in 21 women with new or worsening joint pain whilst on an AI, compared acupuncture to wait list control (Crew *et al.*, 2007a); followed by a fully powered study using sham acupuncture as the control group (n=44) on outcomes including pain. A clinically meaningful, statistically significant reduction in pain scores was demonstrated in both studies. A recent three armed RCT compared electro-acupuncture to sham acupuncture and usual care in 67 women with AIAA (Mao *et al.*, 2014). Findings were that the electro-acupuncture significantly reduced worst pain at the end of the eight week intervention compared to usual care (-2.2 vs -0, 2, p=0.0004); however sham acupuncture produced a similar magnitude of effect. Although methodological limitations include small samples, and limited follow up, these studies support a potential role for acupuncture in AIAA.

2.10.3 Vitamin D supplementation

An interventional study evaluated the role of vitamin D on joint pain and fatigue in 60 women commencing adjuvant letrozole (Khan *et al.*, 2010). All participants initially received standard dose calcium and vitamin D, and after 4 weeks, only those with vitamin D levels below 40 ng/ml at baseline (i.e. having insufficiency or deficiency), n = 42, received additional vitamin D3 supplementation (50,000 IU per week) for a further twelve weeks. After sixteen weeks of letrozole, the absence of joint disability was reported in more women with Vitamin D levels above rather than below 66 ng/ml (52% (*n*=11), vs. 19% *(n*=4), P = 0.026). This suggests that there may be a role of vitamin D, although limitations of this study include a small sample size, and non randomised design, with no placebo control, making it difficult to determine a causal effect. Similarly, a prospective longitudinal study evaluated the effect of additional 12000 IU weekly vitamin D supplementation in AI users with levels below 30ng/ml (Prieto-Alhambra *et al.*, 2011). The authors compared self report of pain on a visual analogue scale at three months compared to baseline, and found that in those reaching adequate vitamin D levels, pain VAS increased by a smaller margin than in those whose levels did not increase. However, the authors found that the

dose of Vitamin D supplementation used was not enough to raise levels to adequate levels in 50% of participants. Whilst longitudinal studies cannot imply AIs as a cause of Vitamin D deficiency, this does suggest there may be a role for supplementation, however, further research is warranted.

2.10.4 Switching therapy

A prospective longitudinal cohort study assessed the effect on AIAA of switching AI therapy from one to another (Briot *et al.*, 2010). Participants (*n*=179) were switched to letrozole after stopping anastrozole for one month. Pain levels were assessed at baseline (stopping anastrozole treatment), one month after stopping, and then one, three and six months after switching to letrozole. Six months after switching therapy, 71.5 % of women had not stopped letrozole, and reported a statistically significant reduction in mean (SD) pain score from baseline (4.9 +/- 1.6 to 3.8 +/- 2.4). However, it could be argued that changes observed in pain levels were not clinically significant. Furthermore, as this was a non randomised study without a control group, it is possible that if women had continued on anastrozole, their pain levels would have reduced over time regardless. Alternatively this could have been a placebo effect.

2.10.5 Summary of evidence on interventions for AIAA

In summary, there is some support for the role of acupuncture in the management of AIAA, and switching treatment is a strategy that may provide benefit, although both require additional testing. Further studies investigating the role of Vitamin D are also warranted, using randomised controlled designs, higher dose supplementation and with longer follow up. There also appears to be evidence for the role of exercise in AIAA, although there has been no published research testing exercise in a UK population. Furthermore, the HOPE study only recruited women with gym membership which may have led to bias in the sample; as it may have limited the sample to younger women, those more likely to exercise, and those with higher income. The feasibility study by Nyrop et al (2013) was not powered, but did demonstrate that a walking intervention was acceptable in this population, by the increased duration of walking that women achieved.

Nevertheless, in view of the evidence demonstrating the effectiveness of exercise in other musculoskeletal conditions, and the preliminary research findings in women with AIAA, there is an indication that exercise may be of benefit. Consequently, an exploration of pain theories is necessary in order to understand the process by which exercise might help women with AIAA, as this will inform the development of a theoretical framework for a definitive exercise intervention. The next section will therefore discuss models of pain, with particular focus on the development of the biopsychosocial model, which has been particularly influential in the management of chronic musculoskeletal conditions.

Table 2.7: AIAA interventional studies literature review table

Author/yr	N=	Study design	Intervention	Outcome measures	Attrition	Results	Comments
Crew et al 2010	43	RCT (blinded)	Acupuncture vs sham acupuncture for twice a week for 6 weeks vs sham acupuncture	BPI-SF WOMAC M-SACRAH	5 (no ITT)	BPI-SF worst pain score at 6 weeks 3.0 vs 5.5 (TA vs SA, p,0.001) Other measures indicated similar effect	Superficial needle insertion used for sham acupuncture considered by some not to be a true placebo Small sample size, although power described Attrition = (5/43) Not ITT analysis Less pts in sham acupuncture gp believed they were actually receiving it which could indicate a bias from therapist
Crew et al 2007a	21	RCT pilot (wait list control)	Acupuncture twice a week for 6 weeks vs wait list control	BPI-SF WOMAC M-SACRAH FACT-G	2	BPI SF reduced from 5.3-3.3 (p=0.01)	Small sample size but descriptive statistics used Attrition = 2 No blinding to intervention
Briot et al 2010	173	prospective, non-randomised, multicenter study	Switching AI treatment in women c/o aiaa at point of discounting tx from arimidex to letrozole	Continuation of letrozole BPI-SF	-	71.5% continued with letrozole Mean(SD) BPI score reduced from baseline to end of study (4.9 +/-1.6) to 3.8 +/- 2.4)	Note authors received supportive grants from Novartis who manufacture letrozole. ? Would same effect be noted in pts intolerant of letrozole, switched to arimidex e.g. Hawthorne effect. No comparator group
Khan et al 2010	60	Prospective longitudinal Cohort study	Supplemental weekly high dose(50,000) Vit D for women on arimidex with suboptimal Vit D levels at baseline	HAQ-II (Health assessment questionnaire)	9 /60	More women with 25OHD levels >66 ng/ml reported no disability from joint pain than did women <66 ng/ml (52 vs. 19%; P = 0.026)	Observational study therefore causality cannot be assumed. Require RCT to further investigate
Mao et al 2014	67	RCT (three armed)	Electro-acupuncture (EA) vs waitlist control (WLC) vs sham acupuncture (SA)	BPI-SF worst pain	4/67	8 weeks: EA vs WLC vs SA: -2.2 vs -0.2 vs -2.3	No difference in effect between sham and electro acupuncture
Prieto-Alhambra et al 2011	290	Prospective longitudinal cohort study	Additional 12, 000 iu oral Vit D every 2 weeks to women on AI	Pain VAS at 3/12 compared to baseline	0	Pain VAS increased overall but in those reaching adequate Vit D levels increase was attenuated	Observational study therefore causality cannot be assumed. Require RCT to further investigate
Irwin et al 2013	121	RCT	Aerobic exercise vs usual care	BPI-SF	5/61 in exercise gp	BPI-SF worst pain scores reduced by 20% in intervention compared to 2% in usual care	Published result awaited. However, exercise programme involving aerobic exercise and muscle strengthening may reduce AIAA
Nyrop et al 2013	20	Cohort	Walking vs usual care	VAS pain, stiffness, and fatigue % walking 150min/ wk	1/21	VAS pain reduced by 10% Walking 150min per week increased from 21% to 50%	Structured walking programme can increase physical activity levels in women with AIAA and may reduce pain, stiffness and fatigue, further research warranted

BPI-SF=Brief Pain Inventory Short Form; WOMAC Western Ontario and McMaster Osteoarthritis index; M-SACRAH = Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands

2.11 Pain models

2.11.1 Review of historical models

Specificity theory originated with the work of Descartes' theory of dualism, in which injury caused pain in a linear fashion (akin to pulling a rope causing a bell to ring at the other end). This was developed by von Frey (1894), who claimed there were unique spinal pain pathways along which pain signals were transmitted, with differing types of pain ascribed to specific nerves. Psychological influences were not accounted for; furthermore this model could not explain the existence of pathological pain states such as phantom limb pain. Patterning theory, first suggested by Goldsheider (1884), acknowledged the limitations of specificity theory by introducing the concept that pain was the result of spatial and temporal patterns of nerve transmission (as opposed to individual pathways) leading to summation in the dorsal horn of the spinal cord; with pain only being transmitted if exceeding a certain threshold. This model also had weaknesses in that it ignored evidence that nerve receptors do have a degree of specificity. However, the model advanced conceptual understanding of pain mechanisms (Horn and Munafo, 1997).

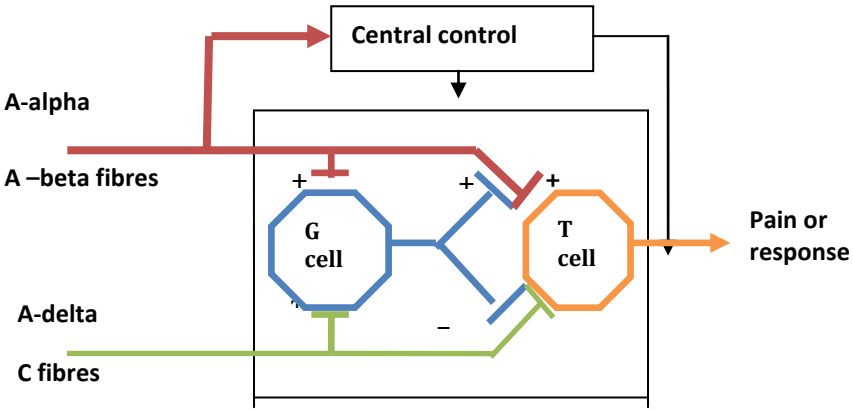
2.11.2 Gate control theory

Elements of both models were assimilated into the Gate Control Theory (GCT), proposed by Melzack and Wall (1965) (figure 2.1), the most widely known and accepted pain theory of current times. This described the existence of large and small diameter peripheral nerve fibres implicated in the process of nociception, and a 'gating mechanism' situated in the dorsal horn of the spinal cord which could modulate the experience of pain (Melzack and Wall, 1965). It was argued that large diameter fibres (a- beta and A-alpha) could close the gate (decrease pain), whereas small diameter fibres (A-delta and C fibres) could open the gate (increase pain). The major conceptual contribution of the GCT was that it replaced the mind-body dichotomy of pain described by specificity theory, by claiming that impulses from higher centres in the brain also modulated pain perception, a concept which has become known as descending inhibition. This concept has been clarified further with the identification of neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin, and endorphins involved in these inhibitory pathways descending from the brain to dorsal horn of the spinal cord (Melzack and Wall, 1988). Thus the GCT moved away from the concept of tissue damage as being the sole determinant of pain, and instead focused on the central nervous system as being the determinant, and in particular, whether or not the gate was open.

Limitations of the Gate Control Theory are that it is still largely a physiological model which, whilst acknowledging the importance of psychological factors, provides little in the way of elaboration or evidence to support this claim (Horn and Munafo, 1997). However, its strength is in the integration of psychological, behavioural and physical elements of nociception within a single holistic system. It remains the most important model for pain researchers (Corner and Bailey, 2008)

and recognition of cognitive influences on the pain pathway has allowed significant advances in the understanding of psychosocial factors affecting pain perception (Main *et al.*, 2008). This has led to the development of holistic models of pain perception and management, such as the biopsychosocial model, which have proven effective in the treatment of chronic pain conditions.

Figure 2.1: Gate control theory (Melzack and Wall, 1965)



The next section will discuss the differences between acute and chronic pain, and therefore why chronic pain, including AIAA, may respond more effectively to a biopsychosocial model. This will be followed by a review of the biopsychosocial model in the management of musculoskeletal pain.

2.11.3 Acute versus chronic pain

Acute pain is said to be the normal, predicted physiological response to an adverse chemical, thermal, or mechanical stimulus, is short lived, and is often associated with surgery, trauma, and acute illness (Warfield and Bajwa, 2002). It is claimed that acute pain states have a more straightforward relationship with a physiological model, and as a result are more likely to respond to pain treatments such as analgesia.

Chronic pain can be classed as pain that persists beyong normal healing time (Melzack and Wall, 1996). Some pain experts claim that acute and chronic pain have similar mechanisms, but lie at each end of a spectrum (Horn and Munafo, 1997); however, others classify them as distinct phenomena (Melzack and Wall, 1996). Although AIAA usually resolves on discontinuation of treatment (Donnellan *et al.*, 2001), it is argued that it should be categorised as chronic pain due to the duration of treatment and the evidence presented in section 2.7.3 on the likely underlying pain mechamisms.

Chronic pain is now known to be associated with reorganisation of the nervous system (peripheral and central sensitisation) with the potential for spontaneous nerve excitation, known as neuroplasticity (Melzack *et al.*, 2001). There is considerable evidence that neuroplasticity has a role in chronic musculoskeletal pain such as arthritis (Kidd, 2006) and possibly AIAA (Coleman *et al.*,

2008). It arises as a result of mediators released from damaged tissues acting to increase the excitability of all stages of the nociceptive pathway, including peripheral, spinal and cortical levels, as discussed in sections 2.7.3. and 2.8.2. As a result everyday activities can become painful. Due to multilevel sensitisation, for therapy to be effective it must be able to influence both the originating injury and additional factors which may infleunce nociceptive activity. Furthermore, prolonged pain states present greater scope for psychological, social, and behavioural factors to mediate the individual's response to their condition. The multitude of factors affecting the individuals response to chronic pain makes it difficult to treat effectively and often requires more than pharmacological treatment (Bergman, 2007). All of these factors together are considered in the biopsychosocial model.

2.11.4 The Biopsychosocial model

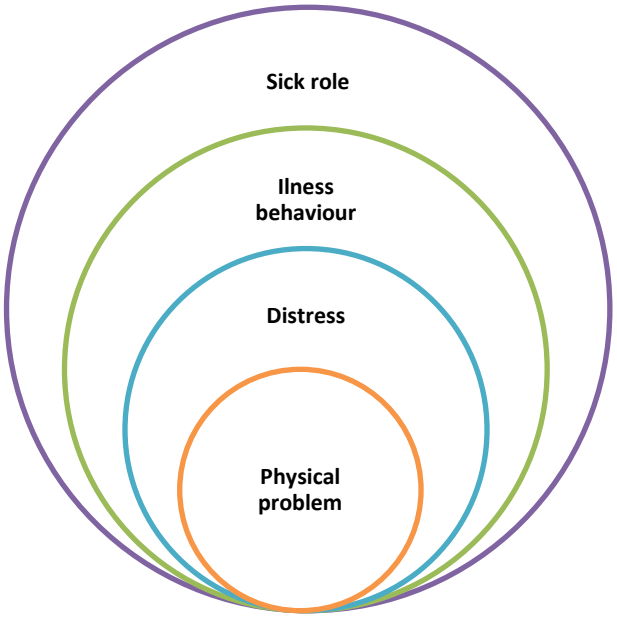
Engel (1977) was credited as one of the first to call for the need for a new approach to the traditional biomedical reductionist philosophy that had historically dominated the field of medicine. He proposed instead a conceptualisation of illness in which symptoms were considered to be the result of a dynamic interation between psychological, social and pathophysiological variables. This account led to the development of the biopsychosocial model of illness, and versions of it have been particularly influential in the area of chronic pain. The biopsychosocial model focuses on both disease and illness; with disease as the objective pathohysiological condition, and illness and symptoms such as pain, as the subjective experience of a disease, involving a complex interaction between biological, psychological and social factors. Research on the the effect of these factors is reviewed by several authors who conclude that psychosocial factors such as negative affect (depression and anxiety); coping strategies, (locus of control, self efficacy, helplessness), social support, and pain beliefs and appraisal (catastrophizing, fear avoidance), may modulate the pain experience (Keefe *et al.*, 2002; Turk and Okifuji, 2002; Gatchel *et al.*, 2007). This is in addition to pathophysiological factors which are individual to the particular physical disorder.

Versions of the biopsychosocial model have been effective in the management of chronic musculoskeletal conditions including low back pain (Waddell, 1987) and arthritis (Keefe *et al.*, 2002) and thus merit consideration in the development of an intervention for AIAA .

Waddell was the first to apply a biopsychosocial model to musculoskeletal pain in his seminal paper on the treatment of chronic low back pain (Waddell, 1987). The Glasgow Illness model (Waddell *et al.*, 1984) incorporates the physical disorder, distress and illness behaviours, and sick role as components of this biopsychosocial model (figure 2.2). His research demonstrated a poor correlation between both pain and disability, and pathophysiological change within the spine. As a consequence, traditional medical treatments such as analgesia and bed rest aimed solely at

correcting the presumed pathophysiological change had proven unsuccessful, and in some cases harmful (Waddell, 1987). Of interest, discrepancy between pathophysiology and pain experienced

Figure 2.2 The Glasgow Illness Model (Waddell, 1987)

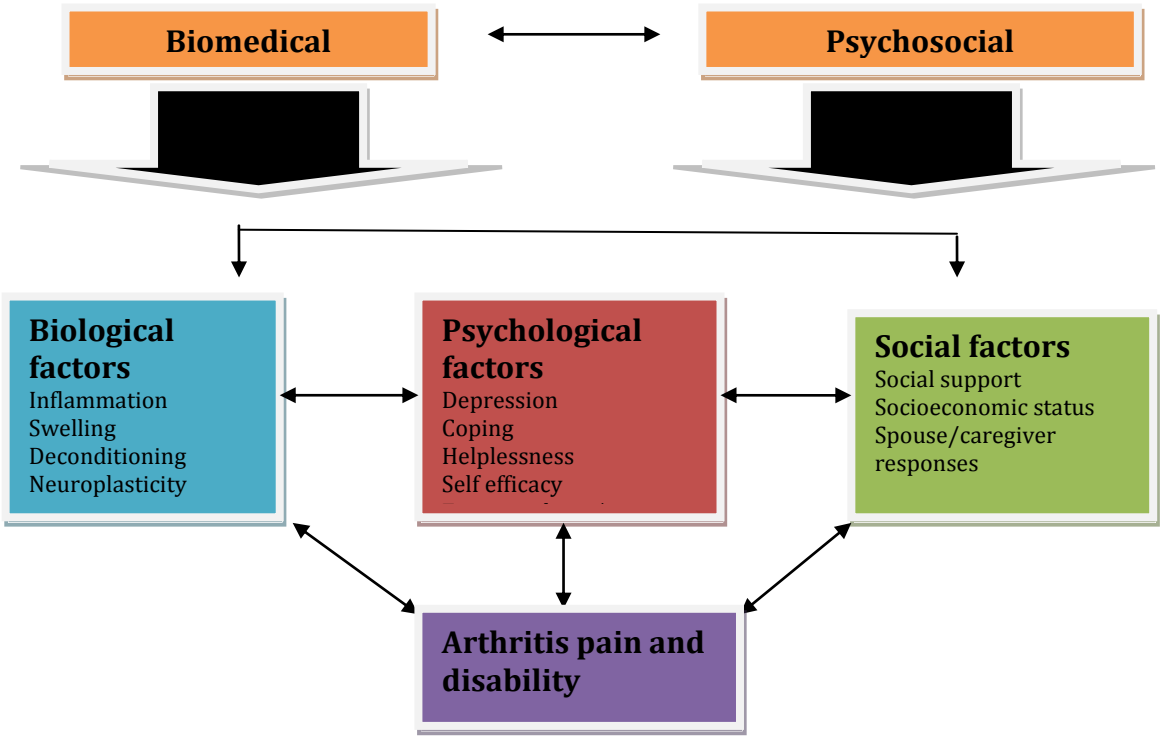


has also been established in arthritis (Dieppe, 2005), and has also been observed in studies of AIAA (Dizdar *et al.*, 2009) where a third of women with AIAA have no evidence of pathophysiological change within joints. Waddell's data suggested that disability from low back pain was a recent Western epidemic perpetuated by medical treatment. His biopsychosocial model aimed not only to alleviate pain but to restore function and reduce disability. Thus, physical activity was recommended as treatment based on evidence demonstrating its benefits, including bone and muscle strengthening, improved disc and cartilage nutrition, and increased endorphin levels. On a behavioural level, there was evidence that physical activity programmes reduced learned pain avoidance behaviours (Fordyce *et al.*, 1986), increased self estimate of exercise capability (Dolce *et al.*, 1986), and decreased anxiety about the effects of exercise.

The biopsychosocial model has also been used to assess and manage arthritis pain and disability by Keefe and colleagues; who argue that symptoms of pain, stiffness and joint damage arising from arthritis not only lead to physical disability, but have important psychological and social consequences which can worsen pain (Keefe *et al.*, 2002). Furthermore, they argue that addressing psychosocial aspects can improve pain and disability. For example, increases in pain can lead to an increase in depression and anxiety (psychological change) and decreases in the ability to work or perform normal social roles (social changes), both of which can, in turn, heighten pain and disability. In contrast, improvements in a person's self efficacy in regard to controlling arthritis pain (a psychological change); and facilitative rather than solicitous support from others (social

change), can reduce pain and disability. Components of the biopsychosocial model of arthritis pain and disability as proposed by Keefe et al (2002) are illustrated in figure 2.3.

Figure 2.3: Keefe's (2002) biopsychosocial model of pain as applied to arthritis.



It is argued that aspects of Keefe's et al's (2002) model may be more relevant and transferrable to women with AIAA as pain mechanisms and duration are more comparable to OA than low back pain, and thus may result in similar psychological and social sequelae. However it is recognised that some elements of Waddell's (1987) model may also be transferrable to women with AIAA, including the benefits of physical activity in increasing endorphin levels and reducing pain avoidance behaviours.

In summary, many biological, psychological and social factors interplay in a complex manner to contribute to the pain experience. Consequently, the biopsychosocial model provides an opportunity to focus on how these factors may be modulated by exercise in order to reduce AIAA, and improve patient experience, as will be discussed in the next section.

2.12 Biopsychosocial theory of pain reduction in aerobic exercise

Aerobic exercise (such as jogging, swimming, cycling, Nordic walking) involves the rapidly alternating contraction of large muscle groups at low resistance for a sustained period. This increases aerobic capacity, or maximal oxygen uptake (VO_2). As a result of endurance training, the number and size of mitochondria in muscle increase, the activity of mitochondrial enzymes

increase, and blood flow to muscle increases because of the increased numbers of capillaries and improved efficiency of blood flow shunting (Pollock and Wilmore, 1990).

Examining the likely mechanisms of pain reduction using a biopsychosocial model (which appears to be a feasible model to use in chronic musculoskeletal pain); aerobic exercise may have benefits for women experiencing AIAA, by targeting the following biological, psychological and social aspects.

2.12.1 Biological factors

Targeting of central sensitisation

Inflammation and swelling within joints, which may be a feature of AIAA, can lead to peripheral and central sensitisation (neuroplasticity) as discussed in section 2.7.3 and 2.11.3. Therefore, interventions may be required that can target all levels of the pain pathway including peripheral, spinal and cortical levels.

- *Stimulation of large diameter neurons.*
  Based on the Gate Control Theory, it is believed that exercise decreases pain through stimulation of A-beta joint afferent neurons which have larger diameters and carry information at higher speeds that the lower smaller pain fibres (Hall and Brody, 2005), thus the 'gate' is closed and pain is reduced.

- *Increase beta-endorphin levels.*
  Endorphins are endogenous pain relieving chemicals found in the central nervous system (Mann and Carr, 2006). A recent review of the literature has found that in the majority of studies, endurance activity increases beta endorphins in the plasma (Bender *et al.*, 2007), theoretically 'closing' the gate (through descending inhibition) and thus reducing pain.

Reversal of loss of muscle strength/deconditioning

Evidence from epidemiological studies suggests that subjects with lower limb OA have reduced quadriceps strength, as a result of pain experienced (Roddy and Doherty, 2006). This is supported by evidence from cross sectional studies. For example, a case control study comparing 300 individuals with knee pain compared to 300 controls without found that reduced quadriceps strength was independently associated with knee pain (O'Reilly *et al.*, 1998). Although this evidence does not imply a causal relationship in one particular direction, there is data to suggest that loss of muscle strength may arise as a result of arthrogenic reduction of voluntary contraction and reflex inhibition (Hurley *et al.*, 1997). However, further research supports additional mechanisms including joint effusions (Jones *et al.*, 1987) and pain (Arvidsson *et al.*, 1986) as a cause of muscle weakness. Furthermore, it has been observed that as a result of pain experienced when performing more strenuous activities, individuals with joint pain may also avoid activity and

become physically deconditioned as a result i.e. develop further muscle weakness, pain and difficulty tolerating activity (Keefe *et al.*, 2002). Whilst there have been no studies examining the quadriceps in women taking AIs, as discussed in section 2.7.2., grip strength has been found to be reduced in AI users (Morales *et al.*, 2008). Exercise can help to develop strength and endurance in muscles surrounding joints (Hurley, 2002), thus reversing the deconditioning process that can occur in chronic musculoskeletal conditions.

2.12.2 Psychological factors

Improving mood

Although there are no studies to date examining the effect of AIAA on mood, research suggests that there are high levels of depression generally in populations with chronic pain. For example, a large epidemiological study carried out by the World Health Organisation found a fourfold increase in associated depressive or anxiety symptoms in people complaining of pain persisting beyond six months (Gureje *et al.*, 2001). Of relevance, studies have shown a correlation between depression and adjustment in individuals with arthritis (Keefe *et al.*, 2002). There is conflicting evidence as to whether pain increases the risk of depression or depression increases the risk of chronic pain, and it has been suggested that they may exist in a mutually reinforcing relationship (Gatchel, 2004). However, it is proposed that for the purposes of designing interventional studies, it is irrelevant which is the causative factor, as treatment of one condition should improve the other. Nevertheless, a review of the research suggests that in the majority of cases depression is reactive (Gatchel, 2004), and mediated by patients' appraisals of their ability to exert any control over their pain and lives (Turk *et al.*, 1995). This is supported by research in the arthritis population which found that loss of valued activities significantly predicted subsequent depression (Katz and Yelin, 1995). This suggests that an intervention which gives individuals more control over their lives and allows them to return to valued activities may improve mood and possibly pain.

There is evidence that exercise can elevate mood which may in turn reduce pain perception (Hoffman and Hoffman, 2007). A Cochrane systematic review of 28 randomised controlled trials involving 1101 adults with depression compared exercise with a control group (Rimer *et al.*, 2012). A moderate reduction in depression was found in those exercising (SMD -0.67 (95% CI: -0.90 to -0.43), although this was reduced to a small effect size when only methodologically robust studies were included (SMD -0.31, 95% CI -0.63 to -0.01). There is less research linking the effect of mood elevation on pain tolerance. However, a randomised controlled trial involving 55 participants with low back pain found that artificially elevating mood reduced pain perception at rest and raised pain tolerance during activity, with the reverse true when inducing depressed mood (Tang *et al.*, 2008). This study was small with limited power but is consistent with other small studies demonstrating positive affect can raise pain thresholds (Hoffman and Hoffman, 2007).

Increased Self efficacy

Self efficacy , a concept developed by Albert Bandura (Bandura, 1977) is the belief in ones capabilities to organise and execute the courses of action required to manage prospective situations (Bandura, 1995). The primary sources of efficacy information include performance experience, verbal persuasion, vicarious experience, and physiological and affective states.

There is good evidence that self efficacy as a concept is useful in understanding reaction to pain experience. For example, in populations with arthritis, those with high levels of self efficacy will be confident about their ability to cope with pain and those with low self efficacy may feel unable to manage their pain (Lorig and Holman, 1998). A cohort study of 40 people with knee OA which examined how self efficacy related to judgments of controlled thermal pain stimuli (Keefe *et al.*, 1997) found that participants scoring high at baseline on self efficacy for arthritis pain rated the laboratory pain as less unpleasant, and had higher thresholds and tolerance for lab pain than those with low self efficacy. This study supports the hypothesis that higher self efficacy may lessen pain, although this finding may not be generalisable to practice based situations.

Furthermore, it is claimed that self efficacy can be modified through factors including vicarious experience (e.g. observing others successfully executing behaviours); reinforcements (e.g. use of incentives); verbal persuasion; physiologic and affective states and performance accomplishment (Wood and Bandura, 1989). If this is the case, interventions which improve self efficacy through these factors may lessen the pain experience. This has been demonstrated in a longitudinal cohort study of individuals with OA taking part in a self-management intervention (Lorig *et al.*, 1989). The authors found that increases in self efficacy which occurred after taking part in the programme were correlated with long term improvements in pain and psychological functioning. Similar findings are reported with interventions including exercise and pain coping skills training (Keefe *et al.*, 1996; Keefe *et al.*, 1999), which are also components of many self-management programmes, as they help people to feel in control of their own symptoms. Supporting people to gradually introduce their exercise threshold has been found to increase self efficacy for pain reduction through exercise and give confidence to carry out other daily activities (Main *et al.*, 2008). In addition exercising in groups may provide people with vicarious experience by observing others in a similar situation manage to increase their activity.

Reduce fear avoidance behaviour

It has been suggested that fear of chronic pain can lead to a desynchronisation of two components of pain that normally operate together, sensation and affective response. This often happens when a fear of pain leads to avoiding behaviours such as rest and avoidance of social activities that might cause further pain (Lethem *et al.*, 1983). As discussed in 2.11.1, this can spiral into significant

deconditioning of the individual which can in turn exacerbate pain, as muscles weaken. However, a study by Dolce et al (1986)demonstrated that graded increases in activity can both increase levels of activity and expectancy whilst reducing worry and concern about exercising. Behavioural research based on operant conditioning (Fordyce *et al.*, 1986) suggests that exercise programmes can reduce fear avoidance behaviours.

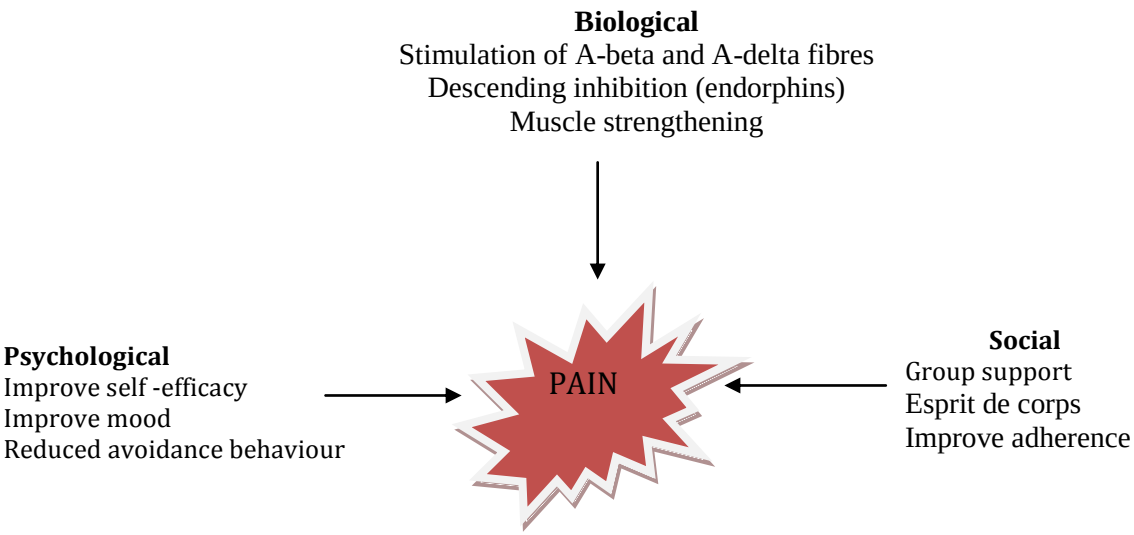
2.12.3 Social factors.

Social support

There is evidence that social support can have an influence on pain and functional ability in both musculoskeletal and breast cancer populations. A longitudinal study of 78 people with early RA found that low levels of social support consistently predicted increased functional disability and pain at three years and five years follow up (Evers *et al.*, 2003). Furthermore, a longitudinal of 164 breast cancer survivors found that women with lower social support at time of diagnosis had higher levels of pain and depressive symptoms six months after completing treatment (Hughes *et al.*, 2014). However, it remains unclear from these studies whether social aspects directly affect pain experience or service as a buffer against related stressors (Keefe *et al.*, 2002). Nevertheless, it is suggested that early interventions targeting social support might be one mechanism which can improve physical and psychological outcomes.

Exercising in groups as a form of social support may facilitate exercise adherence, which in turn may promote the beneficial effects of exercise on pain. For example, a mixed methods of 55 participants with advanced cancer found that exercising in groups encouraged participants to develop a special 'esprit de corps' that encouraged group cohesion. Longitudinal quality of life data demonstrated improvements in mental health, social, and emotional functioning from baseline to the end of the intervention (Midtgaard *et al.*, 2006).

Figure 2.4: A biopsychosocial model of exercise and pain reduction in AIAA



2.12.4 Summary and conclusions

It is proposed that due to a combination of psychological, biological and social factors, that an aerobic exercise intervention may reduce arthralgia in women taking AIs as breast cancer treatment thus making a case for the biopsychosocial model on which to base an intervention. Specifically, exercise may have a physiological effect on pain pathways by stimulation of large diameter neurons, increasing endorphin release, and strengthening muscles. Psychosocial mechanisms may include improving mood, self efficacy and social functioning, and reducing avoidance behaviours which can lead to deconditioning. However, it is entirely possible exercise may not reduce arthralgia in view of the fact pathophysiological mechanisms underlying AIAA are not yet fully understood.

2.12.5. Rationale for type of aerobic exercise intervention for AIAA

There is a paucity of studies which compare differing types on aerobic activity on pain reduction in musculoskeletal conditions which makes it difficult to recommend one over another. However, a systematic review comparing the effects of different aerobic activities in populations with arthritis (Westby, 2001) concluded that compared to cycling, dance, running and aquatic exercise, walking resulted in the greatest reduction of pain. In addition, there is evidence to suggest that walking is one of the preferred methods of aerobic exercise in women with cancer (Jones and Courneya, 2002; Rogers *et al.*, 2009; Stevinson *et al.*, 2009).

Furthermore, it is proposed that Nordic walking (walking with the addition of handheld poles) might provide additional benefits in reducing joint pain compared to normal walking. The rationale and evidence for this will be explored in the next chapter.

Chapter 3. Nordic walking for AIAA

In order to identify whether Nordic walking would be a suitable intervention for women with breast cancer and arthralgia following breast cancer, the evidence surrounding Nordic walking was explored, specifically;

a) The mechanisms by which Nordic walking may reduce joint pain, using the biopsychosocial model
b) The safety and acceptability of Nordic walking in breast cancer populations
c) The extent of evidence supporting Nordic walking in related musculoskeletal conditions

3.1 Description

Nordic walking, or pole walking, is an outdoor, non competitive exercise, which originated in Finland in the 1980s, where it was developed as a summer conditioning exercise for cross country skiers. It is a form of walking with the addition of handheld poles which are used in opposition to the lower limb locomotion (Fritschi *et al.*, 2012).

Research into the health benefits of Nordic walking is growing, with particular focus on areas including benefits in cardiac rehabilitation (Kocur *et al.*, 2009), Parkinson's disease (van Eijkeren *et al.*, 2008; Reuter *et al.*, 2011), peripheral vascular disease (Collins *et al.*, 2003; Collins *et al.*, 2012) musculoskeletal conditions (Strombeck *et al.*, 2007; Hartvigsen *et al.*, 2010; Mannerkorpi *et al.*, 2010), and chronic obstructive pulmonary disease (Breyer *et al.*, 2010). A recent systematic review of pole walking in health in adults concluded that Nordic walking has beneficial effects on many physical and psychosocial outcomes, as well as being a well tolerated and safe exercise for diverse populations (Fritschi *et al.*, 2012).

A recent qualitative study has also explored the experience of Nordic walking in people with chronic musculoskeletal pain (O'Donovan and Kennedy, 2014). Themes to emerge surrounded the

educational, physical, psychological and social benefits of Nordic walking. Specifically, participants reported physical gains including improvements in posture, mobility, walking speed, balance and stability. Psychologically participants described increases in self confidence and self determination, that Nordic walking in groups provided distraction, and an improvement in mood. A strong theme to emerge also was the value of a group based activity which provided social support by way of shared experience, motivation, mutual understanding, commitment and uniqueness.

In summary, Nordic walking appears to be of benefit in people with a variety of long term health conditions. This may be partly because once the basic concepts of Nordic walking have been mastered, it is an exercise that can be carried out independently, facilitating self management for individuals with a variety of levels of fitness. Furthermore, the limited qualitative data available suggests it brings not only gains in physical wellbeing, but psychological and social benefits also.

3.2 Nordic walking and the biopsychosocial model of pain reduction

Nordic walking may provide additional benefits to normal walking for women with AIAA because of various biopsychosocial factors. It is possible that the increased aerobic expenditure involved in Nordic walking may result in higher exercise related endorphin release, with a further reduction in pain and improved mood, over and above that provided by normal walking. Further potential benefits may include reduced loading on joints(Willson *et al.*, 2001; Hansen *et al.*, 2008; Stief *et al.*, 2008; Fregly *et al.*, 2009), and increased muscular strength , making it particularly suitable for an exercise intervention aimed at reducing joint pain. Evidence for this, although limited, is presented below.

3.2.1 Biological factors

Reduced joint loading

Several studies have been carried out to determine whether Nordic walking results in less impact of the joints than normal walking. A study carried out to determine whether walking with poles reduces loading to the lower extremity during level over ground walking (Willson *et al.*, 2001) performed gait analysis on thirteen healthy adults with and without poles, and concluded that use of walking poles enabled subjects to walk at a faster speed with reduced vertical ground reaction forces, vertical knee joint reaction forces, and reduction in the knee extensor angular impulse and support moment, depending on the poling condition used. Furthermore, a case study examining different gait patterns (Fregly *et al.*, 2009) concluded that pole walking gait may allow people with knee osteoarthritis or a knee replacement to reduce medial, lateral, and total contact forces. In contrast to these findings, two further studies have either found no difference in joint loading (Hansen *et al.*, 2008)or increased joint loading (Stief *et al.*, 2008). A study examining the gait of seven experienced Nordic walking instructors found no difference in compression or shear forces at the knee (Hansen *et al.*, 2008). Furthermore a cross sectional study of fifteen experienced Nordic

walkers found that Nordic walking involved greater knee joint loading just after heel strike compared with walking, as well as greater ankle movement (Stief *et al.*, 2008).

The contradictory results of the above studies may be due to several factors, such as differences in walking speed, sample size, population, pole walking technique and definition of knee joint load. In particular it is noted that most studies examined experienced Nordic walkers, younger in age, who will have a very different gait pattern to older populations with pre-existing musculoskeletal conditions, and thus the ability to generalise findings will be limited. A systematic review of all studies in this area is called for to clarify the situation, as well as replicating these studies in other populations.

Increased aerobic endurance

In terms of aerobic fitness, several studies have demonstrated that Nordic walking may enable participants to increase their endurance (and thus walk for longer) compared to controls (Rodgers *et al.*, 1995; Porcari *et al.*, 1997; Schiffer *et al.*, 2006). For example, a field test comparing Nordic walking to walking and jogging in fifteen healthy middle aged women, found that at comparable speed, Nordic walking increased oxygen consumption compared to normal walking (Schiffer *et al.*, 2006). This effect has been reproduced in other studies on the treadmill (Rodgers *et al.*, 1995; Porcari *et al.*, 1997). Furthermore, in two of the three studies, perceived exertion was measured and it was found that Nordic walking resulted in greater energy expenditure for the same effort.

Improved muscular strength

One study has specifically evaluated the effect of Nordic walking on muscular strength (Malicka *et al.*, 2011). This RCT randomised women who had undergone surgical treatment for breast cancer to eight weeks of Nordic walking for 60 minutes twice per week or a control group, and found that that Nordic walking increased upper body muscular strength whilst not increasing the risk of lymphoedema. However, the study had a small sample size (n=38), with multiple significance testing therefore increasing the chances of a false positive finding. Women were also on average seven years out from diagnosis when shoulder morbidity secondary to treatment has largely resolved, which the ability to limits the ability to generalise findings to women earlier on after diagnosis. Further research is also required to establish whether other muscle groups are also strengthened by Nordic walking.

3.2.2 Psychosocial factors

Various studies testing the effect of Nordic walking in chronic disease have demonstrated improvements in psychosocial functioning as secondary outcomes (Strombeck *et al.*, 2007; Breyer *et al.*, 2010). Furthermore, a randomised controlled trial directly examining the effects of Nordic walking on depression in 45 healthy elderly individuals, found that depression scores improved post intervention compared to those in a control group who undertook stretching only (Willemer *et*

al., 2009). This was a small study with limited details of the study reported in the literature; however, these findings suggest that Nordic walking may have a beneficial effect on mood.

3.2.3 Summary of evidence for Nordic walking and the biopsychosocial model

In summary, Nordic walking may demonstrate benefits over normal walking in terms of reduced joint loading, and increased aerobic endurance for the same perceived effort as walking; and preliminary studies have demonstrated potential benefits in terms of improving muscular strength and psychosocial functioning. However, evidence is currently limited as Nordic walking is a new and emerging physical activity, and therefore further research is required to confirm these early findings.

3.3. Acceptability and safety in breast cancer populations.

Nordic walking has been found to be a popular form of exercise for women with breast cancer at my workplace. A service improvement evaluation of 38 breast cancer survivors undergoing a Nordic walking programme demonstrated that 62% increased their physical activity and 71% lost weight, whilst in the qualitative evaluation women reported improved fitness, increased peer support and mood elevation (Neate, 2011).

There is preliminary data in women with breast cancer to suggest that it is a safe and effective form of exercise, both in terms of increasing shoulder function (Sprod *et al.*, 2005) and upper body strength (Sprod *et al.*, 2005; Malicka *et al.*, 2011) and not increasing the risk of lymphoedema (Jonsson and Johansson, 2009; Malicka *et al.*, 2011).

A randomised controlled trial investigated the effect of walking with poles on muscular endurance in twelve women previously treated for breast cancer (Sprod *et al.*, 2005). Participants were randomised to either eight weeks of twice weekly pole walking for twenty minutes plus muscle strengthening exercises, or normal walking for the same frequency and duration with muscle strengthening. Muscular endurance was assessed with bench press, lat pull down and shoulder press exercises at baseline and the end of the intervention. Participants in the Nordic walking arm significantly improved their number of latissimus dorsi pull down (+6.83 repetitions per minute) and bench press exercises (+13.00 repetitions per minute), whereas the control group did not (0.8 and +5.2 respectively). Shoulder press exercises did not change significantly in either group. This study only recruited twelve participants, of whom 33% (n=4) dropped out during the study which may have led to significant bias in results. Allocation concealment was not reported and it was not clear who performed the outcome measurements. There was no long term follow up so it was not clear whether improvements were sustained. Safety issues and adherence were not reported on. Whilst these methodological weaknesses will limit the ability to generalise findings, the results

suggest there may be a benefit from Pole walking on upper body muscular endurance. However a further fully powered randomised control trial with more robust methodological reporting could confirm these early findings.

A longitudinal study was carried out to assess the safety of Nordic walking in women with breast cancer and lymphoedema (Jonsson and Johansson, 2009). Participants (*n*=26) underwent a one off hour long Nordic walking session, with arm volume recorded before Nordic walking, immediately after and then 24 hours later. The participants' contralateral arm was used as a control in this study. There was no worsening of lymphoedema observed following the Nordic walking sessions or 24 hours later. Whilst a one off Nordic walking session may limit the ability to generalise to practice in the real world, the findings suggest that Nordic walking may be safe for women with lymphoedema. Further safety data was established in Malicka et al's (2011) study testing the effect of Nordic walking on upper extremity strength in women previously treated for breast cancer, as discussed in section 3.2.1. Women with lymphoedema in the study had no changes in arm volume pre-post intervention. Other safety data, attrition, and adherence were not reported in either of these studies.

3.3.1. Summary of evidence on Nordic walking and breast cancer

In summary, there may be a role for Nordic walking in improving upper body muscular endurance and function whilst not increasing the risk of lymphoedema, a key factor for any exercise study being considered in women who are at increased risk of developing lymphoedema following breast cancer treatment. However, the methodological issues highlighted limit the ability to draw firm conclusions. Acceptability and safety issued were also not fully explored. For example, it is not apparent from these studies in women with breast cancer, whether there were difficulties recruiting and retaining women to Nordic walking, whether women adhered to the intervention and whether there were any other safety issues detected, all important consideration when conducting an interventional study.

3.4 Effect of Nordic walking in chronic musculoskeletal conditions.

A literature review was conducted to gather information about the effectiveness of Nordic walking and its impact on pain and related biopsychosocial outcomes, in populations with chronic musculoskeletal pain. Additionally, this review aimed to explore the extent of the evidence supporting the use of Nordic walking in populations with a chronic musculoskeletal condition, to identify any safety issues that occurred during the research intervention in these populations, and to uncover practical considerations arising from the research which may help to inform the design of future research studies of Nordic walking in chronic musculoskeletal conditions.

A total of three studies were identified from the literature search that were original research papers using randomised controlled designs and examining the effect of Nordic walking in chronic

musculoskeletal conditions. All studies had group sizes of less than 50. Populations studied included fibromyalgia (Mannerkorpi *et al.*, 2010), Sjogren's syndrome (Strombeck *et al.*, 2007) and low back pain (Hartvigsen *et al.*, 2010). No research papers were identified examining populations with arthritis despite an extensive literature search (Appendix II). All of the studies used an element of supervised Nordic walking as part of the intervention. The frequency of the intervention varied from two to three times per week, and varied in total length from eight (Hartvigsen *et al.*, 2010) to fifteen weeks. Two of the three studies measured pain as a primary outcome, and two measured health related quality of life. One study measured mood as a secondary outcome. Follow up differed in all three studies, from twelve weeks to twelve months.

A summary of each study is presented in appendix I. Further details are provided below, including study characteristics, findings, and an appraisal of the methodological issues which may have led to bias.

Hartvigsen et al (2010) investigated the effect of Nordic walking in 136 individuals who had been referred to a low back pain clinic with pain of at least eight weeks duration. Treatment group (A) (n= 45) engaged in 45 minutes (average) of supervised Nordic walking twice per week for eight weeks and were compared to two control groups: group B (n=46) who self managed Nordic walking for eight weeks after a single hour of instruction, and Group C (n=45) who received written advice on exercise only. Exercise levels were determined by the instructor who wore an accelerometer for the first two sessions and the average pace achieved determined the pace set for future sessions. Recruitment occurred through a secondary care back pain clinic in Denmark. Outcomes included pain as measured by the Low Back Pain Rating Scale (LBPRS), and Quality of Life measured by the EQ-5D three point scale. Outcomes were measured at three time points: post intervention (10 weeks), 26 and 52 weeks. Findings were that there were within group improvements in low back pain as measured by the LBPRS in all groups at all time points, with the largest effect seen in the Nordic walking group (8.8 supervised Nordic walking; vs 3.4 unsupervised Nordic walking; vs 4.8 advice to remain active). However, these improvements were only statistically significant in the intervention group. No statistically significant differences in pain were found between the groups at any time points. There were very small mean changes in health related quality of life described in all groups, although figures were not given in the paper.

The study size was small, with less than 50 participants per group. Allocation concealment was performed using sealed opaque envelopes; however these were arranged in clusters of fifteen which could have led to the ability to predict future allocations. Measures of exercise adherence were not reported. Furthermore, sample measurements of physical activity levels during weeks four and five using accelerometers revealed there was no observed difference in activity between group A and group B during this period. This might mean that there was exercise contamination of the

comparator, or a lack of prescribed activity in the supervised Nordic walking group. Exercise diaries may have discriminated between these two factors, but were not part of the research design. This may have explained the within group improvements in back pain but lack of statistically significant difference between groups. It is therefore difficult to ascertain whether the within group improvement in back pain and quality of life were due to exercise, or a therapeutic effect due to participant involvement with exercise therapists during the study. No adverse effects were reported with those participants in the study, however, safety issues were not commented upon. Attrition was acceptable at 7%, and was reported to be primarily due to difficulties complying with the intervention schedule.

Mannerkorpi et al (2010) investigated the effect of Nordic walking in 67 women with fibromyalgia, using a randomised controlled design. The treatment group (*n*=34), who completed 20 minutes of supervised moderate to high intensity supervised Nordic walking (within a 45 minute session) twice per week for fifteen weeks, were compared to a control group (*n*=33) who carried out one session of low intensity exercise per week. There was no untreated control group. Outcomes measured included pain using the Fibromyalgia Impact Questionnaire (FIQ) pain score, activity limitation using the FIQ physical subscale and health status using the FIQ total score. Outcomes were measured at baseline, post intervention (16 weeks), and at 6 months. No difference in self-reported pain was found between groups at completion of the intervention at 16 weeks (-4.0 (14.5) vs -5.3 (16.3), or at a six month follow up point. There were however within group improvements in pain in both groups following the intervention, although these were not statistically significant. Post intervention there was a significant improvement in activity limitation in the intervention group compared to the control group (FIQ physical -7.9 (12.6) vs1.3 (15.6)), and although not reaching significance, this was reflected in the overall health status of the intervention group as measured by the FIQ total (change = -4.8 vs1.9), which also improved. However, these effects were not sustained at six months follow up. In terms of safety, one patient interrupted the exercise programme due to chronic trochanteritis, which became worse after a few exercise sessions and it is possible this could have been related to exercise. An increase in post exercise pain was experienced after the initial phase of the exercise programme in both the treatment and control group. This is an expected and recognised phenomenon in the fibromyalgia population, and was managed with analgesia and a reduction in walking speed until pain was controlled.

The study size was small, with less than 50 participants per group. Statistical power was described for one of the primary outcomes although not for the outcomes of interest for this review, therefore may not have been powered to detect significant differences in these. In terms of potential bias, inclusion criteria included an age cut off of 60 which could have led to selection bias and future problems with generalisability. Allocation concealment was performed and baseline measures were taken by examiners blinded to treatment allocation, although no comment was made as to whether

follow up outcome assessments were also blinded. There was a wide variation in baseline pain scores which could have led to a dilution in treatment effect post intervention. Adherence in both the intervention and control groups was low at 62% and 52% respectively, and this also could have led to reduced treatment effect. There was a 13% attrition rate, and although intention to treat analysis was described, this was not evident from the flow diagram, which described analysis of data from people completing the study only. This could have led to a bias in outcomes from those benefiting from the intervention.

Strombeck et al (2007) undertook an RCT to test the effect of a Nordic walking intervention on aerobic capacity and fatigue in 21 women aged 21-45 with Sjogren's syndrome, a type of rheumatic disease. Women in the intervention group (*n*=11) completed three x 45 minute sessions of Nordic walking per week for twelve weeks and were compared to a control group (*n*=10), who were instructed in range of movement exercises to be carried out at home three times per week. The intervention group had one 45 minute supervised Nordic walking session per week and was asked to complete two more 45 minute sessions independently at home per week. They wore heart rate monitors and were told to exercise for 8 weeks at 60-70% of age predicted maximum heart rate (220-age of individual) and then at 70-80% of age predicted maximum for the remaining 4 weeks. Logs of exercise duration, average heart rate and perceived exertion were kept by the participants. Primary outcomes were fatigue as measured by the Profile of Fatigue questionnaire, and aerobic capacity as measured by VO_2 max. Secondary outcomes measured included depression as measured by the Hospital Anxiety and Depression Scale (HADS) and health related quality of life (HrQoL) as measured by SF-36, which were taken post intervention at twelve weeks. Baseline data for outcome measures were not presented in the paper. No statistically significant difference was reported for total health related quality of life between the Nordic walking group and those carrying out range of movement exercises post intervention. However, there was a statistically significant improvement in physical function as measured by the subscale of the SF-36 in the treatment group. There was no change in bodily pain measured as a subscale of the SF-36, although this was not commented on in the text and as baseline measures were not described in the paper, this could not be confirmed. Depression scores were significantly reduced in the Nordic walking group compared to control (p=0.02) as measured by the HADS scale, although this contradicted findings from the mental health subscale of the SF-36, which deteriorated within the treatment group.

In terms of methodological limitations, the sample size was very small and powered only to detect a difference in aerobic capacity (as measured by VO_2 max), and not powered to detect changes in depression, pain or quality of life scores. Therefore, although depression scores were seen to reduce in the Nordic walking group compared to control, this could be a false positive finding due to the small sample size and should be interpreted with caution. In addition there was a within group deterioration in the mental health subscale of the SF-36 which is contradictory. Those assessing

objective outcome measures were blinded to treatment allocation. Random sequence generation and allocation concealment was not performed. Attrition was 10% which was acceptable; however both drop outs (2/11) were in the treatment group which may have led to performance bias. The drop outs were not due to injury and no safety issues were highlighted during the study although these were not specifically commented upon.

3.4.4 Summary of Nordic walking for chronic musculoskeletal conditions

This literature review revealed that there are very few randomised controlled trials exploring the effect of Nordic walking as a specific form of exercise in chronic musculoskeletal conditions, with only three studies identified across three very different populations. Furthermore, these studies had small samples (all less than 50 per group), and none evaluated the effect of Nordic walking on osteoarthritis or rheumatoid arthritis, which may most closely resemble the syndrome of AIAA.

The interventions used in the studies shared some similarities, such as all including elements of supervised group Nordic walking, but were different in terms of exercise dose and length of the intervention. Therefore, it was not possible to establish which elements influenced effectiveness or adherence.

While none of these three studies showed a significant improvement in pain or quality of life compared to control, none were adequately powered. Furthermore, all had control groups which carried out exercise, so all groups showed an improvement in pain.

There was a high risk of methodological bias across all studies, as judged by Cochrane Handbook criteria (appendix II; Higgins *et al.*, 2011) In particular, there was a lack of blinding of assessors and participants, although this is a common predicament in exercise studies using patient reported outcome measures. In addition, randomisation methods and allocation concealment were inadequately described or not present, and there was no evidence of intent to treat analysis despite all three studies being RCTs. A large variation in pain scores at baseline (Mannerkorpi *et al.*, 2010), exercise contamination in the comparison group in two of the studies, and poor adherence to exercise interventions may have diluted the effect on outcomes post intervention. Exercise diaries were not kept in two of the studies. This information may have added useful information with regard to physical activity undertaken during the study.

Safety issues were not formally reported on within the three studies. However, there were only reports of one dropout in one study due to injury (Mannerkorpi *et al.*, 2010) which could have been related to the exercise. Therefore from the limited information available, Nordic walking appeared to be well tolerated and safe for the remainder of the participants in the studies reviewed.

These studies have raised practical considerations which provided useful information to inform the design of future research. Firstly, safety issues should be methodically reported. Other recommendations include that allocation concealment and randomisation methods should be clearly described to facilitate estimation of bias. In addition, it is recommended that a usual care control group be used as a comparator, as in two of the studies, the control groups had some form of prescribed physical activity which may have contributed to a lack of 'between group' differences. However, it is recognised that a usual care control group may still undertake exercise (as it would be unethical to stop them from doing so), and thus it is recommended that activity levels during the intervention period be systematically recorded in both intervention and control groups with an exercise diary. Finally, no reduction in adherence was observed in the study with an element of self managed Nordic walking, suggesting this would be feasible in a future study.

3. 5 Conclusions.

There is insufficient evidence in the current literature to determine whether Nordic walking improves pain and related biopsychosocial outcomes in people with chronic musculoskeletal pain. However, this is likely to be due to the limitations of the research available to date. Firstly, there were only three studies identified for inclusion in this review. Secondly, the methodological issues and small sample sizes in all three studies limit the internal and external validity of these studies. Finally, due to differences in underlying pathophysiological mechanisms contributing to fibromyalgia, Sjogrens syndrome and chronic low back pain, caution must be taken when generalising findings from these studies to women with AIAA.

However, as previously discussed, there is platinum based evidence to support the use of aerobic exercise in general to reduce pain in musculoskeletal conditions (Fransen and McConnell, 2008). In addition, justification has been given as to why Nordic walking in particular might reduce joint pain using a biopsychosocial model, by reducing joint loading, improving muscular endurance and strength, improving mood and providing an opportunity for social support. There is also preliminary evidence suggesting exercise may help women with AIAA as discussed in section 2.10.1 (Irwin *et al.*, 2013) and that exercise interventions can increase activity in this population (Nyrop *et al.*, 2013).

Furthermore, there is now widespread evidence of the benefits of exercise in populations with cancer generally (Speck *et al.*, 2010), with most research carried out in those with breast cancer. This makes the testing of an exercise intervention for AIAA more desirable and acceptable as there may be additional benefits to individuals. The evidence on exercise in people with cancer and breast cancer is considered below.

3.6 Exercise and cancer

There is evidence to suggest that exercise can enhance quality of life (Speck *et al.*, 2010) and improve survival (Ballard-Barbash *et al.*, 2012) in people with cancer, as well as having a low incidence of adverse effects and good acceptability (Maddocks *et al.*, 2009). A systematic review and meta-analysis of controlled trials examining physical activity interventions in cancer survivors during and post treatment revealed important benefits (Speck *et al.*, 2010). These include a large effect on upper and lower body strength, moderate effects on fatigue and breast cancer specific concerns; as well as small to moderate effect sizes for physical activity levels, aerobic fitness, muscular strength, functional quality of life, anxiety and self esteem. The review by Speck et al (2010) also explored safety aspects and found that there was a low incidence of adverse events related to exercise. A systematic review of studies examining the relationship between physical activity and cancer survival/related biomarkers, has found consistent evidence that physical activity is associated with a reduction in all cause breast and colorectal cancer specific mortality (Ballard-Barbash *et al.*, 2012). Postulated mechanisms include an effect on circulating insulin, insulin-related pathways, inflammation and possibly immunity. A further systematic review examined the acceptability of exercise in people with or cured of cancer in 65 studies involving 7224 participants, the majority of which were in populations with breast cancer (Maddocks *et al.*, 2009). The authors of this review found that rates of uptake and completion were acceptable (63% (IQR 33-80%) and 84% (IQR 72-93%) respectively).

As a consequence, national cancer strategy now recommends physical activity into rehabilitation after cancer (Department of Health, 2011a), and the National Cancer Survivorship Initiative has fostered the development of self management programmes incorporating physical activity programmes as key components (Davies and Batehup, 2010) .

3.7 Exercise and breast cancer

The benefits of physical activity in people with breast cancer include research demonstrating improvements in physical fitness (Courneya *et al.*, 2007b), health related quality of life (Courneya *et al.*, 2003; Daley *et al.*, 2007c; Mutrie *et al.*, 2007; Milne *et al.*, 2008); self esteem (Courneya *et al.*, 2007a); mood (Mutrie *et al.*, 2007), and reduction in fatigue (Mock *et al.*, 2005; Milne *et al.*, 2008). Furthermore these benefits have been demonstrated both during adjuvant therapy (Courneya *et al.*, 2007a; Cadmus *et al.*, 2009) and after. Results from large observational studies also suggest that regular exercise can bring about reductions in mortality and recurrence rates (Holmes *et al.*, 2005; Irwin *et al.*, 2008b; Sternfeld *et al.*, 2009; Irwin *et al.*, 2011).

It is clear, therefore, that in people with breast cancer, exercise is acceptable, carries a low risk of harm, and has many benefits, bringing extra value to the proposal of testing an exercise

intervention in this population. There does however, remain a gap in the research as to whether Nordic walking as a specific form of aerobic exercise might be suitable in women with AIAA particularly in terms of safety and acceptability. The next chapter will describe the development of the Nordic walking intervention, with a rationale given for the design of its components in order to maximise effect, acceptability and adherence.

Chapter 4. Development of the Nordic walking intervention

The next chapter provides an account of how the Nordic walking intervention was developed. Justification is given for how specific components were designed to maximise effect, acceptability and adherence, based on behavioural change theory, and evidence from previous research.

4.1. Behavioural change theory

Adherence to exercise can be a challenge, particularly in individuals who have not previously been active. Interventions which are based on a theory of behavioural change may be more successful in achieving adherence (Markes *et al.*, 2006). Three of the most widely used theories include the theory of Planned behaviour (TPB) (Ajzen, 1991) , the Stages of Change Trans-Theoretical model (TTM) (Prochaska and Velicer, 1997) and Social Cognitive Theory (SCT) (Bandura, 1995).

In brief, The Theory of Planned Behaviour examines the relationship between an individual's beliefs, attitudes, intentions, behaviour, and perceived control over that behaviour. It has been used to explain exercise behaviour in general and specifically in cancer populations (Blanchard *et al.*, 2002). The Trans-theoretical model also describes an individual's motivation and readiness to change a behaviour, however, this model asserts that behaviour change is a process, and as a person attempts to change a behaviour, he or she moves through five stages: pre contemplation, contemplation, preparation, action, and maintenance (Glanz and National Cancer Institute (U.S.), 2005). Social Cognitive Theory states that human behaviour is a product of interactions between personal, behavioural and environmental influences, referred to as 'reciprocal determinism' (Bandura, 1977). Both the TPB and TTM models focus on individual behaviour change, whereas SCT is based on an understanding of how not only individuals but also groups and societies function and adapt (Glanz *et al.*, 2008).

These three theories have been used in previous exercise interventions to examine factors which may affect adherence in cancer populations. A systematic review (Husebo *et al.*, 2013) found that factors predicting exercise behaviour included exercise stage of change from the TTM model, 'intention to engage in a health changing behaviour' and 'perceived behavioural control' from the TPB model, although associations were relatively weak. However, only one of the twelve trials included in this review examined Social Cognitive Theory as a predictor for exercise. Further studies have found Social Cognitive Theory to be helpful in understanding behavioural change in exercise. For example, a study directly comparing Social Cognitive Theory and the Theory of Reasoned Action (TRA; a precursor to TPB) in 328 undergraduates found that two constructs from Social Cognitive Theory, self efficacy and outcome expectations, were better at predicting exercise behaviour than TRA (Dzewaltowski, 1989). Furthermore, a cross sectional survey of 21 women undergoing breast cancer treatment found that aspects of Social Cognitive Theory predicted higher

daily energy expenditure (Rogers *et al.*, 2005). Although limitations of this study include a small sample, convenience sampling and non-randomised controlled design, findings from a larger longitudinal study of 321 middle to older age adults also found that Social Cognitive Theory was useful in predicting physical activity behaviour (White *et al.*, 2012). Self-efficacy influenced physical activity both directly and indirectly via outcome expectations, suggesting that these variables should be targeted in physical activity interventions for middle-aged and older adults.

4.1.1. Social Cognitive theory

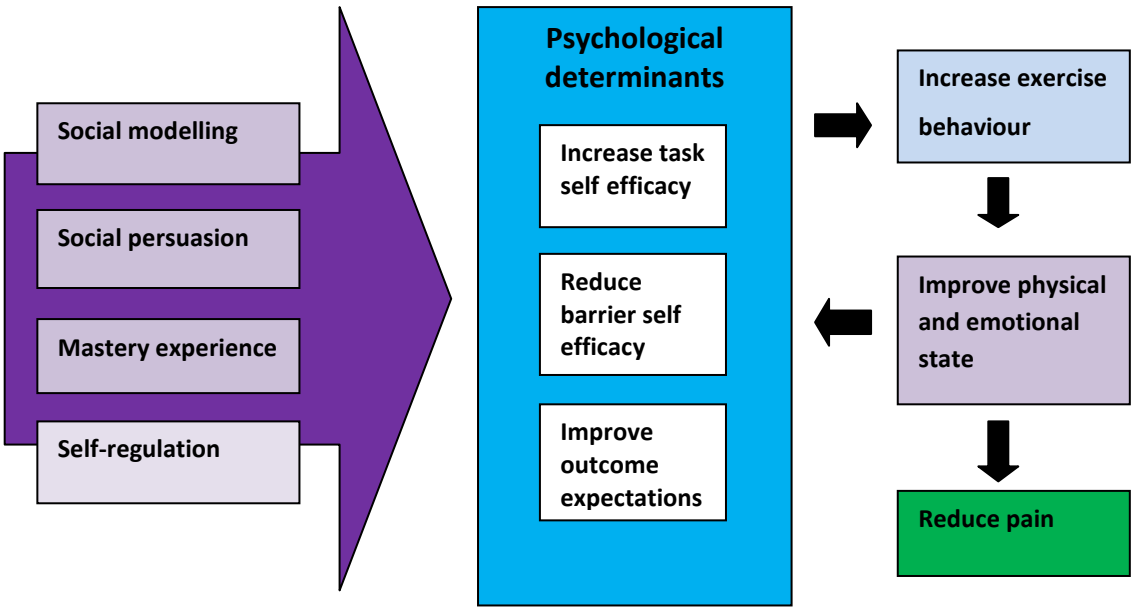
Social Cognitive Theory was selected as the framework to underpin this intervention, as it is an interpersonal theory, and therefore has more relevance where people are interacting with others as part of that intervention. It provides a well elaborated conceptual framework for understanding factors which influence human behaviours and the processes through which learning occurs. Its central construct is self-efficacy, i.e. an individual's confidence in their ability to execute certain behaviours. Self-efficacy can be further split into two components; task self-efficacy, i.e. the confidence in one's ability to execute tasks to achieve goals, and barrier self- efficacy, confidence in the ability to overcome barriers to achievement. Social cognitive theory has been used as the basis for many self management interventions in cancer care, on the basis that it can help to shape interventions targeted at increasing self efficacy (Davies and Batehup, 2010). Research has demonstrated that increasing self-efficacy is a central mechanism which can facilitate behavioural change; and that this in turn can be modified through factors which include:

- Mastery experience: enabling the individual to achieve progressively more challenging goals;
- Social modeling: the process whereby people learn through the experience of credible others;
- Improving physical and emotional states.
- Social persuasion. (realistic encouragement)

(Wood and Bandura, 1989)

Behavioural changes are achieved through a series of small and easily mastered steps. A therapist's guidance is required at first; however, this is gradually replaced by 'self-regulation' as the individual learns to master each step towards the desired behaviour. These aspects of Social Cognitive Theory were synthesised with Biopsychosocial Theory and used to develop a conceptual framework for the Nordic walking intervention (figure 4.1); and shaped components of the intervention, as described in section 4.2. It is theorised that increased exercise behaviour will lead to improved physical and emotional state as per the biopsychosocial theory described in section 2.1.3; which in turn provides positive feedback to increase task self efficacy and outcome expectations, and reduce barrier self efficacy.

Figure 4.1. Theoretical Framework for the Nordic walking intervention incorporating Social Cognitive Theory and Biopsychosocial model of pain



4.2 Components of the intervention

A twelve week Nordic walking intervention was developed, consisting of a supervised group training period in weeks 1-6, with gradually increasing exercise volume, followed by six weeks of self-managed Nordic walking for 30 minutes, four times per week.

4.2.1. Length of intervention

There is no consensus on what constitutes an optimum total duration for an exercise intervention programme in populations with cancer (Markes *et al.*, 2006). However, a systematic review aimed to establish the most effective exercise parameters in breast cancer populations by only including those studies where improvements in health related quality of life were demonstrated (Pastakia and Kumar, 2011). Nine randomised controlled trials from 1999 to 2009 were included in the review. Durations of between 8-24 weeks had the biggest effect on outcomes. A further consideration in exercise studies should be that in order to minimise burden on participants, the intervention should be designed for the shortest duration possible to achieve an effect. Therefore, a twelve week Nordic walking intervention was designed, to allow time for the participants to acquire the technique of Nordic walking and undertake a period of aerobic exercise anticipated to be long enough to achieve an effect. This consisted of an initial supervised training programme of six weeks duration:-four

weeks to learn the Nordic walking technique as recommended by Nordic walking UK (Stewart, 2014), followed by two weeks consolidation; and then six weeks of self managed Nordic walking,

4.2.2. Supervised exercise

A systematic review of exercise interventions in musculoskeletal populations suggests that supervised exercise can improve adherence compared to non supervised exercise (Jordan *et al.*, 2010). This finding is also supported in a systematic review of factors affecting adherence in cancer populations (Husebo *et al.*, 2013), although the difference in adherence between supervised and non-supervised interventions was minimal (70.5% vs 67.5%). Therefore, for weeks 1-6 of the intervention, a six week hour long supervised group training period was developed. The hour included Nordic walking, and warm up (ten minutes)/cool down (ten minutes) exercises, and was standardised for each of the two groups of ten. Six weeks supervised training was thought long enough to allow women to feel confident and competent in the Nordic walking technique ('mastery experience') and thereby would increase self-efficacy, which is an important part of Social Cognitive Theory.

4.2.3 Group intervention

There is conflicting evidence regarding the effectiveness of group versus individual instruction in exercise interventions. A meta-analysis testing whether group versus individual exercise interventions improved quality of life in women with breast cancer found there was no difference in quality of life between group and individual interventions (Floyd and Moyer, 2009). However, the authors, who examined eighteen studies in total, concluded that this could have been because the studies included did not maximise group processes which might have led to improved psychosocial outcomes. In contrast, two studies with qualitative components in their design have revealed benefits with group interventions. A mixed methods study exploring group exercise in 55 people with advanced cancer found that group exercise brought about improvements in mental, social and emotional functioning, as well as developing an 'esprit de corps' and 'purposeful togetherness' in study participants (Midtgaard *et al.*, 2006). In women with breast cancer, a focus group study exploring the experiences of 37 women who had taken part in a supervised group exercise study, found that participants enjoyed exercising with others 'in the same boat'; that they were motivated by seeing others and the trainer exercise; and that they benefited from social interaction with an 'upbeat' context (Emslie *et al.*, 2007). Therefore, in view of the lack of clarity regarding this component, and using aspects of social cognitive theory, a combined approach was taken for the Nordic walking intervention. A group format was designed for the first six weeks to allow for 'social modelling. In other words, as well as observing the instructor, group training gave participants the chance to see that others like themselves could do it (Glanz *et al.*, 2008), thereby increasing self-efficacy. The second six weeks of self managed exercise encouraged self –

regulation. Of particular importance, the Macmillan physical activity diaries encouraged participants to evaluate their achievements to goals set hopefully leading to further self motivation.

4.2.4 Instructor

The same Nordic walking instructor was used throughout to ensure consistency and improve the integrity of the intervention. The training programme, led by the instructor, built up the components of Nordic walking through a series of small and manageable steps each week, to increase self-efficacy. He also provided encouragement ('verbal persuasion') for women to persevere and information on the benefits of Nordic walking. The instructor was experienced in training people in Nordic walking technique and held a level two Nordic walking Central YMCA Qualification (CYQ) as well as a level three qualification in personal training and first aid. He had previous experience training groups of women with breast cancer at the trial centre.

4.2.5 Graded activity

Graded activity can be more effective in increasing adherence to exercise interventions than standard care (Jordan *et al.*, 2010). This also fits with the concept of 'mastery experience' in social cognitive theory i.e. by facilitating individuals to achieve progressively more demanding physical activity, self-efficacy can be increased. This is demonstrated in a previous study which found that graded 'exercise quotas' increased physical activity and expectancies about capability whilst reducing avoidance behaviour and worry about exercising (Dolce *et al.*, 1986). Although this is an old study, findings have been replicated in a more recent study in patients with chronic low back pain (Kernan and Rainville, 2007). Therefore, within the first six weeks whilst undergoing groups supervised training, participants were asked to gradually increase the number of Nordic walking sessions per week. In addition, graded activity was considered important as this group of women were on average older than those usually recruited to exercise studies and thus might be less fit. Specifically, during weeks 3-4 of training, the participants were asked to add in a second session per week of training, and during weeks 5-6 participants were asked to add in a third session of Nordic walking per week. At the end of the six week period, participants were competent to undertake Nordic walking independently as assessed by the Nordic walking instructor.

4.2.6 Self-management/'self-regulation'

Social Cognitive Theory claims that as people become competent in a technique, they should be encouraged to self-direct their own behaviour change. This is because acquiring skills to self-manage, and subsequently setting one's own goals and rewards, can help individuals to endure short term negative outcomes to achieve long term positive outcomes, increasing self-efficacy (Wood and Bandura, 1989). This concept, known self-regulation, is similar in principle to the self-management model developed by Lorig and colleagues which has been demonstrated to be an effective way to manage chronic conditions such as arthritis (Bodenheimer *et al.*, 2002) . Furthermore, it is a concept that is being recommended to improve wellbeing in cancer survivors,

and a variety of self management models are being developed and tested within cancer populations (Davies and Batehup, 2010). Providing exercise diaries for the participants to self-monitor physical activity was part of the self-regulation process. As well as increasing self efficacy, a self-managed exercise component would also maximise flexibility, which has been shown to be important for breast cancer survivors considering an exercise schedule (Irwin *et al.*, 2008a). Therefore for weeks 7-12, participants were asked to complete 4 x 30 minute sessions of 'self managed' Nordic walking per week.

4.2.7 Exercise dose

Current recommendations from the Department of Health (2011b) are that individuals should try to engage in at least 150 minutes of moderate intensity activity per week. These guidelines are the same as those provided by the American College of Sports Medicine, who state that individuals with cancer should aim to carry out similar levels of activity to those of healthy adults of the same age (Schmitz *et al.*, 2010). It is also agreed that these levels are suitable for people with musculoskeletal conditions (Arthritis Research UK, 2014).

However, Pastakia and Kumar (2011) concluded in a review of breast cancer quality of life studies that the most effective exercise dose was a frequency of three times per week, at moderate intensity (50–70% of maximal heart rate); for at least 30 minutes.

Therefore the exercise dose was set at 30 minutes, four times per week, which was mid way between national recommendations and results from Pastakia et al's (2010) review. This 'exercise dose' is also in line with recommendations that to achieve an endurance effect, the participant needs to engage in 15-60 minutes of continuous aerobic activity three to five times per week at sufficient intensity to raise the heart rate to 60-90% of maximum. Short, frequent sessions are recommended in deconditioned people, and these can be as effective as equal amounts of sustained activity (Pollock and Wilmore, 1990). See figure 4.2.

4.2.8 Intensity

There is general consensus that moderate aerobic activity is required to achieve therapeutic effects (Pollock and Wilmore, 1990). Contrary to this opinion, a Cochrane Review of studies examining the effect of differing intensities of physical activity on joint pain in people with OA concluded that both high and low intensity aerobic exercise are equally effective in improving a patient's functional status, gait, pain and aerobic capacity (Brosseau *et al.*, 2003a). However, only one study involving 39 participants fulfilled inclusion criteria in this systematic review, therefore further research would be required to further support these findings. Therefore moderate intensity activity was recommended for this intervention. Participants were instructed on how to achieve the desired exercise intensity using the Borg scale of perceived exertion (Borg, 1982). This is a widely tested fifteen point exercise exertion scale ranging from six to twenty (appendix IV). It can be used as a

proxy measure to estimate heart rate and level of exertion (Utter *et al.*, 2011). Level eleven to thirteen is equal to an endurance of moderate intensity.

4.2.9 Other components

A review of exercise parameters in effective breast cancer exercise trials demonstrated that aerobic only, and aerobic and muscle strengthening interventions can be effective in improving quality of life (Pastakia and Kumar, 2011). Although Nordic walking is predominantly an aerobic exercise, there is evidence that it can also improve muscular endurance and strength as described in section 2.14.2 (Sprod *et al.*, 2005; Malicka *et al.*, 2011).

Figure 4.2 Graph demonstrating graded Nordic walking intervention exercise dose.

Session frequency	Supervised group Nordic walking training						Self-managed Nordic walking.					
4												
3												
2												
1												
Week no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**

The Nordic walking intervention described above was therefore deemed suitable for use in a study for women with AIAA. However, due to the lack of evidence of acceptability in breast cancer populations, it was first necessary to determine whether women with AIAA in the UK were willing to be recruited into to the Nordic walking exercise intervention and would adhere to it. Also aside from data on lymphoedema, data regarding overall safety of Nordic walking in women with breast cancer has not been reported in previous studies. Therefore a feasibility study was necessary before testing the intervention for effectiveness. The research design and methods used to test feasibility will be discussed in the next chapter.

Chapter 5: Methods

5.1 Rationale for research methodology and design

The Nordic walking intervention was considered complex as it contained a number of interacting components and therefore fulfilled the Medical Research Councils criteria for a complex intervention (Craig *et al.*, 2013). These included the type of exercise, the exercise dose (frequency /duration), and the mode of delivery (supervised and independent, group/ individual), all of which had the potential to exert their own effect on the outcomes being measured.

In their guidelines on the development of complex interventions, The Medical Research Council (MRC) advise that these should undergo a systematic development phase, starting first with a detailed review of available evidence followed by a phased testing approach, starting with preliminary studies which test uncertainties in the study design (Craig et al., 2013). This preliminary testing phase helps to establish whether the intervention can be delivered as intended, before testing it for effectiveness. It also is important to ascertain whether the intervention can work in everyday practice. A review of the available evidence was undertaken in chapters 2-4, in order to develop an intervention that might benefit women with AIAA. Findings suggested that although Nordic walking might produce a positive effect on joint pain, preliminary research was first required to test whether a Nordic walking intervention was acceptable and safe in women with breast cancer and joint pain. Thus the research question arrived at was:

'Is it feasible to conduct a trial testing the effectiveness of a Nordic walking intervention in women with AIAA?'

Specifically, it was important to establish a) whether it would be possible to identify and recruit women with breast cancer to an exercise intervention when they also have joint pain and stiffness, b) whether they would carry out Nordic walking at the prescribed duration and frequency, c) to evaluate the safety of the intervention, and d) to obtain crucial information about study processes to inform a future definitive trial.

Preliminary studies are often defined as 'pilot' or feasibility'. The differences between feasibility and pilot studies are debated by Arain et al (2010), who found in their review that that many preliminary studies fail to distinguish between the two. However, The NIHR Evaluation, Trials and Studies Coordinating Centre provide useful clarification and suggest that whereas feasibility studies are pieces of work done before the main study to test important parameters needed to design the main study; pilot studies are a version of the main study run in miniature, to test whether all components work together (NETSCC. 2011).

The gold standard to test cause and effect is an experimental design, with the randomised controlled trial as the optimum design to minimise bias (Bowling, 2009). Therefore the preliminary study would test the feasibility of a randomised controlled trial as the design.

As the effects of Nordic walking in women with AIAA were unknown, a research design was required which allowed comparison between the intervention and usual care. Therefore a control group of women not exposed to the Nordic walking intervention was included in the design. Comparison to the correct type of control group is essential in randomised controlled trial designs to reduce the variability of factors which might introduce bias into results (Lindquist *et al.*, 2007) . To improve internal validity in this study, a comparison group was employed which would be exposed to the same input from the research team as the intervention group wherever possible, apart from the Nordic walking intervention itself. Including a control group was considered an essential part of feasibility testing, as many previous exercise studies have found exercise contamination is encountered within the control group, in other words, that the control group increased their level of activity (Pickett *et al.*, 2002; Mock *et al.*, 2005). To monitor for this in my feasibility study, women in the control group were also asked to record their physical activity in an exercise diary.

Randomisation was employed to test out the acceptability of this process in a group of women with the potential to access Nordic walking as part of their breast cancer rehabilitation. To attenuate the ethical dilemma of randomising participants to no intervention (control), a waiting list control group was utilised, so that the control group could receive the intervention at the end of the study.

The next section will set out the aims and objectives of this feasibility RCT, in addition to the methods used to collect data.

5.2 Aims and objectives

Aim:

To explore the feasibility of a trial testing a Nordic walking exercise intervention for women complaining of joint pain and stiffness whilst on AI treatment

Objectives

1. Establish recruitment rates to determine:
    a. effectiveness of recruitment strategy (sampling and screening tool)
    b. feasibility of eligibility criteria
    c. demand for the intervention
    d. time needed to recruit target sample size
    e. feasibility of recruiting a representative sample
2. Determine acceptability of Nordic walking intervention schedule through
        a. Attrition
        b. Adherence to specified exercise dose
        c. Questionnaire survey responses
3. Describe and quantify safety issues or untoward consequences
4. Ascertain suitability of research methods for use in future RCT, to include:
    a) Permuted blocks randomisation
    b) Enhanced usual care control group
    c) Acceptability/burden of proposed outcome measures (questionnaire response rate and completion)
    d) Proposed outcome measures
5. Describe the effect of NW intervention on outcomes

5.3. Design

A feasibility study using a small scale randomised controlled trial design with waiting list control was used. Participants either received a twelve week Nordic walking intervention or enhanced usual care as a waiting list control.

5.4. Participants and setting

5.4.1 Inclusion criteria

Postmenopausal women with early breast cancer, taking one of the AIs as adjuvant endocrine therapy (anastrozole, letrozole or exemestane) with joint pain, as indicated by the amended Checklist for Patients on Endocrine Therapy (C-PET) questionnaire, appendix IX; fulfilled the inclusion criteria for this study. Women were recruited from a single site, Poole Hospital NHS Foundation Trust (PHFT).

5.4.1. Exclusion criteria

Patients were excluded if:

- diagnosed with metastatic disease
- failed Physical Activity Readiness to exercise Questionnaire (PAR-Q; appendix V) by answering 'yes' to any of the questions, and not felt by their GP to be safe to undertake Nordic walking
- unable to understand written English
- undertaking Nordic walking as part of the breast cancer weight management programme

5.5 Recruitment

The following systematic screening process was employed to minimise bias by targeting the majority of women with AIAA treated at PHFT, i.e. population based sampling.

Data on the side effects of endocrine therapy are routinely collected on women attending the breast cancer follow up clinic at PHFT to facilitate management (amended C-PET questionnaire, (Hopwood, 1996); appendix IX). Patients taking an AI and reporting joint pain and or stiffness on the amended C-PET questionnaire from January 2011 to January 2012 were sent written participant information sheet (appendix VI) by their treating consultant inviting them to enter the study in January 2012. If the women wished to take part in the study they were asked to return a form giving consent to share data from the amended C-PET questionnaire with the researcher. On return of the consent form, the researcher contacted the patient to confirm initial eligibility by checking they still had joint pain and/or stiffness, and if so arranged a baseline visit with the researcher. See figure 5.1.

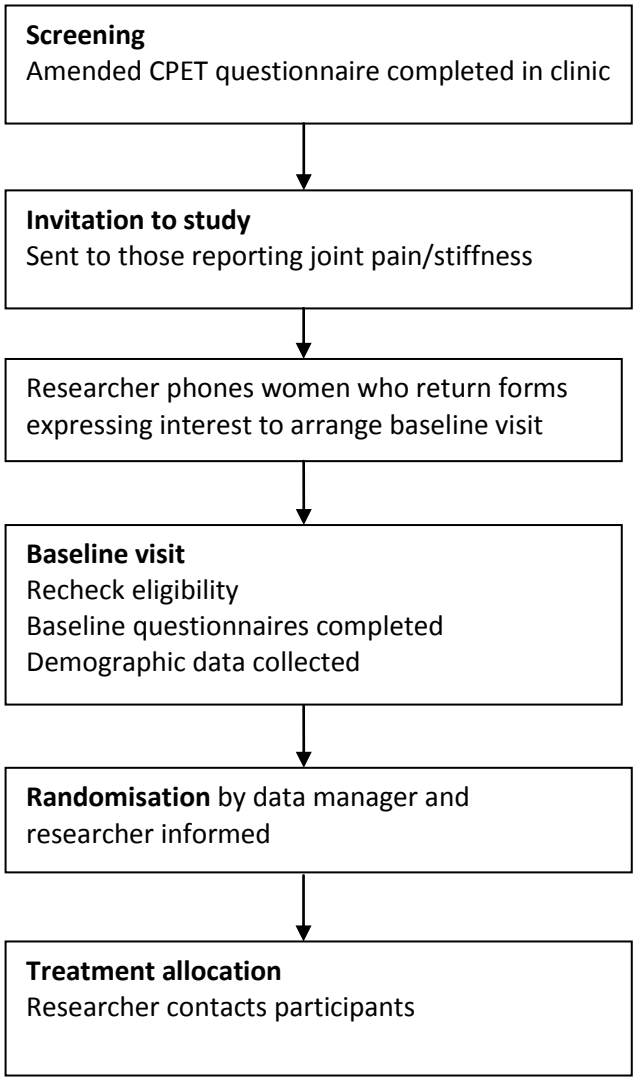
5.6. Baseline visit/data collection

At the baseline visit further information regarding the study was provided, including explanation of the two treatment allocations and the procedure for randomisation and outcome data collection. Written informed consent was taken. Only women fulfilling the inclusion criteria proceeded to randomisation. Numbers were kept of those who were ineligible and reasons why.

5.7 Randomisation

Participants were randomised by a data manager at the trial centre with no other involvement in the research study, to either intervention or waiting list control. A random permuted blocks method with block size of twenty was used to ensure a more even distribution of group size in smaller samples (Pocock, 1983). All participants were randomised simultaneously at the end of the twelve month recruitment period in order to facilitate the allocation of participants into two groups of ten for the supervised Nordic walking training which formed the first part of the intervention. Following randomisation, the data manager informed the researcher of the randomisation outcome,

Figure 5.1: Recruitment process



and then participants were contacted by phone by the researcher to inform them of their allocated study group.

5.8 Treatment of participants

During the data collection period, all participants were contacted by phone every two weeks by the researcher to check for attendance, and provide support and encouragement. An additional purpose of this contact was to collect data on safety aspects of the trial by checking for new symptoms of injury, lymphoedema and pain. These were systematically recorded and action taken as per the risk management flow chart in appendix IX.

5.8.1 Intervention group

The underlying rationale for the components of the Nordic walking intervention was discussed in chapter 4. Specific details of the twelve week Nordic walking intervention received by participants is provided below.

During weeks 1-6, a supervised group training period was provided, comprising one hour Nordic walking per week for six weeks with a trained Nordic walking instructor. The same instructor was used for all sessions to maximise consistency of the session content, and also so that participants were exposed to the same therapeutic relationship. The instructor was experienced in running previous Nordic walking training sessions for women with breast cancer.

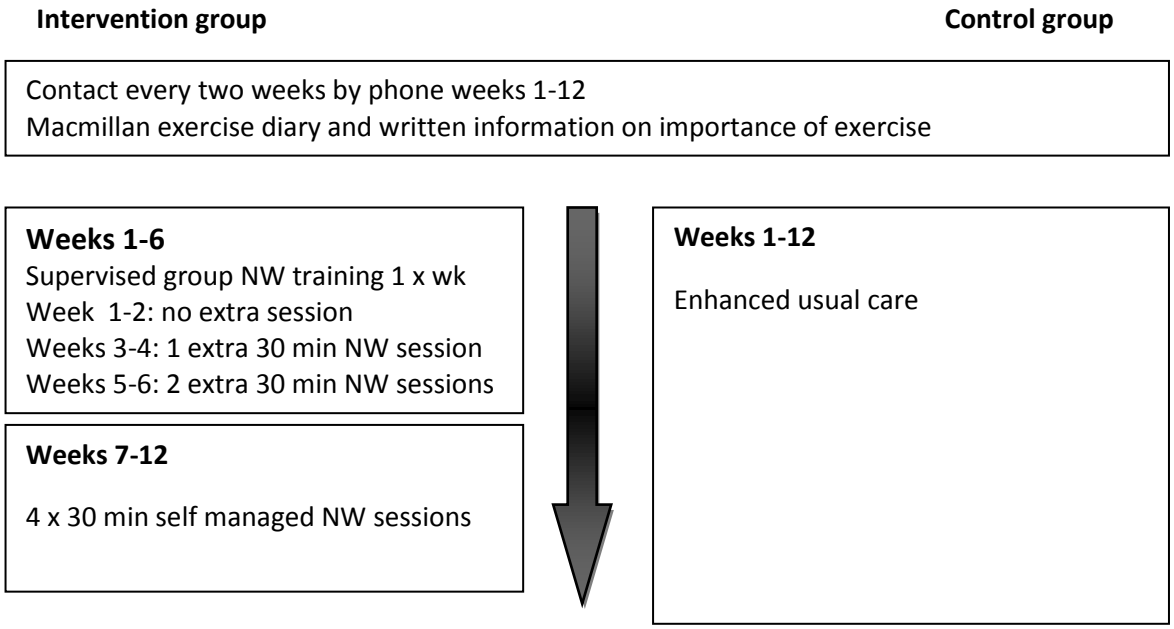
All sessions were carried out outside, in two country parks local to the hospital where participants had been treated. Spring/summer was chosen to carry out the study to maximise the chance of good weather conditions. Consideration was given to access and so these locations were chosen on the basis that they had car parks and good public transport links. Participants were asked to provide their own transport to the intervention, but were provided with Nordic walking poles (Leki Supreme), which they were allowed to keep after the study had finished. A choice of two times was given for the session, either afternoon (2-3pm) or evening (630-730pm) to offer flexibility for those at work or with children. Participants were asked to wear comfortable/loose clothing and trainers, and to bring a bottle of water with them.

The hour included thirty minutes Nordic walking, and warm up (ten minutes)/cool down (ten minutes) exercises, and was standardised for each of the two groups of ten participants who were randomised to receive the intervention. During the first four training sessions, the instructor provided detailed instruction on the correct use of Nordic walking poles, and on the technique of Nordic walking, with a consolidation period during each of the subsequent sessions, so that by the end of the six weeks, participants felt competent in the Nordic walking technique. Verbal encouragement and persuasion was provided by the instructor to increase motivation of participants. During the Nordic walking, due to the varying abilities of individual participants, the instructor would monitor all women by walking with those at the front, going at the fastest pace, then turning back to walk with those at a slower pace to check the progress and technique of all participants.

Within this first stage participants were asked to gradually build up the number of self managed Nordic walking sessions per week. During weeks 3-4 of training the participants were asked to add in a second thirty minute session per week of Nordic walking per week which would be self managed, and in weeks 5-6 participants were asked to add in a third session (again, self managed). At the end of the six week period, participants were competent to undertake Nordic walking independently as assessed by the Nordic walking instructor. In weeks 7-12, participants were asked

to complete 4 x 30min sessions of self managed Nordic walking per week for a period of six weeks. Participants achieved the desired heart rate using the Borg scale of perceived exertion (Borg, 1982). This is a widely tested fifteen point scale going from six to twenty (appendix IV) which can be used as a proxy measure to estimate heart rate and level of exertion, with level eleven to thirteen equaling an endurance effect.

Figure 5.2 Treatment of participants



5.8.2. Waiting list control group

The rationale for using a waiting list control is given in section 5.1. In weeks 1-12, participants in the control group received enhanced usual care, in that they did not receive the intervention but were contacted every two weeks (whilst the intervention group undertook the Nordic walking) to check for any new onset of pain, injury or lymphoedema. They also received the Macmillan exercise diary, which they were asked to complete during weeks 1-12. This included an information booklet on the importance of physical activity. After this period they were offered the chance to carry out the Nordic walking intervention.

5.8.3. Intervention Fidelity

Treatment fidelity refers to the methodological strategies used to monitor and enhance the reliability and validity of behavioural interventions (Bellg *et al.*, 2004). It is important to maximise fidelity as it has been demonstrated to be a mediator of study outcomes (Mars *et al.*, 2013). For example, where an intervention lacks impact, this may represent a failure to optimise fidelity to the intervention rather than genuine ineffectiveness.

In this study fidelity was optimised by standardising the Nordic walking intervention. Evidence from previous studies was utilised to implement a potentially effective 'dose' of Nordic walking, and then steps were taken to maximise adherence to this dose. These included providing written instruction on the content of the intervention to both participants and the Nordic walking instructor. Phone calls were made to all participants every two weeks during the intervention period, by two members of the research team (principle investigator and assistant), in order to encourage adherence to the intervention. Two people were used based on what was considered feasible for the number of participants recruited for this feasibility study (ten phone calls per week per member of the research team). These calls followed a written script which included the provision of verbal encouragement, and to check on progress and any new symptoms. In order to assess fidelity to the exercise dose and to assess for exercise contamination, adherence was recorded through the use of self report in physical activity diaries by the participants. The instructor also recorded attendance at supervised sessions. The instructor received no intervention specific training, but had a qualification in Nordic walking training, and variability of session content was minimised by using the same trainer for all participants.

5.9 Data collection: Feasibility

Data were collected on different aspects of trial feasibility to meet objectives 1-4.

5.9.1. Objective 1: Recruitment

- Percentage of women at trial centre taking an AI who were screened for joint pain, to determine whether the sampling method was population based.
- Prevalence of joint pain at trial centre, compared to prevalence in previous cross sectional studies of AIAA, to aid with an estimation of whether the screening tool was valid.
- Percentage of women screened fulfilling inclusion and exclusion criteria
- Percentage of women invited to study who accepted, to determine the demand for a Nordic walking intervention in this population.
- Recruitment index i.e. the number of days to recruit one analyzable patient (to evaluate the efficacy of the recruitment strategy; help with planning the duration of the recruitment period for a full study; and the number of participating sites required to give a certain number of participants in a certain time period).
- Comparison of baseline sample characteristics (age, pain,) to other studies with AIAA, to check sample was representative of broader population with AIAA.

5.9.2. Objective 2: Acceptability

The acceptability of the intervention schedule and components was measured through the analysis of adherence and attrition, and through participants' responses to the questionnaire survey on

aspects of the Nordic walking intervention. This information was an essential part of the feasibility study in order to assess to what extent the intervention could be implemented as planned, and what elements would require redesign. This data also determined to what extent the prescribed exercise dose had been achieved, and included:

- Attrition rates at all points along study process (randomisation, allocation, intervention-training and independent exercise. This was collected through researcher datasheets, Nordic walking instructor contact sheets and, and the two weekly phone contact with participants.
- Adherence rate to Nordic walking frequency and duration. These data were collected via self report in the Macmillan exercise diaries. The average frequency and duration per participant per week was calculated, as well as what frequency was feasible for the majority (75%)
- Adherence to supervised Nordic walking exercise sessions, collected via Nordic walking instructor contact sheets.
- Adherence to total exercise frequency, calculated as average exercise sessions per week, in order to ascertain whether other types of exercise were favoured, (and also to assess how much exercise the control group carried out; see 5.9.4).
- A retrospective participant questionnaire survey (appendix VIII) administered at the end of the exercise intervention for both groups (week 24) to provide qualitative data on:
  -Acceptability of the type, duration, frequency, location, and intensity of exercise.
  -Subjective perception of benefit/harm of exercise.

5.9.3 Objective 3: Safety.

Injury

Injury type and rates were assessed by collecting data on self report to the researcher; through Nordic walking instructor contact sheets; and through the two week phone contact with participants when they were asked whether they had sustained any injury. Data on injury treatment and recovery in those referred to a physiotherapist was collected retrospectively through physiotherapy treatment reports on the electronic patient record (appendix XII).

Lymphoedema

Data on lymphoedema was collected in the same manner: through self report directly to the researcher, through Nordic walking instructor contact sheets, and by direct questioning of patients every two weeks via telephone contact with the researcher. Data on lymphoedema was collected retrospectively via lymphoedema assessment and treatment forms which were in the participants' medical notes (Appendix XIII).

5.9.4. Objective 4: Feasibility of research methods

The research methods were tested for their capacity to reduce methodological bias in the study. These included:

Randomisation method

Permuted blocks randomisation was assessed by calculating whether it resulted in balanced characteristics between the intervention and control group at baseline.

Waiting list control group receiving enhanced usual care.

Exercise frequency and duration was measured in the control group, to check for exercise contamination which could potentially lead to a treatment effect in the control group.

Acceptability/burden of outcome measure questionnaires

Adherence to and completeness of questionnaires was calculated, to assess outcome measure acceptability/burden.

Suitability of outcome measures

The validity and reliability of the outcomes measures was explored to assess their suitability for measuring the effectiveness of the intervention. Face and content validity was assessed for each measure by considering whether they appeared relevant and adequate to the subject under study. Internal consistency, i.e. the reliability of the scale in terms of all items measuring the same construct was tested using Cronbach's alpha at T0, T1 and T2. Responsiveness was assessed by describing the degree of change from baseline to T2.

5.10 Data collection: Outcome measures

In order to meet objective 5, which was to describe the effect of NW intervention on outcomes, data were collected on outcomes which were considered to be the mediating variables in pain perception within the biopsychosocial model discussed in section 2.11. This included physiological, psychological and social components. The focus of this study is to reduce perception of pain in order to enhance adherence to medication. Data was therefore collected on perceived pain, but no physiological measures were included. The psychological factor considered most important in this study was a measure of depression. As an important part of the study would be to enable people to take up and continue this intervention, measures were included of self efficacy and behaviour change, as well as whether participants adhered to the walking programme or increased their physical activity.

Furthermore, the World Health Organisation encourages consideration of bio-psychosocial factors in the measurement of disability, including musculoskeletal pain (Ustun *et al.*, 2003). Depression may exist in a mutually reinforcing relationship with chronic pain and therefore improving one of these variables may improve the other. Self efficacy is a central component of the Social Cognitive

Theory and it has been demonstrated that physical activity may improved pain indirectly via improvements in self efficacy; therefore it was felt important to measure this particular construct. Specific measures were chosen on the basis that they had proven validity and reliability. In addition, measures were selected that were comparatively brief, in order to keep respondent burden to a minimum.

5.10.1 Brief Pain Inventory-Short Form (BPI-SF)

Pain was measured using the Brief Pain Inventory Short Form (BPI-SF). This scale has been widely used in populations with cancer and is also validated in studies evaluating the impact of osteoarthritis (Williams *et al.*, 2006), therefore it seemed a suitable measure to use in studies with cancer populations experiencing musculoskeletal pain. The two-factor structure (pain severity and pain interference) was confirmed in a large US study involving outpatients with recurrent/ secondary cancer (Cleeland and Ryan, 1994). Internal consistency was also demonstrated in this study, with Cronbach's alphas ranging from 0.80 to 0.87 for the four pain severity items, and from 0.89 to 0.92 for the seven interference items. The test-retest reliability of the BPI has been studied in populations with cancer and other chronic pain. Initial short-term (1 day to 1 week) reliability for ratings of pain "worst"(0.93) and "average" pain (0.78) was high, which signals acceptable reliability (Daut and Cleeland, 1982).

As currently there are no validated measure for AIAA, this questionnaire is being used to measure self report of pain in the majority of studies researching AIAA, both cross sectional (Crew *et al.*, 2007b; Fenlon *et al.*, 2013), and randomised controlled trial designs (Crew *et al.*, 2010; Irwin, 2012). Thus selection of the same measure will assist in future comparisons.

Primary outcome measure

Although it is not a requirement to define a primary outcome measure for feasibility studies, it was decided that this might be useful in order to test its utility in measuring AIAA and also its responsiveness to change. Worst pain in the last 24 hours as measured by the BPI-SF single item measure was selected on the basis that that this single item was the primary outcome used in several RCTs investigating AIAA (Crew *et al.*, 2010; Irwin, 2012) and thus might aid comparison. Furthermore, the use of single items in the BPI-SF is supported by IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) recommendations for assessing pain in clinical trials (Dworkin *et al.*, 2005; Turk *et al.*, 2006). The primary endpoint was selected as worst pain as measured by the BPI-SF at twelve weeks (T2).

5.10.2. Center for Epidemiological Studies Depression Scale (CES-D)

Depression was measured by the Centre for Epidemiological Studies Depression Scale (CES-D). This is a twenty item self-report measure developed to screen for depressive symptoms and has

excellent reliability and validity in community and cancer patient samples (Radloff, 1977; Hann *et al.*, 1999). A higher score indicates greater depressive symptoms, with a cut off of 16 identifying individuals at risk of clinical depression. The benefits of using CES-D in a cancer population are that it focuses primarily on cognitive and affective components of depression rather than its physical manifestations, which could arise as a consequence of cancer and its treatment (Hann *et al.*, 1999). The test takes less than ten minutes and can be self administered (Burgess *et al.*, 2005) thus also holds minimal burden for participants in multi-questionnaire testing. Internal consistency in cancer populations as measured using Cronbach's Alpha coefficient is good at between 0.87-0.89 (Devins *et al.*, 1988; Conerly *et al.*, 2002). Test-re-test reliability and construct validity are also satisfactory (Hann *et al.*, 1999). Research has also demonstrated its sensitivity to improvement after treatment (Burns *et al.*, 2000), although this testing was in a non cancer population.

5.10.3. Pain Self-Efficacy Questionnaire (PSEQ)

Self efficacy for managing pain was measured using the Pain self efficacy questionnaire (Nicholas, 1989). This ten item questionnaire assesses confidence in performing activities whilst in pain, and has excellent reliability and validity in chronic pain populations (Asghari and Nicholas, 2001), with a possible score of 0-60 (higher score indicates higher self efficacy). Although there has been no previous testing in cancer populations, a review of suitable scales concluded this might be the most appropriate in view of its focus on assessing confidence in activities despite pain. However, as part of feasibility, in view of its lack of testing, an assessment of its internal consistency and responsiveness to change will be carried out in this sample.

5.10.4. Medical Outcomes Short Form -36 (SF-36).

Quality of life was measured using the Medical Outcomes Short form-36 (SF-36) (Ware and Sherbourne, 1992). This is a multidimensional, self-administered questionnaire with 36 items divided into eight subscales that assess perceptions of overall health status. It is frequently recommended as the generic core in disease specific batteries of health related quality of life, including cancer populations (Moinpour *et al.*, 1989; Bowling, 2001). The eight domains include physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/vitality; mental health; well-being; social functioning; bodily pain; and general health perception. This measure has been validated with various populations such as cancer, diabetes, acute myocardial infarction, and clinically depressed populations (Bowling, 2001) and validated in the UK on a large sample drawn from GP records (Jenkinson *et al.*, 1999). As with the BPI-SF, it was chosen for use in this study as it is appropriate for use in both cancer and musculoskeletal disorders and its extensive prior psychometric testing.

5.10.5. The General Practice Physical Activity Questionnaire (GPPAQ)

Change in physical activity levels were measured using the General Practice Physical Activity Questionnaire (Department of Health, 2009a);(Appendix XI) . This questionnaire has been

developed from a longer questionnaire on physical activity used in the European Investigation into Cancer (EPIC) study, a large epidemiological study investigating diet and physical activity (Riboli and Kaaks, 1997). It has been validated in a sample of 334 people in general practice and it is described as having good face and construct validity in this population (Department of Health, 2009a). This questionnaire was used to assess changes in levels of physical activity from T0 to T2, in particular, changes in walking and vigorous activity.

5.10.6. Exercise adherence measure: The Macmillan Physical Activity Diary

Recording of exercise volume in both the intervention and control group was essential as part of feasibility, to assess adherence to the prescribed exercise dose in the intervention group and thus acceptability; and also to check for exercise contamination in the control group which might confound findings.

A review of exercise adherence measurement in breast cancer survivors identified that the most commonly used methods are total number of supervised exercise sessions attended (frequency), total number of minutes (duration), and exercise actually attained divided by exercise prescribed (Husebo *et al.*, 2013). Jordan et al (2010) reports similar measures in musculoskeletal populations. Therefore these measures were recorded in my study, using a physical activity diary designed by Macmillan Cancer Support. This is a twelve week diary which enables users to record physical activity in terms of frequency, type, duration and intensity on a daily basis, and encourages the setting of exercise goals over a twelve week period (Macmillan Cancer Support, 2011).

5.10.7. Data collection Schedule

Baseline data (T0) were collected at the baseline visit prior to randomisation. The same outcome data were collected from intervention and control groups at two time points; at week six (T1; end of group supervised Nordic walking training) and at week twelve (T2; end of Nordic walking self managed Nordic walking). See table 5.1. Feasibility data were collected throughout the trial as appropriate, and the participant questionnaire survey administered at the end of the Nordic walking intervention week period for all participants i.e. at twelve weeks for the intervention group and at 24 weeks for the control group.

Table 5.1: Outcome measures and data collection points

Measure	Baseline (T0)	Six weeks (T1)	Twelve weeks (T2)
Demographic/Medical details	x		x
1.BPI-SF	x	x	x
2. SF-36	x	x	x
3.C-ESD	x	x	x
4. Pain self efficacy scale	x	x	x
5. Physical activity levels	x	x	x
6.Exercise diary (daily completion)			x
7. Participant questionnaire survey			x

5.11. Sample size

There is no minimum number of participants required to achieve the aims of a feasibility study (Thabane *et al.*, 2010). However, the sample size should be adequate to estimate the critical parameters of interest, such as the recruitment rate (NETSCC. 2011). For this study the desired sample size of 40 was based on an estimation of the numbers of participants that could be recruited from the trial centre over twelve months (table 5.2). A recruitment period of twelve months facilitated population based sampling, as every patient under follow up at the trial centre attended the clinic in that time period.

Table 5.2 Estimation of potentially eligible women at trial centre over twelve month's recruitment period

- Approximately 1350 women with invasive breast cancer seen in the trial centre follow up clinic over twelve months
- 75% of whom will ER positive =1012
- 75% of whom are estimated to be postmenopausal and likely to be on AI = 759
- 48% of whom may be experiencing AIAA =364
- Recruitment between 10-20% =36-72

5.12 Data Analysis

Advice was sought from a senior statistician at the University of Southampton. Data handling and analyses were performed using SPSS, version 20 (SPSS Inc, Chicago, IL). Descriptive statistics were used to summarise baseline demographic details. T tests were used to check for differences between baseline characteristics to determine whether randomisation resulted in any significant differences between groups.

Feasibility data were used to answer objectives 1-4 as detailed in 5.9 and analysed using descriptive statistics.

For objective 5, to determine evidence of impact, trends in effect and variation in scores of the outcome measures were described for the two follow up time points, T1 and T2,. As data were not normally distributed, medians and interquartile ranges were used to describe measures of central tendency and dispersion. Analysis of outcome measures was on an intention-to-treat basis (Pocock, 1983).

Change scores, i.e. differences between the two groups in the amount of change from T0 to T2 were calculated. As change scores data (i.e. change between scores at T0 and T2), were normally distributed (unlike raw data), it was appropriate to describe this data using means and standard deviation. Furthermore, student's T-test was used to check whether the difference between the change scores for the primary endpoint: - worst pain at 12 weeks; was significant. As this study was not powered, this was an exploratory analysis.

Data obtained from the retrospective cross sectional survey questionnaire (appendix VII) administered at the end of the study was summarised and presented descriptively.

5.13 Safety Issues

Safety issues relating to new injury, lymphoedema and adverse events related to the intervention were fully explored in the study protocol. Prior to commencement of the intervention, physical fitness to exercise was checked by the use of the Physical Activity Readiness to Exercise Questionnaire (PAR-Q, appendix V), thus reducing chance of injury. If participants indicated that they had pre-existing cardiopulmonary disease or other risk factors deemed to put them at risk from exercise, permission was sought from their GP before they could enter the study.

Screening for metastatic bone disease, lymphoedema, and sports related injury occurred as a continuous process before and during the study as indicated in figure 4 provided in Appendix X. Specifically, the Nordic walking instructor was asked to provide details to the researcher of any participants reporting new onset pain or red flag symptoms (including new unilateral severe pain in weight bearing joints, or back pain that is made worse by physical activity, or bone pain that is worse at night). The researcher had also instructed participants to report these symptoms straightaway. Additionally, the researcher phoned participants every two weeks to enquire about any new onset symptoms of pain, injury or arm/chest wall swelling. In the case of any symptoms suggestive of metastatic disease, investigations were arranged as per the flow diagram in appendix IX and the participants made an appointment with their clinical team.

Safety issues were also collected through self report in exercise diaries, and through Nordic walking instructor and researcher participant contact datasheets. Participants reporting new musculoskeletal pain were referred on to the physiotherapist for assessment and management where indicated, who provided a written report on findings. Participants with lymphoedema who had concerns regarding new arm/chest wall symptoms were referred to the lymphoedema nurse. The lymphoedema nurse assessed these women with manual arm volume measurements and/or perometry, and also provided a written report.

The risk of musculoskeletal injury was minimised by advising participants to exercise on well kept/lit roads/pavements, and to ensure they continue warm up/cool down as in their training period. Contact details of GP and next of kin were taken for all participants in case of any adverse health events occurring during exercise.

5.14 Ethical Issues

Ethical approval was obtained from South Central National Research Ethics service (reference 11/SC/0268; protocol number 7960). Initial recruitment took place outside of the clinical practice

setting (by inviting women by letter) in order that potential participants did not feel any pressure to take part in the research. The researcher had experience of working with women with breast cancer and taking informed consent for current trials and understood the principles underlying informed consent as per Good Clinical Practice guidelines (National Institute for Health Research, 2011) and Department of Health guidelines (Department of Health, 2009b). Consent was not sought from those who were judged to lack capacity (Department of Health, 2009b). Patient information sheets (PIS) and consent forms were designed in accordance with Good Clinical Practice guidelines and NHSE guidance. The PIS included detailed information about the study, that data would be confidential and anonymised, the right of the participants to withdraw at any point, and that declining to take part would not affect care. A waiting list control was used to avoid the dilemma of withholding Nordic walking from women.

Chapter 6: Findings

Findings related to the feasibility and acceptability of conducting the trial will be presented in this chapter. Data will be presented in order to answer the study objectives. This includes information on recruitment to determine the suitability of eligibility criteria, the effectiveness of the recruitment strategy and time taken to recruit. Attrition and adherence will be described in order to give an indication of the acceptability of the Nordic walking intervention. This will be followed by an account of the feasibility of aspects of research design. Safety issues or untoward consequences will be described and quantified in terms of new pain, injury or lymphoedema occurring during the study. Finally, changes in scores for the outcome measures will be explored over time, comparing the intervention and control groups.

6.1. Recruitment

The recruitment process for this feasibility study and numbers recruited is illustrated in figure 6.1.

6.1.1. Effectiveness of recruitment strategy/screening method

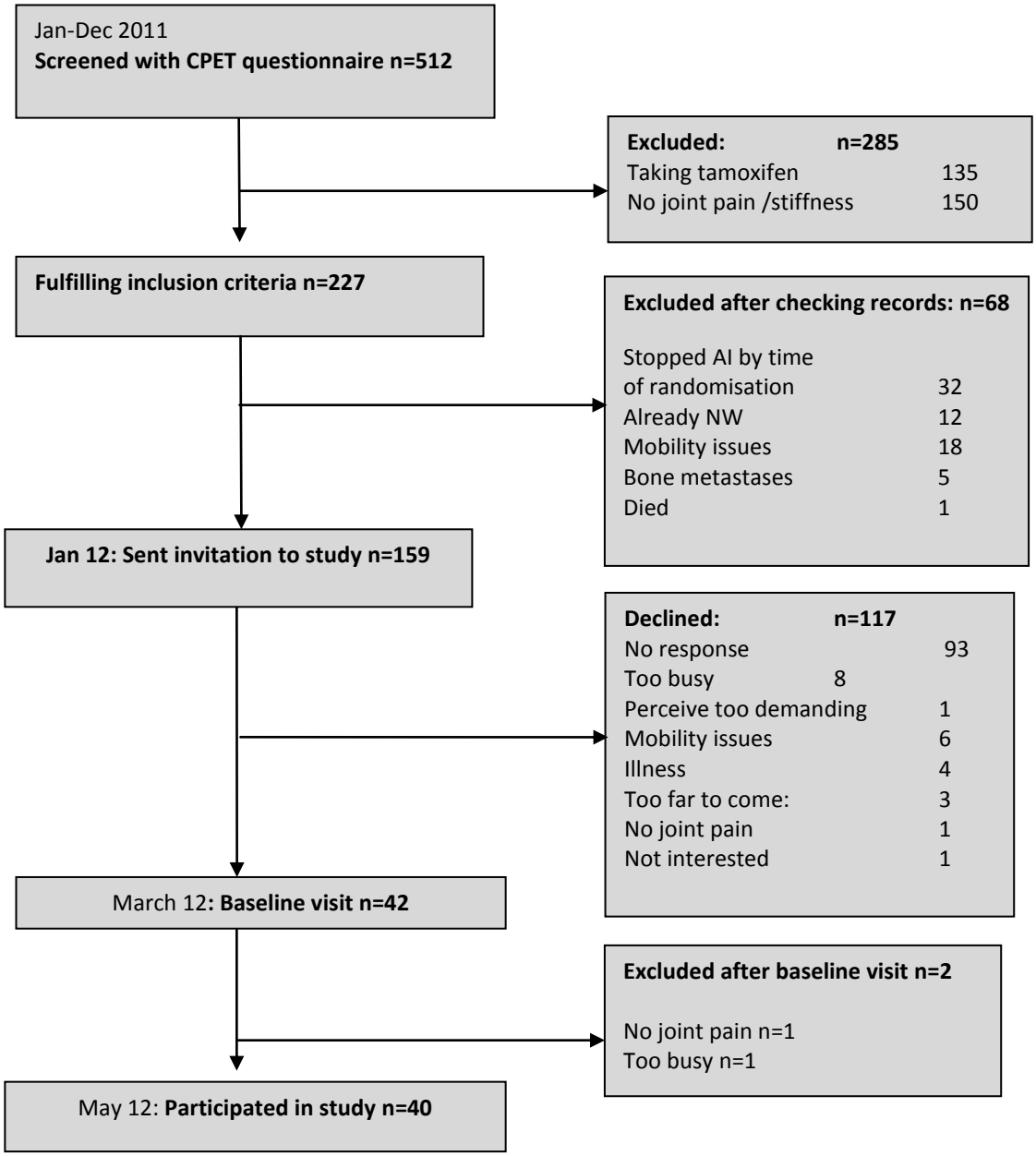
Forty women were recruited over 12 months from January 2011 to December 2011 (Figure 6.1). Five hundred and twelve women attending a nurse led breast cancer follow up clinic over this period, who were taking hormone therapy, were screened for eligibility through the use of the amended CPET questionnaire. Women with breast cancer attending other breast cancer follow up clinics at the trial centre were not included as the researcher had insufficient capacity to cover these clinics. 377 of women screened were taking an AI. Therefore the estimated percentage of women on an AI screened to participate in the study, whilst in active breast cancer follow up at PHFT, was only approximately 50% of those estimated to be taking an AI (377/759; refer to section 5.11, table 5.2). Of those on an AI, 60% (n=227) reported joint pain/stiffness and therefore fulfilled the inclusion criteria for the study.

6.1.2. Feasibility of exclusion criteria

Of the 227 women taking an AI who reported joint pain/stiffness, sixteen percent (n=36) were excluded on the basis of the exclusion criteria specified. Three percent had been diagnosed with metastatic (n=5) disease or had died (n=1) by the end of the recruitment period. Eight percent (n=18) had significant mobility issues (requiring help with stick/rollator etc), which suggested they would be unable to participate in a walking programme, which was assessed by reading their medical case notes. A further five percent (n=12) were already enrolled in a Nordic walking weight management programme running concurrently at the trial centre. Although this had not previously been listed in the exclusion criteria it was decided, after discussion with the research team, that these women should not be invited to participate in the study as they would be receiving a longer duration of the Nordic walking intervention than the rest of participants. In addition to the sixteen percent excluded by application of the exclusion criteria, a further fourteen percent (n=32) were

due to discontinue their AI medication by the end of the recruitment period, Thus 68 (30%) of the identified 227 women identified as fulfilling inclusion criteria were excluded, and the remaining 70% (159/ 227) were sent an invitation to participate in the study.

Figure 6.1: Flow diagram of recruitment process



6.1.3 Demand for/interest in the intervention.

Twenty six percent (*n*=42/159) of eligible women were interested to take part in the study. Information about the study was mailed to the 159 women who met the eligibility criteria in January 2012, asking for an indication of expression of interest in the study. Of these, 58% (n=92) failed to reply and 15% (n=24) replied but declined participation. Reasons included being too busy

due to family or other commitments (n=8); perceiving themselves as having mobility issues (n=7); concurrent illness (n=4), being too far away geographically (3), and pain resolved (n=1).

6.1.4. Determine recruitment rate to estimate time needed to recruit for definitive trial.

Twenty-six percent of those eligible (n=42/159) accepted the initial invitation to the study. These women were contacted by phone between January 8th to February 15th 2012 and all accepted the invitation to attend an appointment at the research clinic to confirm eligibility, take consent to enter the study and obtain baseline data. Of the 42 attending clinic, one reported that she no longer had joint pain and so was not eligible, and one declined due to work commitments. Thus the final recruitment rate was 25%; in other words, 40/159 eligible women were consented and randomised to intervention or waiting list control. By using this method of pre-screening people prior to invitation and recruitment to participate in the study, it took twelve months (January 2011 to January 2012) to recruit the planned sample size of 40 people. Thus it took approximately nine days (365/40) to recruit one analyzable patient for the study

6.1.5 Feasibility of recruiting a representative sample

Forty women were enrolled and randomly assigned, twenty to the Nordic walking intervention and twenty to wait list control. The sample as a whole was exclusively Caucasian, and predominantly married or living with partner (70%). Just over half were retired (52.5%, n=21), with the remainder working full time (42.5%) or part time (27.5%), and had a college or higher education (57.5%). The mean age of the intervention group was 60 (range 47-74) and the mean age of the control group was 66 (range 53-77), which represented a significant difference between groups (p=0.009). Time since diagnosis was 35 months for the intervention group and 39 months for the control group (p=0.59). Further demographic and treatment details are provided in table 6.1. Of those declining to enter the study the mean age was 65. The sample lived on average seven miles from the hospital (median; IQR=3-10).

In terms of treatment received, all had received surgery (100%, n=40), 75% (n=30) received radiotherapy and 50% (n=20) had received chemotherapy. Of those receiving chemotherapy, 50% received FEC and 40% FEC-T. Almost twice as many women in the intervention groups as the control group received chemotherapy (13 vs 7). All had received hormone therapy which was the only current breast cancer treatment for the sample. 52% of the sample was taking anastrozole, 32.5% letrozole and 15% exemestane. For 65% of the sample, their current hormone therapy was first line (i.e. they had not received any other form of hormone therapy); however, 25% had previously received tamoxifen, 7.5% had previously received letrozole, and 2.5 % exemestane. None had previously taken anastrozole.

Table 6.1: Baseline data: demographic and medical details

Variable		Nordic walking intervention Mean (SD)	Control Mean (SD)	Total sample Mean (SD)	P=
Age (years) at 1.5.12		60 (8)	66 (7)	63 (8)	0.009
Time since diagnosis (months)		35 (19)	38 (17)	36 (18)	0.59
Time since last menstrual period (years)		11 (8)	15.00 (7)	13.00 (7)	0.08
Duration current hormone therapy (months)		23 (13)	30 (16)	27 (15)	0.17
Duration of arthralgia (months)		21 (13)	24 (15)	22 (14)	0.48
Living Distance from hospital (miles)		7 (7)	9 (8)	8 (8)	0.47
Marital status	Married	14	12	26	65
	Single/Divorced/widow	6	8	14	35
Living arrangements	Alone	5	5	10	25
	With husband/partner	14	14	28	70
	Other	1	1	2	5
Education	Primary/Secondary	7	10	17	42.5
	school	6	8	14	35
	College/Diploma	6	1	7	17.5
	University/Degree	1	1	2	5
Occupational status	Working	13	5	18	45
	Not working	7	15	22	55
Religious affiliation	Christian	11	13	24	60
	Other	9	7	16	40
Ethnic origin	Caucasian	20	20	40	100
	Other	0	0	0	0
Past Treatment	a. Surgery	20	20	40	100
	b. Chemotherapy	13	7	20	50
	c. Hormone therapy	20	20	40	100
	d. Radiotherapy	15	15	30	75
Chemotherapy type	FEC	5	5	10	25
	FEC-T	7	1	8	20
	No chemotherapy	7	13	20	50
	missing	1	1	2	5
Current hormone treatment	Tamoxifen	0	0	0	0
	Anastrozole	10	11	21	52.5
	Letrozole	7	6	13	32.5
	Exemestane	3	3	6	15
Previous hormone treatment	Tamoxifen	4	6	10	25
	Anastrozole	0	0	0	0
	Letrozole	3	0	3	7.5
	Exemestane	1	0	1	2.5
	None (first line tx)	12	14	26	65
Previously diagnosed musculoskeletal disease	OA	3	5	8	20
	RA	0	0	0	0
	Fibromyalgia	0	0	0	0
	Other	2	2	4	10
	none	15	13	28	70

22.5% had their last menstrual period within the last five years, a further 20% within five to ten years and the remainder over ten years ago. Mean duration of current hormone therapy was 27 months, and mean duration of arthralgia was 22 months. 20% of the sample had previously been diagnosed with osteoarthritis and 70% (n=28) had no previous musculoskeletal problems.

Self report of pain at baseline

Thirty five percent of the entire sample reported mild pain as rated by a score of between 0 and 4 on the Brief Pain Inventory worst pain measure, 62.5% of the sample had moderate pain (score of 5-7), and 2.5% had severe pain (8-10).

6.2. Acceptability of Nordic walking intervention schedule and components.

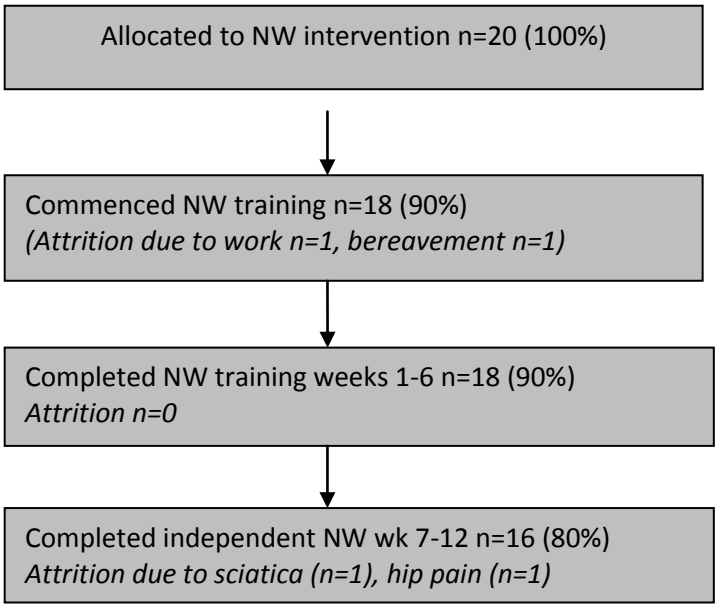
The acceptability of the intervention was assessed by:

- Attrition throughout the intervention
- Adherence to the prescribed frequency and duration of Nordic walking activity.
- Questionnaire survey administered at the end of the study period.

6.2.1. Attrition in Nordic walking intervention group

The length of time between the baseline visit of the first participant recruited until the intervention commenced was twelve weeks (as participants waited for the group to begin). In this period, two (10%) participants allocated to the Nordic walking intervention dropped out, one due to work commitments and one due to sudden bereavement, leaving eighteen who took part in the intervention. A further 10% (n=2) dropped out at week six after Nordic walking training, due to pre-existing or recurrent musculoskeletal pain. Therefore 16/20 (80%) participants in the intervention group completed the Nordic walking intervention.

Figure 6.2: Attrition rates at different time points for intervention.



6.2.2. Adherence to the prescribed frequency and duration of Nordic walking activity

To determine adherence to the Nordic walking intervention, three dimensions were measured throughout the twelve week period of Nordic walking:

- Adherence to the weekly supervised group Nordic walking training sessions
- Adherence to prescribed Nordic walking frequency
- Adherence to prescribed Nordic walking duration

In addition, frequency of other aerobic exercise was measured to establish whether other forms of exercise were carried out in addition to Nordic walking, and to give an estimation of overall aerobic activity.

Adherence to supervised weekly Nordic walking group training

Participants starting the course (*n*=18) attended a total of 90% of the supervised group Nordic walking training sessions: 97 out of 108 training slots. Six sessions were missed due to holiday, one due to work and four due to illness on the day. The median number of supervised sessions attended per participant was five out of six (range=4-6). One participant attended four sessions, ten participants completed five sessions, and seven attended all six.

Adherence to prescribed Nordic walking frequency

In the first six weeks, while participants were attending weekly supervised walking sessions, they were asked to gradually increase the number of their own personal Nordic walking sessions (table 6.2). There was considerable variation in the number of Nordic walking sessions completed by individual participants, which ranged from one to six sessions per week. The prescribed frequency was only fully adhered to in weeks one and three.

Table 6.2: Frequency of Nordic walking sessions during supervised group Nordic walking

Week number	1	2	3	4	5	6
Number of completed diaries	15	15	15	14	15	14
Prescribed frequency of Nordic walking sessions (inc supervised)	1	1	2	2	3	3
Median Nordic walking sessions wk achieved (range)	1.0 (1-3)	2.0 (1-4)	2.0(1-4)	1.5(1-4)	2.0 (0-4)	1.0 (0-6)
Adherence	100%	200%	100%	75%	66%	33%

In week's seven to twelve, participants were asked to complete four sessions of Nordic walking per week and no supervision was given. On average, participants only did not attain this prescribed frequency (table 6.3). The median frequency of Nordic walking sessions completed by participants

per week during independent walking was 2 (range = 0-5), and the majority (>75%) of participants managed at least one to two sessions per week. On average, participants attained four sessions or more per week 10% of the time; three sessions or more per week 36% of the time and two sessions or more per week 68% of the time.

Table 6.3: Frequency of Nordic walking sessions during the period of self managed Nordic walking

Week number	7	8	9	10	11	12	
Number of completed diaries	14	14	14	14	13	13	
Prescribed frequency Nordic walking sessions	4	4	4	4	4	4	
Median Nordic walking sessions per week actually achieved (range)	2.0 (0-5)	2.0 (0-5)	2.0 (0-4)	2.0 (0-5)	2.0 (0-3)	3.0 (0-4)	
Adherence rate	50%	50%	50%	50%	50%	75%	
Minimum number of Nordic walking sessions achieved/week	Number of participants attaining (cumulative %)						Median
4	1(7%)	2(14%)	1(7%)	2 (14%)	1 (8%)	1 (8%)	8%
3	3 (21%)	5 (36%)	5 (36%)	6 (46%)	3 (23%)	7(54%)	36%
2	10 (71%)	11 (79%)	10 (71%)	9 (64%)	8 (62%)	8 (62%)	68%
1	2 (84%)	1 (86%)	3 (93%)	4 (93%)	2 (77%)	2 (73%)	85%

Adherence to prescribed Nordic walking duration

In weeks 1-6 of Nordic walking (period of supervision), as the number of prescribed Nordic walking sessions per week increased, so did the total duration as a result. On average, participants were able to attain the prescribed duration in weeks 1-4, but fell short in weeks 5-6 (table 6.4). The average Nordic walking duration per participant per week was 98 minutes, which is over 80% of that prescribed.

Table 6.4: Average duration Nordic walking per participant during period of supervised Nordic walking.

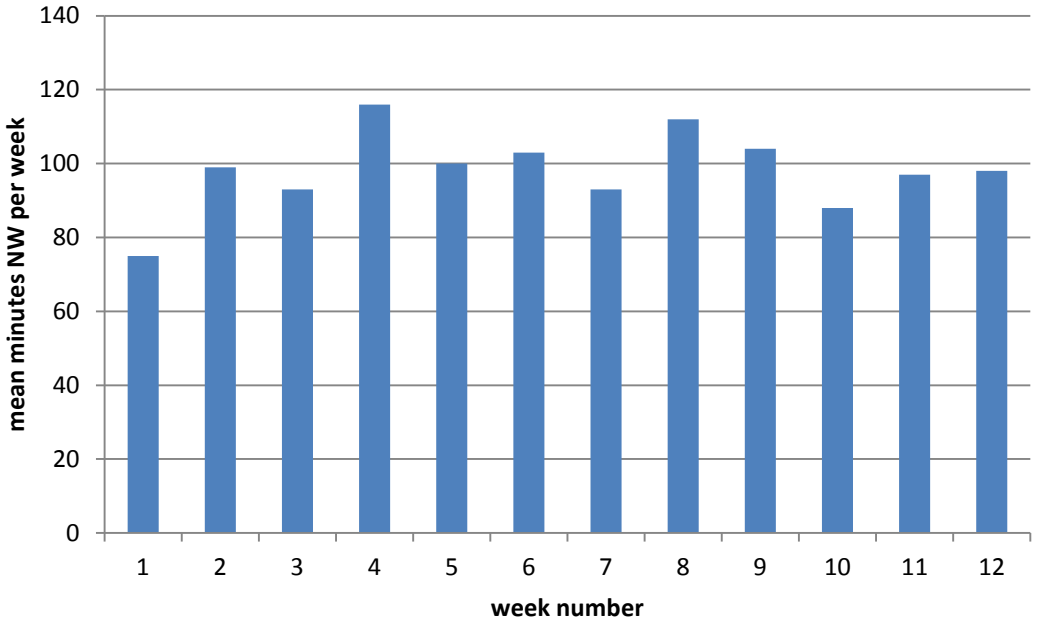
Week number	1	2	3	4	5	6
Number of completed diary entries	14	15	15	14	14	13
Prescribed Nordic walking duration (minutes)	60	60	90	90	120	120
Mean minutes Nordic walking/wk achieved (SD)	75 (39)	99 (44)	93 (54)	116 (62)	100 (65)	103 (57)
Adherence	125%	165%	100%	129%	83%	89%

In weeks 7-12 (independent walking), participants were requested to complete 4 x 30 min sessions of Nordic walking per week (120min total). The average duration of Nordic walking per participant per week was 99 minutes in this period, which is over 70% of that prescribed. Figure 6.3 gives an overview of the duration per week over the whole twelve weeks.

Table 6.5: Duration Nordic walking per participant per week during self managed Nordic walking

Week number	7	8	9	10	11	12	
Number of completed diary entries	13	13	14	13	13	13	
Prescribed Nordic walking duration (minutes)	120	120	120	120	120	120	
Average NW/wk achieved (minutes) Mean (SD)	93 (79)	112 (59)	104 (52)	88 (53)	97 (77)	98 (62)	
Average adherence	77.5%	93%	87%	73%	81%	82%	
Minutes achieved per week	Number of participants attaining (cumulative %)						Mean
>150min	3 (23%)	3 (23%)	5 (38%)	3 (21%)	2 (15%)	4 (31%)	15%
>120min	3 (46%)	0 (23%)	1 (46%)	3 (43%)	3 (38%)	2 (46%)	38%
>90min	0 (46%)	5 (62%)	2 (62%)	4 (71%)	1 (46%)	0 (46%)	54%
>60min	6 (92%)	2 (77%)	0 (62%)	2 (86%)	4 (77%)	4 (77%)	79%
>30min	1 (100%)	0 (77%)	4 (92%)	1 (93%)	2 (92%)	0 (77%)	89%

Figure 6.3. Average duration of Nordic walking activity per participant per week



In the period of independent walking (weeks 7-12), on average, just over a third of participants (38%) attained at least the prescribed 120 minutes Nordic walking per week (range=23-46%). Just over half (54%) attained at least 90 minutes (range 46-71%); and the majority (79%) managed at least 60 minutes of Nordic walking per week (table 6.5).

Total aerobic exercise session frequency per week

The median frequency of total aerobic exercise sessions achieved per week by participants in the intervention group was also calculated, and also what percentage of participants attained two, three and four sessions to determine what was feasible for most. This illustrated that the average frequency achieved was four sessions per week, but varied widely, and that the majority (>75%) attained three sessions per week.

Table 6.6 Frequency of total aerobic exercise per participant per week (Nordic walking group)

Week number	7	8	9	10	11	12	Median
No. completed exercise diary entries	14	14	14	14	13	13	14
Median aerobic sessions per week achieved including NW and other (range)	3 (1-9)	5 (2-9)	4 (1-9)	4 (2-10)	4 (1-9)	4 (1-11)	**4**
Minimum frequency achieved/week	Number of participants attaining (cumulative %)						
4	6/14 43%	9/14 64%	6/14 43%	9/14 64%	8/13 62%	8/14 57%	59.5%
3	9/14 64%	12/14 86%	13/14 93%	12/14 86%	10/13 77%	9/13 69%	81.5%
2	13/14 93%	13/14 93%	14/14 100%	14/14 100%	11/13 85%	12/13 92%	93%

6.2.3. Acceptability of intervention as self reported by questionnaire survey

Data on the acceptability of the intervention were collected via the questionnaire survey administered via post to participants at the end of the study period. 77.5 % (31/40) completed the questionnaire survey about taking part in the study. Figures given below are percentages of the 31 that responded.

All participants (100%) who responded reported that they had enjoyed taking part, with general comments such as *'it was fun';* and *'invigorating'*. Having supervised training was found to be helpful: - *'the trainer pushed you and encourages you more than you push yourself on sessions without the trainer '* (p14).

Being in a group was mentioned as a specific component of the intervention by five participants who commented: '*being in company…gave a feeling of wellbeing'* (p5); '*it was lovely to meet others in the same situation'* (p12); '*enjoying activity as part of a group'* (p1) and '*the girls were encouraging*' (31).

In terms of the duration of each Nordic walking training session, 90 % (*n*= 28) felt they were of the right length. However, there were comments from four participants that the sessions often over ran. 13% (*n*=4) of respondents commented that the warm up and cool down was too long and tiring. The majority (87%; n=27) thought that the duration of the training programme (six weeks) was the right length, with two participants stating that no more could be learnt regarding technique after six weeks. However, 13 % (n=4) thought that it was too short. Reasons given were that three of the participants had missed part of the programme and therefore would have liked more sessions to catch up; and another commented that direct supervision from instructor helped with motivation.

The majority (87.1%; n=27) felt that the physical effort required was about right, 6.5% (n=2) felt that it was too difficult and 3.2% (n=1) too easy. Comments regarding effort required reflected the varying age within the groups with three older participants finding warm up and cool down too difficult. However it was also commented that Nordic walking enabled participants to go at their own pace suggesting Nordic walking suited groups with mixed abilities: '*We all worked at our own pace so I was able to choose my effort'.*

Most respondents (87.1%, n=27) found there was no problem with the venues offered. However, three participants mentioned parking problems at the first venue, one stated that 'you would need a car' and one expressed difficulties due to family commitments. One commented that at participants were 'on show' to the public at the venue chosen: '*We were the weekly entertainment';* and another commented on goose poo all over the ground. Most negative comments were directed at the first of the three venues.

Participants were asked how they felt about the frequency of prescribed Nordic walking for weeks seven to twelve of the study (i.e. the independent exercise period), which was four times per week for 30 minutes. Although 51.6% (n=16) felt this frequency was 'about right', 45.2% (n=14) felt it was too much. Specifically, participants commented upon existing work (n=4) and exercise commitments (n=2), pain (n=2), and the heavy rainfall occurring during the period of the study (n=4), as being reasons why it was difficult to fit in four sessions. Two women commented it was easier to exercise twice a week for an hour.

Despite this, the majority (80.7%) reported that it was likely that they would continue to exercise three to four times per week. 77.5% said they would continue with Nordic walking and another exercise type; 6.5% (n=2) with just Nordic walking, and 6.5% (n=2) with some other form of exercise. The most commonly preferred type of future physical activity was walking (32% of respondents, n=10), followed by swimming (16%, n=5)) and cycling (13%, n=4).

6.3. Safety

6.3.1 Pain/ Injury

30% (6/20) participants in the intervention group reported new pain during the study which required further investigation. The pain preceded Nordic walking in four cases, one developed during Nordic walking and one turned out on investigation to be due to metastatic disease. Three were referred to physiotherapy (one declined referral and one had finger symptoms which were treated with steroid injection by the GP). There were no new musculoskeletal injuries sustained during the study that related to the Nordic walking.

Table 6.7: Numbers of participants reporting pain during study

Type of pain	Nordic walking group	Referred to physio	Treated by GP	Pain resolved following treatment	
				Y	N
Pre-existing musculoskeletal pain	4	3	1	4	0
New musculoskeletal pain	1	1	0	1	0
Metastatic disease	1	referred to oncologist		0	1

6.3.2 Lymphoedema

No participants reported new lymphoedema during the study. Fifteen percent (n=3) of participants in the intervention group had pre-existing arm lymphoedema on entering the study. During Nordic walking, two in the intervention group reported aching of their affected arm, but on assessment in the lymphoedema clinic with perometry and/or manual arm volume measurements, lymphoedema had improved. The third participant thought that her lymphoedema had improved and this was confirmed by objective measurement.

Table 6.8: Lymphoedema changes pre-post Nordic walking in intervention group.

		Lymphoedema pre/post Nordic walking		
	Lymphoedema	**Worse**	**same**	**improved**
Intervention	new	0	0	0
	Pre-existing	0	0	3

6.4. Suitability of research methods

The feasibility of the research design and method used for this study are described below, focusing on the method of randomisation, the choice of comparison group, the response rate to

questionnaires (indicating the burden of the data collection process for participants), and the suitability of the outcome measures.

6.4.1. Randomisation process

Random permuted blocks randomisation resulted in equal numbers between treatment arms (twenty in each group), thus sequence generation was successful. Allocation concealment was not possible as the researcher had to be aware of the participants' allocation in order that they could be given details of the timings/location of the intervention. Demographic data in terms of age and chemotherapy differed between treatment arms despite randomisation (table 6.1). Block randomisation resulted in 32 women becoming ineligible for the study as they waited for randomisation at the end of the twelve month recruitment period.

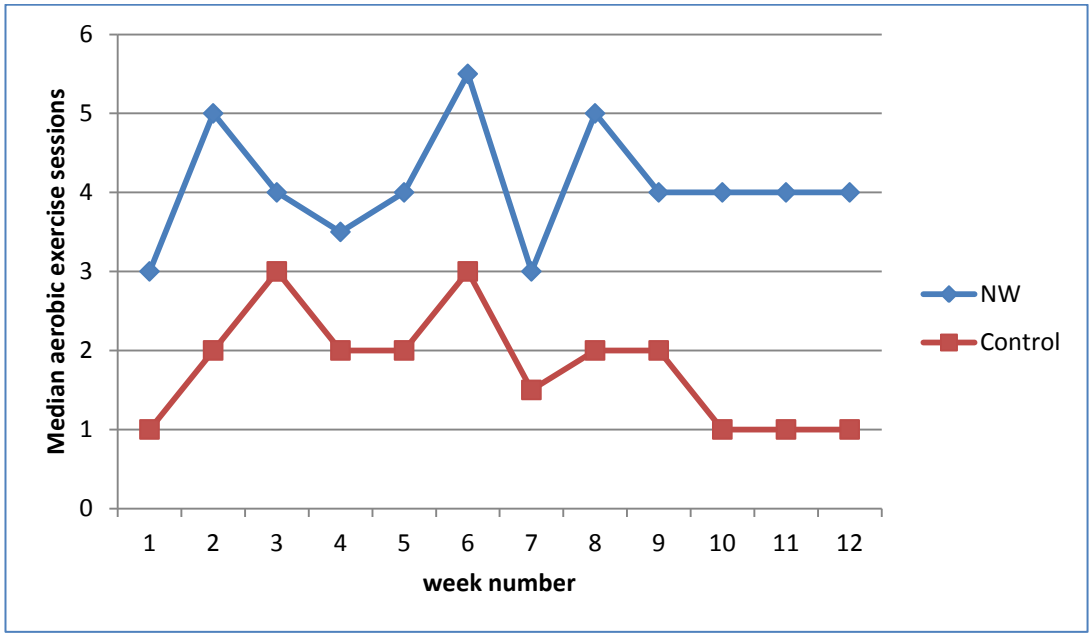
6.4.2. Suitability of waiting list control group receiving enhanced usual care

To assess the feasibility of using a wait list control group who received enhanced usual care, the frequency of aerobic exercise per week was collected in both the intervention and control groups (self reported as 30 mins of at least moderate effort activity). This was to determine whether there was any exercise contamination in the control group and thus potential for bias through dilution of treatment effect. The median total aerobic exercise sessions (including Nordic walking) carried out by was four per week in the intervention group and two per week in the control group (table 6.9, figure 6.4).

Table 6.9: Median number of exercise sessions per participant per week, weeks 1-12

	Nordic walking group			Control group	
Week number	**Diary entries completed**	**Median (range) aerobic sessions (not inc Nordic walking)**	**Median (range) aerobic sessions inc Nordic walking**	**Diary entries completed**	**Median (range) aerobic sessions**
1	15	2.0	3.0 (1-8)	16	1.0 (0-8)
2	15	3.0	5.0 (2-8)	16	2.0 (0-9)
3	15	2.0	4.0 (1-10)	15	3.0 (0-9)
4	14	2.0	3.5 (2-13)	15	2.0 (0-8)
5	15	2.0	4.0 (0-11)	15	2.0 (0-9)
6	14	4.5	5.5 (2-9)	15	3.0 (0-10)
7	14	1.0	3.0 (1-9)	16	1.5 (0-8)
8	14	3.0	5.0 (2-9)	16	2.0 (0-9)
9	14	2.0	4.0 (1-9)	15	2.0 (0-6)
10	14	2.0	4.0 (2-10)	16	1.0 (0-5)
11	13	2.0	4.0 (1-9)	16	1.0 (0-6)
12	13	1.0	4.0 (1-11)	15	1.0 (0-7)

Figure 6.4: Median number of exercise sessions per participant per wk



6.4.3 Questionnaire response rates/completion

Outcome questionnaires

All (100%; n=40) participants in the intervention group completed outcome questionnaires at T1 and T2 (including those who did not actually participate in the intervention); and 90% (n=18) of participants in the control group completed questionnaires at T1 (6 weeks) and 95% (n=19) at T2. At T1 reminder phone calls were made to nine participants (three in intervention and six in control) who had not returned questionnaires by requested return date which yielded a further seven questionnaires returned. Second reminder calls elicited no further response. At T2 reminder phone calls to seven participants (three in intervention and four in control group) yielded five further questionnaires and a second reminder call elicited the return of one further questionnaire.

Exercise diary

75 % (15/20) in intervention group and 80% (16/20) in control group completed the exercise diaries. Reasons for non return included: put out with recycling (n=2); lost (n=1); preferred filling in alternative sheet (n=2); left on holiday in USA (n=1); no reason given (n=3). Reminder calls elicited reasons for non return in some cases but no further diaries.

Questionnaire survey

Eighty percent (n=16/20) of intervention group and 75% (n=15/20) control group completed the questionnaire survey administered at the end of the study. Reminder calls did not elicit any further response.

Figure 6.5. Response rates to questionnaires

Data completeness: intervention group		
Outcome questionnaires		
T0 (baseline)	Obtained	n=20
	Missed	n=0
T1 (6 weeks)	Obtained	n=20
	Missed	n=0
T2 (12 weeks)	Obtained	n=20
	Missed	n=0
Exercise diary		n=15
Questionnaire survey		n=16

Data completeness: control group		
Outcome questionnaires		
T0 (baseline)	Obtained	n=20
	Missed	n=0
T1 (6 weeks)	Obtained	n=18
	Missed	n=2
T2 (12 weeks)	Obtained	n=19
	Missed	n=1
Exercise diary		n=16
Questionnaire survey		n=15

Outcome questionnaire individual item completion

Table 6.10 summarises the completeness of the different outcome measures administered via questionnaire at the three time points. At baseline (T0) there were only 14 data omissions (99.6% completion). At T1 overall 93% complete data, and 94% at T2. At T1 and T2 most missing answers were due to either non returned questionnaires or the participant missing out 2 opposing pages. For example, missing questionnaires or participant missing opposing pages accounted for 100% of the omissions on the BPI-SF at all time points and all but one question on the PSEQ at all time points. For the SF-36 again these systematic omissions accounted for all but two omissions at T1, and 3 at T2.

For the CES-D however, there were many more random omissions: six at T0, fifteen at T1, and eight at T2. On closer inspection this may have been due to the tabular format of the scale. Furthermore, a manual inspection of answers to this questionnaire revealed that a couple of questionnaires had been answered with ticks all down one column. Whilst this may have represented a true reflection of the participant's mood, this seems unlikely as four of the questions contradicted each other (where reverse scoring was in place). It seems more likely that the scale was not properly read or understood. The NHS physical activity questionnaire also resulted in a high number of non systematic omissions; 34/240 (14.2%) at T1 and 38/240 (15.8%) at T2.

In summary, The BPI-SF, PSEQ and SF-36 appear to have been understood and filled in correctly, whereas in the format used in this study, the CES-D and GPPAQ had more omissions and thus are less likely to have produced valid results.

Table 6.10 Individual item omissions in questionnaires

		Items missing per questionnaire		
Time point/scale		**T0**	**T1**	**T2**
BPI-SF	% complete	100%	95%	95%
	Data items missing	0	14/560	14/560
PSEQ	% complete	100%	92.5%	97.25%
	Data items missing	0/400	30/400	11/400
CES-D	% complete	99%	91%	91.5%
	Data items missing	6/800	72/800	68/800
SF=36	% complete	99.5%	94.6%	95.1%
	Data items missing	8/1440	78/1440	71/1440
GPPAQ	% complete	100%	86%	84%
	Data items missing	0/240	34/240	34/240
Total completion		99.6%	93.4%	94.1%

6.4.4. Suitability of outcome/adherence measures

The suitability of the outcome measures was considered in terms of their ability to assess the effect of Nordic walking on AIAA and related biopsychosocial outcomes.

Internal consistency for each measure as measured by Cronbach's alpha is presented in table 6.11. A scale is viewed as having satisfactory internal consistency if Cronbach's α coefficient >0.7 (Pallant, 2001). The internal consistency of all subscales/ and scales was satisfactory with the exception of the SF-36 pain subscale at T0 at 0.6.

Table 6.11 Internal consistency of measures at T0, T1 and T2 (Cronbach's alpha)

Measure/subscale	**Reported by scale developers**	**T0**	**T1**	**T2**
BPI-SF pain severity	0.9	0.8	0.9	0.9
BPI-SF pain interference	0.9	0.9	0.9	0.9
CES-D total	*	0.9	0.9	0.8
PSEQ total	0.9	0.9	0.8	1.0
Sf-36 physical functioning	0.9	0.9	0.8	0.7
SG-36 mental health	0.8	0.8	0.8	0.9
SF-36 social	0.8	0.8	0.7	0.8
SF-36 pain	0.8	0.6	0.8	0.9
SF-36 energy vitality	0.9	0.8	0.8	0.9
SF 36 general health perception	0.8	0.8	0.8	0.8

Evidence of floor or ceiling effects (i.e. lack of sensitivity) was assessed as 25% of sample achieving scores at the bottom or top of each scale (Bowling, 2009) . This demonstrated that there was a ceiling effect in the PSEQ for the control group at T2. No other floor or ceiling effects were observed in other measures or at other time points.

Construct validity (the degree to which the questionnaire represents the construct it purports to measure), was assessed for the BPI-SF by comparison to the pain subscale of the SF-36. Trends and direction of effect were similar in both measures, suggesting they were measuring the same phenomena. Construct validity for the CES-D was assessed by comparison to the mental health subscale of the SF-36. Again, trends and direction of effect were similar in both scales suggesting they were measuring the same construct.

Responsiveness was assessed by the degree of change from T0 to T2, and is described for each of the measures in section 6.5. All scales appeared responsive to change with the exception of the PSEQ in the intervention group. These are discussed in more detail in section 6.5.

6.5. Effect of the intervention

As part of feasibility, the characteristics of the outcome measures in terms of trends, variance and direction of any effect are described below for Nordic walking and control groups over the three time points, T0 (baseline); T1 (6 weeks, at the end of group supervised Nordic walking); and T2, (12weeks, at the end of independent Nordic walking). As data were not normally distributed and the sample size was small, measures of central tendency and dispersion are described using medians and interquartile ranges, as these are less prone to influence from outliers and skewed data distributions.

Results in relation to each variable now follow with a description of the measures for each variable, a table of scores for each variable, and graph depicting change in scores over the three time points.

6.5.1. Pain

Self report of pain was measured using

- The Brief Pain Inventory Short Form (BPI-SF)
- The pain subscale of the SF-36 quality of life scale (a composite of two items from the scale measuring self report of pain over the last week.
- Participants were also asked in the questionnaire survey administered at the end of the study whether they thought any changes in pain were related to the Nordic walking intervention.

Overall, pain scores improved from baseline to twelve weeks for both the intervention and control group (table 6.12). This effect was consistent across all pain measures including BPI-SF worst pain measure, BPI-SF pain severity composite score, BPI-SF pain interference composite score, and the SF-36 pain subscale. Most of the change in the intervention group was observed in the first six weeks.

BPI –SF

Three measures were reported on as recommended by the scale developers (Cleeland, 2009): 'Worst Pain' (a single item), and 'Pain Severity', and 'Pain Interference' which are composite measures.

Worst Pain

'Worst pain' as measured by a single item measure in the BPI-SF was proposed as the primary outcome measure for this study and was seen to reduce in both groups (figure 6.6; table 6.12). The biggest change was seen from baseline to six weeks (following supervised Nordic walking) with a 30% reduction in pain in the intervention group (5.0-3.5); and 40% in the control group (5.0-3.0). At twelve weeks, worst pain scores leveled in the intervention group and reduced by a further 10% in the control group.

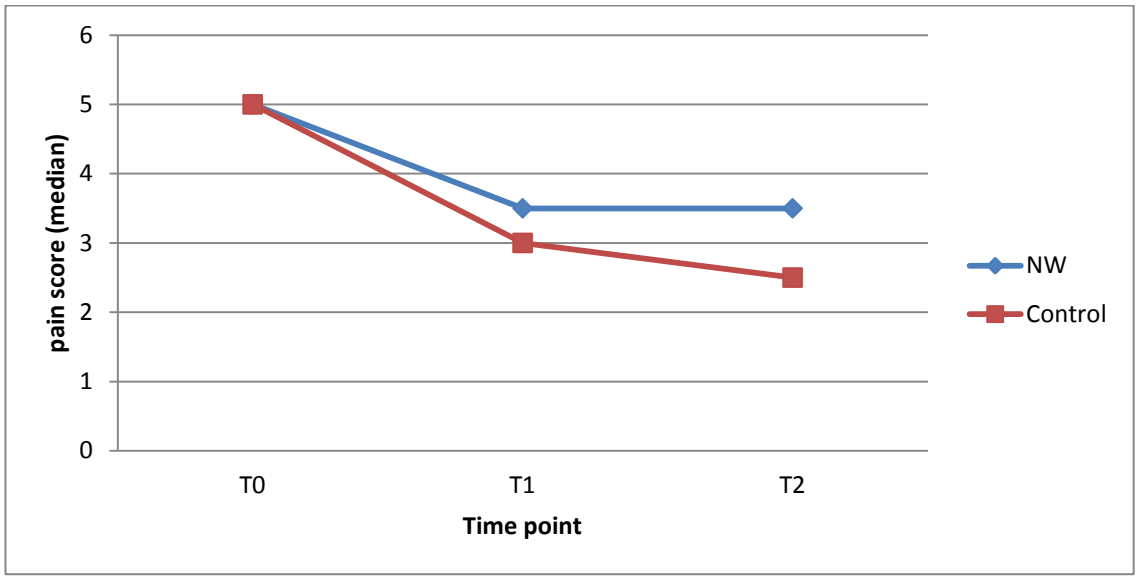
Table 6.12. Comparison of pain scores across time points (T0=baseline; T1=6 wks T2=12 wks)

		Intervention				**Control**			
		T0	**T1**	**T2**	**Change T0-T2**	**T0**	**T1**	**T2**	**Change T0-T2**
BPI -SF worst pain (0-10)	Median (IQR)	5.0 (3-6)	3.5 (2-5.8)	3.5 (2-5)	**-1.5**	5.0 (4-6)	3.0 (0.8-5.5)	2.5 (0-4.3)	**-2.5**
	Mean (SD)	4.7 (1.7)	3.6 (2.4)	3.6 (2.1)	**-1.1** (2.0)	5.0 (2.0)	3.3 (2.7)	2.6 (2.2)	**-2.4** (2.2)
BPI-SF pain severity composite (0-10)	Median (IQR)	3.0 (2.3-3.9)	2.6 (1.2-4.3)	2.3 (1.3-3.8)	**-0.7**	3.0	2.4 (0.8-4.1)	1.4 (0.4-4.0)	**-1.6**
BPI-SF pain interference composite (0-10)	Median (IQR)	2.4 (0.3-4.0)	1.6 (0.6-3.3)	1.4 (0.5-3.0)	**-1.0**	2.0	0.9 (0.1-3.0)	0.6 (0.0-3.6)	**-1.4**
Pain (SF-36 subscale)	Mean (SD)	52 (13)	58(19)	67 (20)	**15**	56 (13)	61 (21)	61 (21)	**5**
	Median (IQR)	56 (44-67)	67 (44-67)	67 (56-89)	**11**	56 (44-67)	61 (44-78)	67 (44-78)	**11**

Primary endpoint

The primary endpoint was the difference in change scores between Nordic walking and control from baseline to twelve weeks for Worst Pain. As change scores data (i.e. change between scores at T0 and T2), were normally distributed, this data was described using means and standard deviations. Mean change scores (SD) were -1.1 (2.0) for the Nordic walking group versus -2.4 (2.2) in the control group (p=0.10).

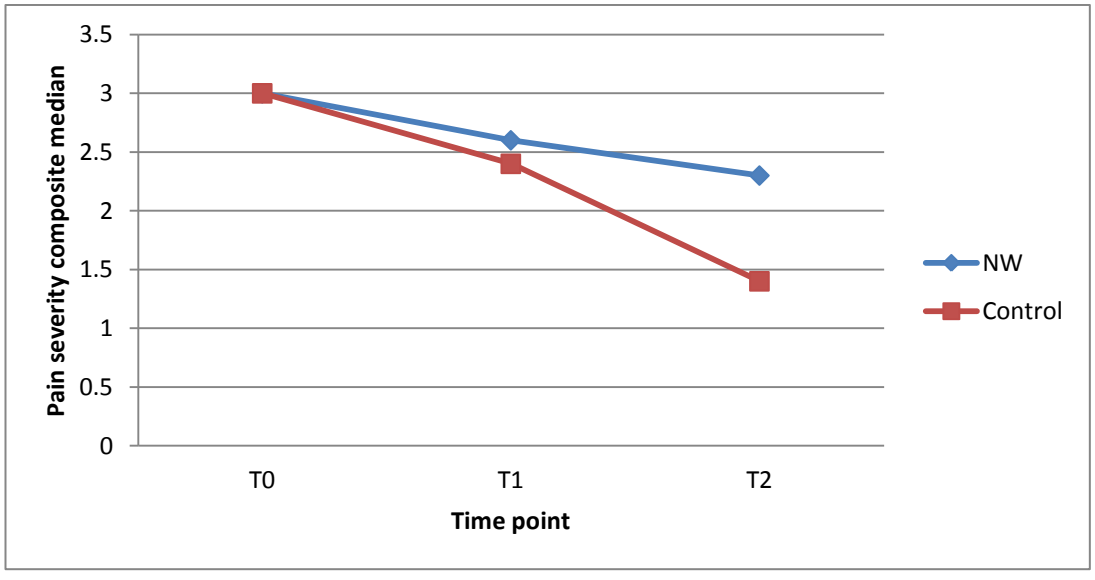
Figure 6.6: Median scores for BPI-SF worst pain at T0, T1 and T2



Pain severity

Pain severity reduced from T0 to T2 in both the intervention and control groups (Figure 6.7; table 6.12). There was a greater reduction in scores in the control group compared to Nordic walking group (0.7 vs 1.6).

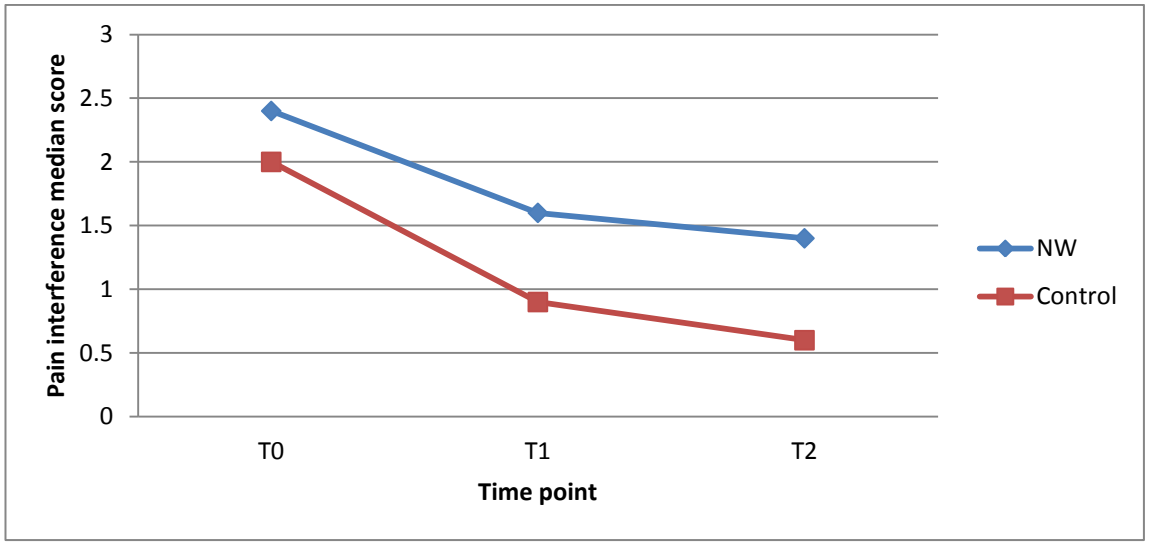
Figure 6.7: Median scores for BPI-SF pain severity at T0, T1 and T2



Pain Interference

Pain interference scores reduced in both the intervention and control group (Figure 6.8; table 6.12). The biggest change was seen from T0 to T1 in both groups, however further improvement was seen at 12 weeks. Again, the biggest improvement in scores T0-T2 was seen in the control group (1.0 vs 1.4).

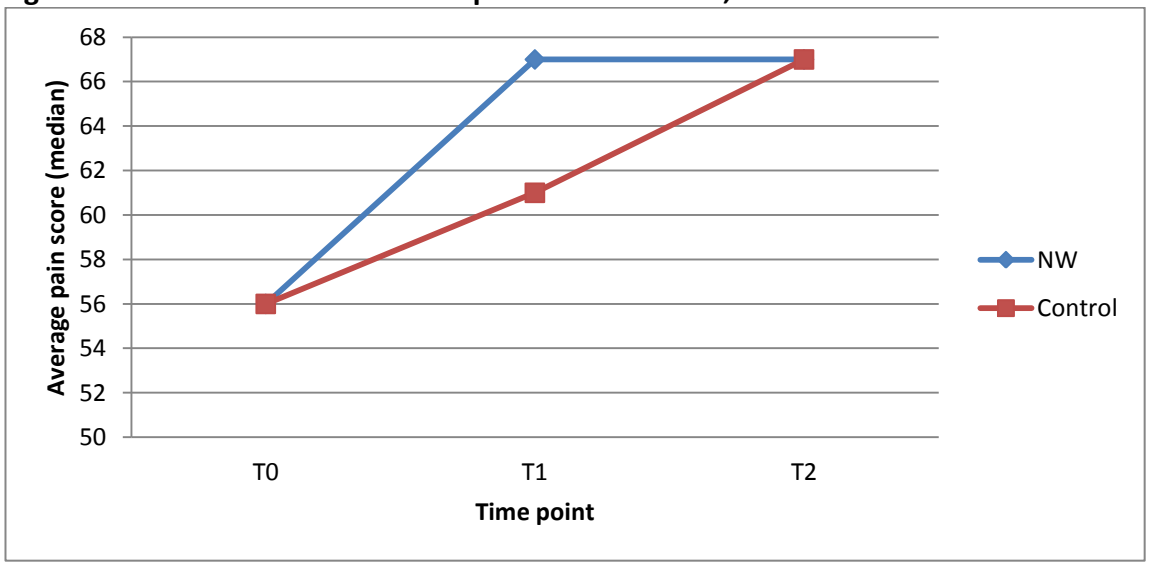
Figure 6.8: Median scores for BPI-SF pain interference at T0, T1 and T2



The SF-36 pain subscale

SF-36 pain scores improved from T0 to T2 in both groups, with scores the same in both groups at T0 and at T2 (Figure 6.9. table 6.12). All improvement in pain scores in the intervention group was recorded from T0 to T1, whereas the scores improved steadily over the twelve weeks for the control group.

Figure 6.9: Median scores for SF-36 pain subscale at T0, T1 and T2.



NB higher score indicates less pain

Pain (as reported in questionnaire survey)

In the questionnaire survey administered to all participants at the end of the study, 74% (n=24) of participants who completed the survey (n=31) thought that joint pain had got much better or slightly better over the preceding 3 months (29%, n=9; much better; 45.2%, slightly better). 16.1% (n=5) thought that it had not changed and 6.5% reported it had got slightly (n=1) or much (n=1) worse. The participant who circled 'slightly worse' also circled 'slightly better' and indicated with free text that all over pain was slightly better but left hip pain was worse. This suggests that this question measure is not a reliable measure of pain. This participant dropped out after 6 weeks due to recurrent hip bursitis.

In those whose pain had not changed or got worse during Nordic walking, the majority thought it was unlikely to be related to the Nordic walking intervention and made comments that it may be related to old age, strain which goes away in time, or other medical conditions. However, one felt it was related to the Nordic walking programme (p5, control group). Triangulating this with her exercise diary and a physiotherapy assessment, this participant had left shoulder pain before starting the Nordic walking programme, which improved during Nordic walking. However she then developed pain in the opposite shoulder during Nordic walking. The physiotherapist diagnosed impingement syndrome (rather than acute tendonitis due to Nordic walking); and the pain improved with 3 physiotherapy sessions.

Of those who reported that their pain had improved, all thought that the improvement was definitely or possibly related to the Nordic walking programme. 68% (n=21) said they would continue to Nordic walking because of this improvement. Comments included that joints appeared suppler and less stiff, that the exercise helped with coping and staying positive, and moving around was easier after the programme.

6.5.2 Depression.

Depression was measured by the Center for Epidemiological Studies Depression scale (CES-D). The mental health subscale scores of the SF-36 were also extracted for comparison (table 6.13).

Table 6.13: Comparison of Depression/mental health scores across time points

	Intervention				Control			
	Baseline	**6 wks**	**12 wks**	**Change score T0-T2**	**Baseline**	**6 wks**	**12 wks**	**Change score T0-T2**
CES-D total Median (IQR)	17 (13-25)	11 (7-17)	14 (11-20)	-3	16 (14-19)	6 (3-12)	15 (11-18)	-1
SF-36 mental health subscale Median (IQR)	76 (61-83)	83 (69-97)	80 (72-88)	4	82 (65-88)	89 (78-100)	84 (70-86)	2

In the CES-D there was an improvement in median scores in both the intervention and control groups from baseline to the end of the 12 week intervention (figure 6.10). Allowing for baseline scores, the change in scores was greater in the Nordic walking group compared to control (-3 vs -1). Furthermore, the improvement in scores was greater at T1 than at T2, and across both group assignments. This effect was also seen with the SF-36 mental health subscale (figure 6.11).

Figure 6.10: Median scores for CES-D total at T0, T1 and T2 (Higher score = more depression)

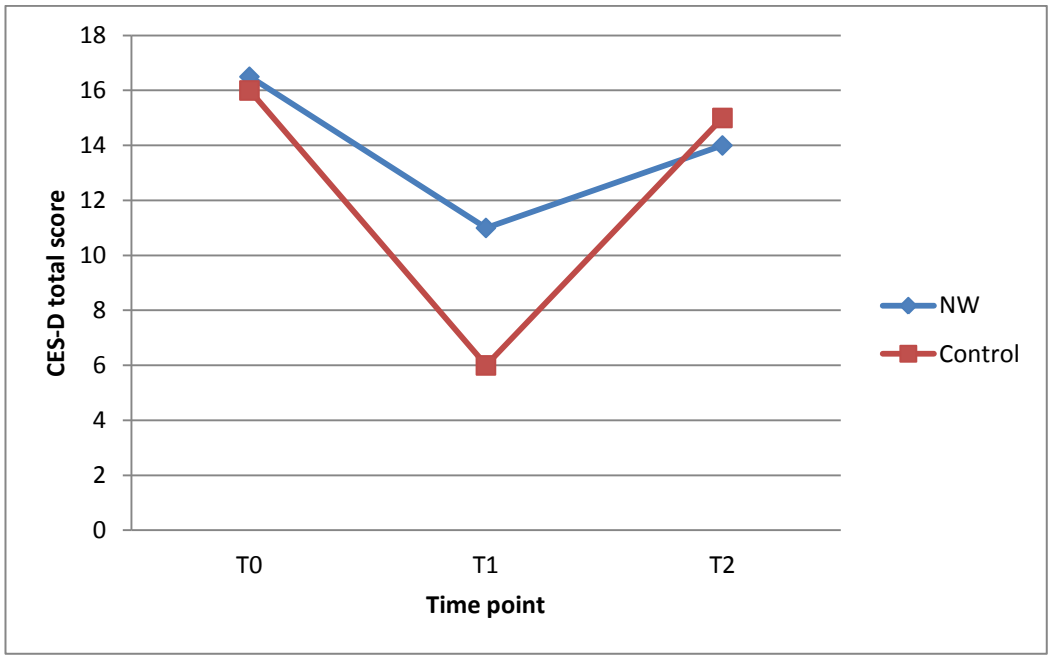
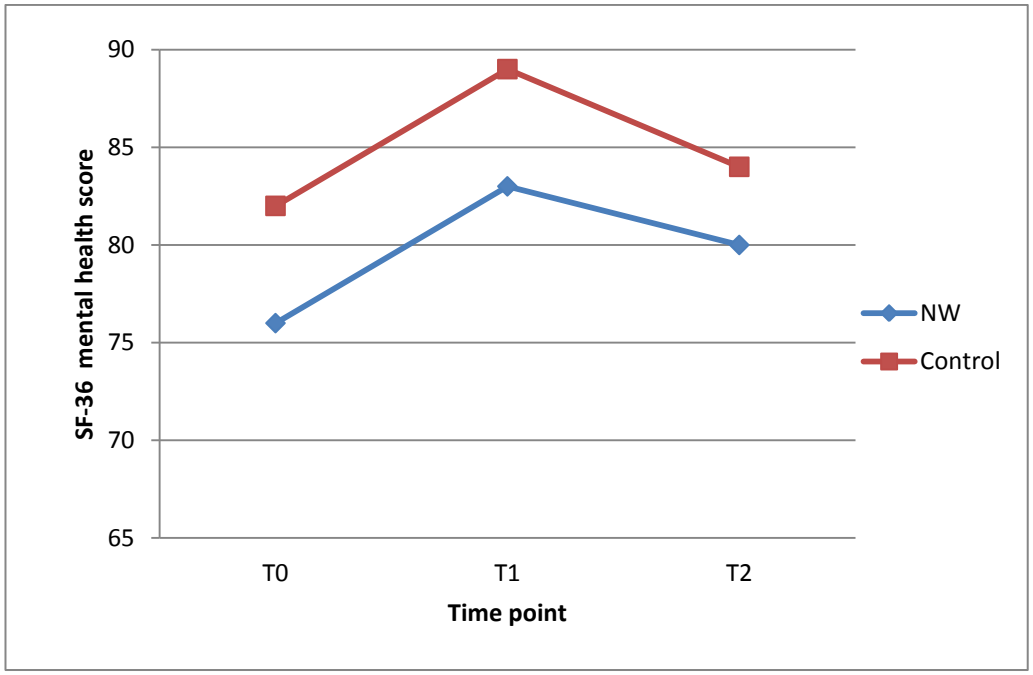


Figure 6.11: Median scores for SF-36 mental health subscale at T0, T1 and T2 (Higher score indicates lower depression)



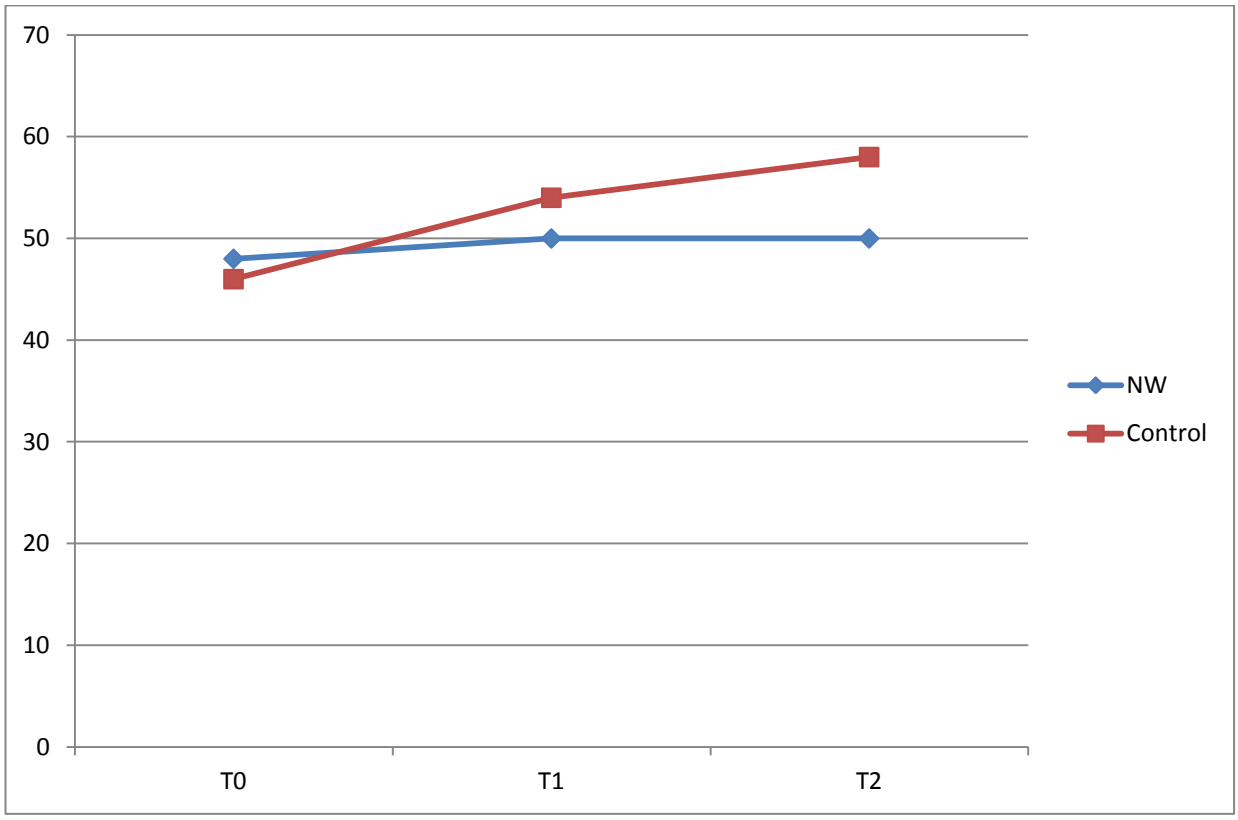
6.5.3. Self efficacy (Pain self efficacy questionnaire)

Self efficacy as measured by total pain self efficacy scores improved in both groups from T0 to T2 (table 6.14, figure 6.12). The biggest improvement was seen in the control group (12 vs 2).

Table 6.14: Comparison of Pain self efficacy scores across time points

		Intervention				Control			
		T0	**T1**	**T2**	**Change T0-T2**	**T0**	**T1**	**T2**	**Change T0-T2**
PSEQ total (0-60)	Median (IQR)	48 (38-52)	50 (44-56)	50 (46-56)	2	46 (38-58)	54 (42-60)	58 (49-60)	12

Figure 6.12: Median scores for PSEQ total at T0, T1 and T2



6.5.4 Health related quality of life (SF-36)

Health related quality of life improved from T0 to T2 in the intervention group in all subscales of the SF-36 (table 6.15, figures 6.13-6.19). Improvement was also seen in the control group, except for the physical functioning and general health perception subscales, where scores reduced fromT0 to T2. Allowing for baseline differences, improvements in quality of life (change scores) were greater in the intervention group than the control group in physical functioning, general health perception, mental health (described in previous section), and change in health.

Table 6.15: Comparison of Health related quality of life SF-36 subscale scores across time points

		Intervention				**Control**			
SF-36		**T0**	**T1**	**T2**	**Change score**	**T0**	**T1**	**T2**	**Change score**
Physical function score	Median (IQR)	63 (43-80)	75 (60-80)	75 (66-84)	12	70 (55-80)	75 58-88)	65 (53-90)	-5
Social functioning score	Median (IQR)	78 (50-100)	78 (69-84)	83 (69-100)	5	83 (67-100)	82 (74-89)	89 (78-100)	6
Energy vitality score	Median (IQR)	48 (31-60)	55 (45-64)	60 (39-71)	12	58 (36-70)	60 (40-75)	70 (48-78)	12
General health perception	Median (IQR)	53 (36-70)	55 (45-70)	58 (40-78)	5	73 (58-80)	73 (63-85)	70 (55-85)	-3
Change in health	Median (IQR)	50 (25-75)	75 (50-100)	75 (50-100)	25	50 (25-69)	50 (50-75)	50 (50-75)	0
Mental health	Median (IQR)	76 (61-83)	83 (69-97)	80 (72-88)	4	82 (65-88)	89 (78-100)	84 (70-86)	2
Pain	Median (IQR)	56 (44-67)	67 (44-67)	67 (56-89)	11	56 (44-67)	61 (44-78)	67 (44-78)	11
Role limitation emotional	Median (IQR)	233 (100-233)	233 (133-233)	233 (158-233)	0	233 (133-233)	233 (133-233_	233 (133-233)	0
Role limitation physical	Median (IQR)	150 (0-325)	200 (106-3250	225 (125-325)	75	225 (125-325)	275 (100-325)	325 (113-325)	100

Figure 6.13: Median scores for SF-36 Physical function subscale at T0, T1 and T2

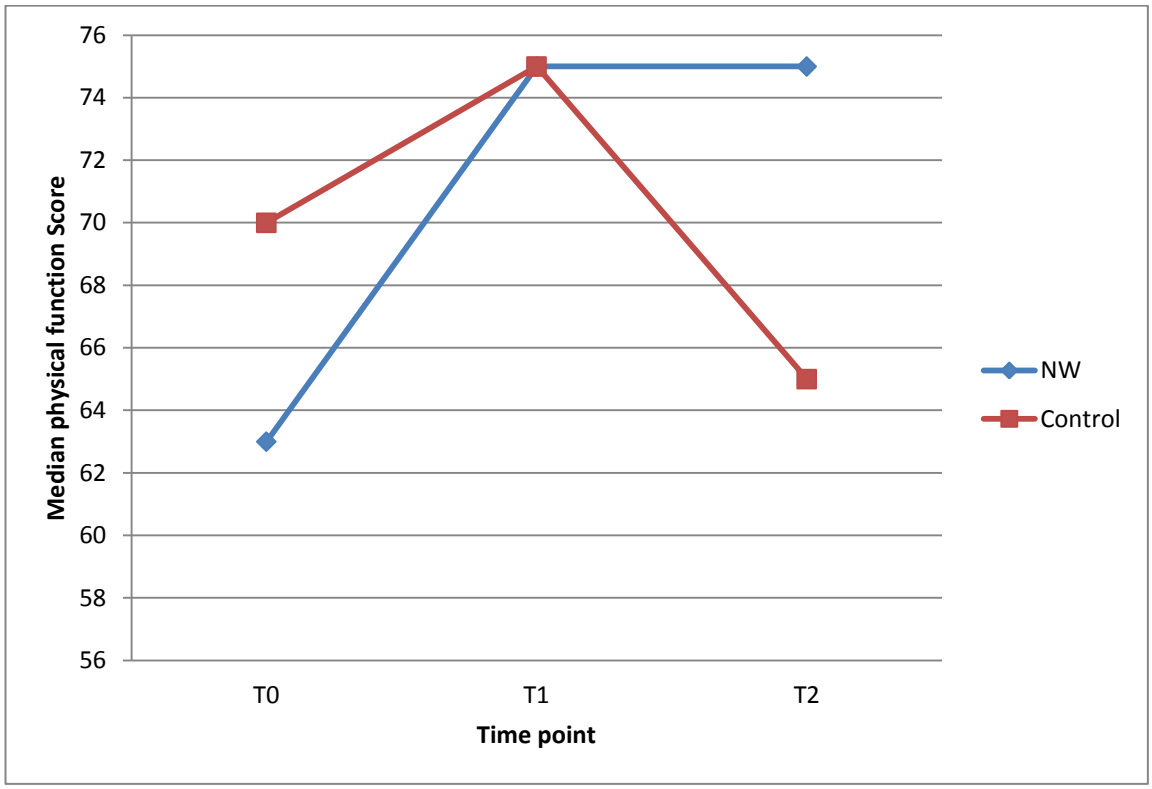


Figure 6.14: Median scores for SF-36 energy vitality subscale at T0, T1 and T2

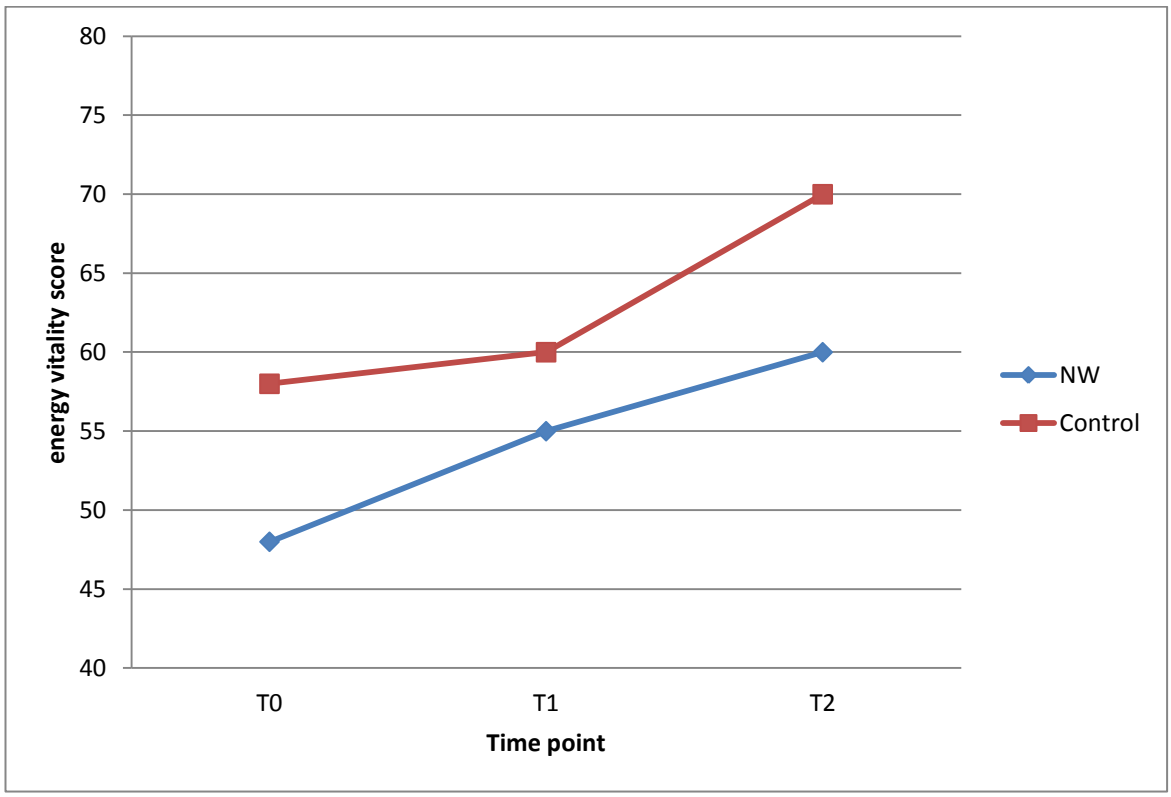


Figure 6.15: Median scores for SF-36 social functioning subscale at T0, T1 and T2

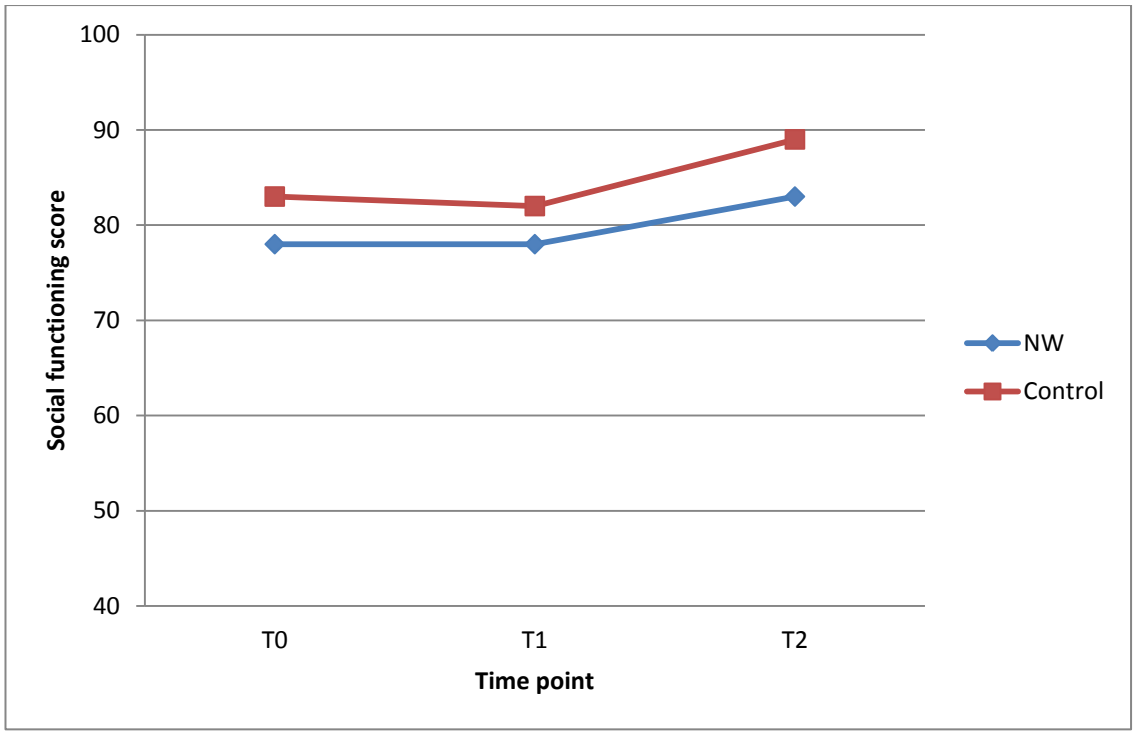


Figure 6.16. Median scores for SF-36 Change in Health subscale at T0, T1 and T2

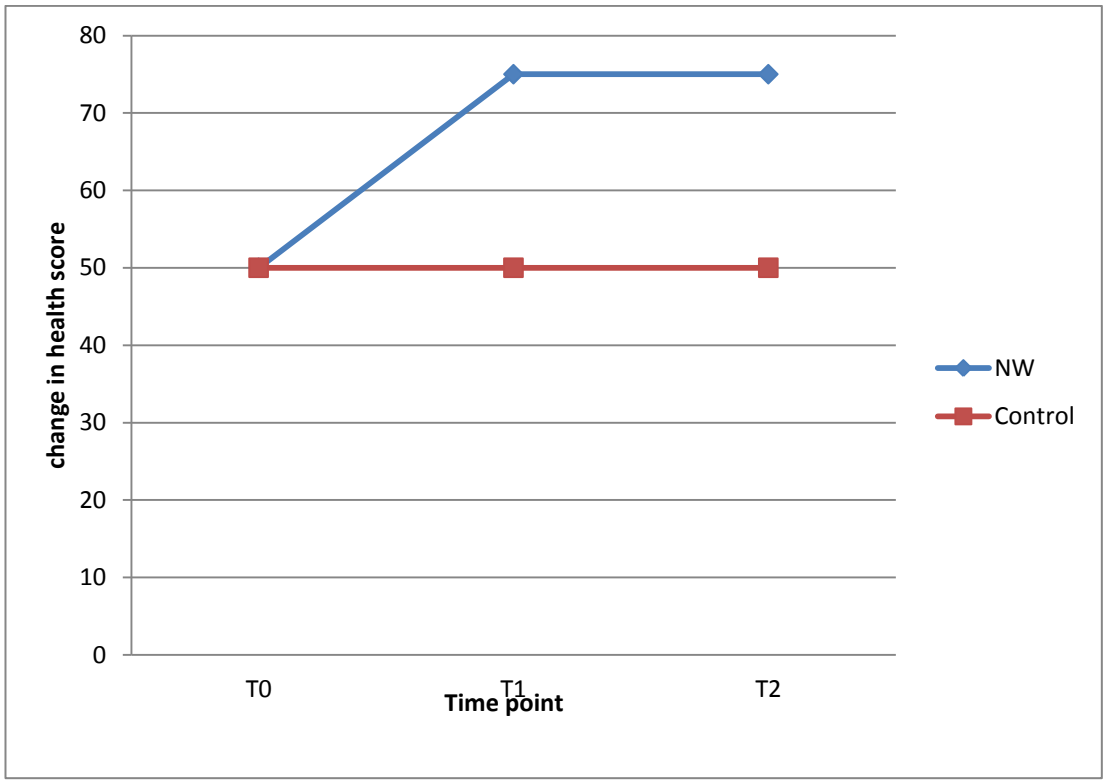


Figure 6.17. Median scores for SF-36 General Health Perception subscale at T0, T1, and T2

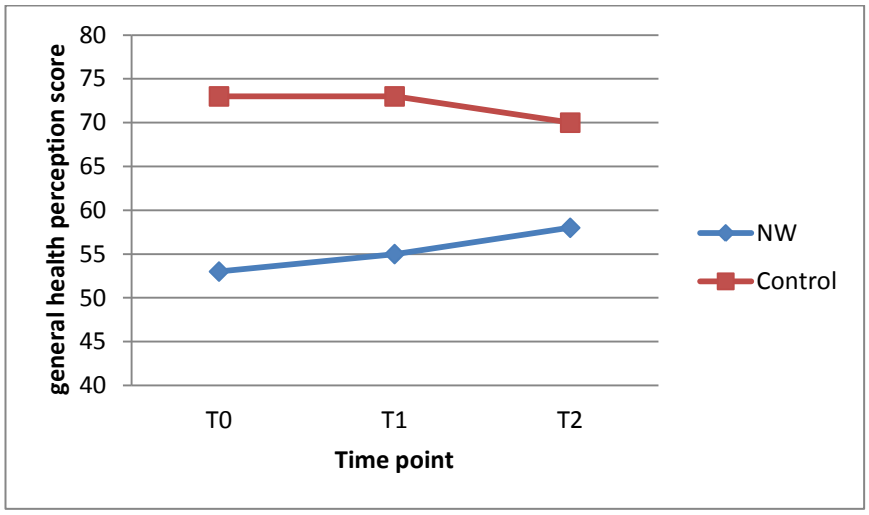


Figure 6.18 Median scores for SF-36 Role Limitation Emotional subscale at 0. T1 and T2

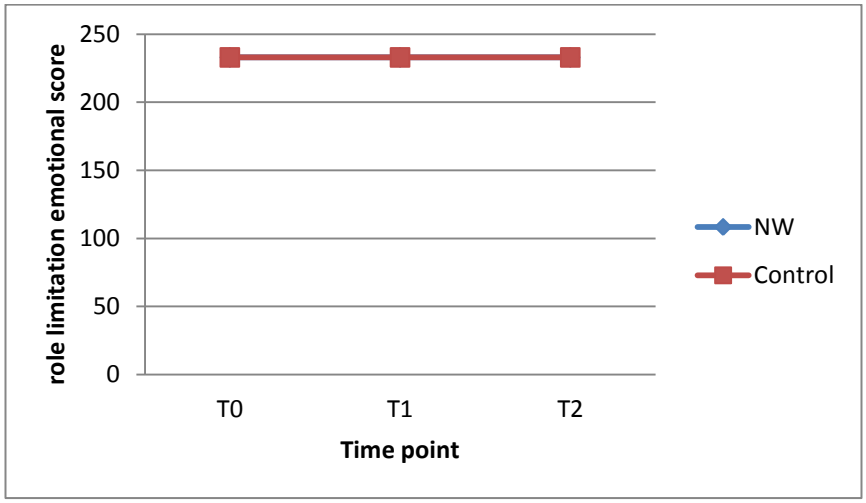
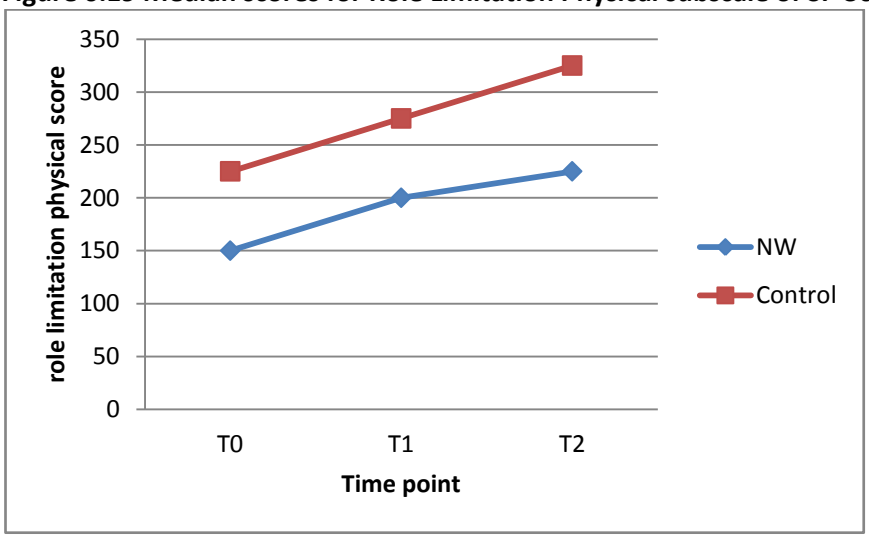


Figure 6.19 Median scores for Role Limitation Physical subscale of SF-36 at T0, T1 and T2



6.5.5. Changes in physical activity

Physical activity levels were recorded through self report on the GP physical activity questionnaire. At baseline, 70% of the sample reported taking part in no vigorous activity at all, 20% reported less than 60mins per week, 20% 1-3 hours per week and 5% over 3 hours per week. All participants reported some walking activity per week. Forty percent reported at least 3 hours, 42.5% 1-3 hours and 15% less than 1 hour. (See table 6.16 overleaf).

Changes in activity from T0 to T2 were difficult to interpret due the high levels of single item omissions at T2, as discussed in section 6.4.3. To rectify this, omissions were imputed where possible from the exercise diaries which provided the same information. Seven women in the intervention group reported increased vigorous activity from T0 to T2 compared to three more women in the control group. Nine more women in the control group had increased their walking activity to more than three hours per week compared to three less women in the intervention group fromT0 to T2.

6.6 Summary of findings

In summary, the main findings from this study were as follows. In terms of recruitment, approximately fifty percent of women estimated to be taking and AI and in follow up at the trial centre were screened. Of those screened and eligible, twenty five percent were recruited to the study and this took twelve months. With regard to acceptability, attrition was ten percent, with all drop outs within the intervention group. Women reported enjoying Nordic walking in the questionnaire survey, and adherence to weekly supervised group Nordic walking training was ninety percent. However, adherence fell for the more intensive self managed Nordic walking, with most women only managing one session per week although higher exercise frequencies were attained when all aerobic activity was considered together. Safety was demonstrated as Nordic walking did not result in any increases in lymphoedema, and new reports of pain during the study were not thought to be related to Nordic walking. In respect of the suitability of study design and methods, block randomisation at the end of the recruitment period resulted in the loss of potential participants as they had stopped their medication by randomisation. The comparison group, who received enhanced usual care with Macmillan exercise diaries, also increased their activity levels. The outcome measures appeared acceptable to participants in terms of burden and most were responsive to change, although the PSEQ demonstrated a ceiling effect at T2. Finally, there was an overall trend for improvement in pain and other biopsychosocial outcomes, although this effect was seen in both the intervention and control group. Most of the improvement in the Nordic walking group was observed in the first six weeks during supervised sessions.

The implications of the above findings will be discussed in the next chapter.

Table 6.16: Physical activity frequency at T0, T1 and T2 as measured by GPPAQ, with change from T0-T2

			n (%)				
	Group assignment	**Time point**	**None**	**<1 hour**	**1-3 hours**	**>3 hrs**	**Missing**
Vigorous exercise	**Intervention**	**Baseline**	16(80)	3 (15)	1 (5)	0	0
		T1 (6 weeks)	9 (45)	2 (10)	5 (25)	0	4 (20)
		T2 (12 weeks	7 (35)	3(15)	4 (20)	4 (20)	2 (10)
		Change	**-9**	**0**	**+3**	**+4**	
	Control	**Baseline**	12 (60)	2 (10)	4 (20)	2 (10)	0
		T1 (6 weeks)	5 (25)	1 (5)	9 (45)	3 (15)	2 (10)
		T2 (12 weeks)	8 (40)	1	5 (25)	4 (20)	2 (10)
		Change	**-4**	**-1**	**+1**	**+2**	
Cycling	**Intervention**	**Baseline**	18(90)	0	0	1 (5)	1
		T1 (6 weeks)	12 (60)	2 (10)	0	1 (5)	5 (25)
		T2 (12 weeks	15 (75)	0	2	1 (5)	2 (10)
		Change	**-3**	**0**	**+2**	**0**	
	Control	**Baseline**	17 (85)	2 (10)	0	0	1 (5)
		T1 (6 weeks)	13 (65)	3 (15)	1(5)	0	3 (15)
		T2 (12 weeks)	14 (60)	3 (15)	1 (5)	0	2 (10)
		Change	-3	+1	+1	0	
Walking	**Intervention**	**Baseline**	0	2 (10)	6 (30)	12 (60)	0
		T1 (6 weeks)	0	1 (5)	4 (20)	14 (70)	1 (5)
		T2 (12 weeks)	0	1 (5)	9 (35)	9 (45)	1 (5)
		Change	**0**	**-1**	**+3**	**-3**	
	Control	**Baseline**	0	4 (20)	11 (55)	4 (20)	0
		T1 (6 weeks)	0	1 (5)	6 (30)	10 (50)	3 (15)
		T2 (12 weeks)	0	2 (10)	4 (20)	13 (65)	1 (5)
		Change	**0**	**-2**	**-7**	**+9**	
Housework/ childcare	**Intervention**	**Baseline**	0	1 (5)	7 (35)	12 (60)	0
		T1 (6 weeks)	2 (10)	1 (5)	4 (20)	12 (60)	1 (5)
		T2 (12 weeks	0	2 (10)	5 (25)	10 (50)	3 (15)
		Change	**0**	**+1**	**-2**	**-2**	
	Control	**Baseline**	1 (5)	1 (5)	7 (35)	11 (55)	0
		T1 (6 weeks)	1 (5)	0	2 (10)	13 (65)	4 (20)
		T2 (12 weeks)	1 (5)	1 (5)	4 (20)	13 (65)	1 (1)
		Change	0	0	-3	+2	
Gardening	**Intervention**	**Baseline**	7 (35)	1 (5)	9 (45)	3(15)	0
		T1 (6 weeks)	5 (25)	1 (5)	5 (25)	7 (35)	2 (10)
		T2 (12 weeks)	0	4 (20)	11 (2)	1 (5)	5 (25)
		Change	**-7**	**+3**	**+2**	**-2**	
	Control	**Baseline**	4 (20)	3 (15)	7 (35)	5 (25)	1 (5)
		T1 (6 weeks)	4 (20)	2 (10)	4 (20)	8 (40)	2 (10)
		T2 (12 weeks)	2 (10)	5 (25)	5 (25)	6 (30)	2 (10)
		Change	**-2**	**+2**	**-2**	**+1**	

Chapter 7. Discussion

This study was set up to explore the feasibility of conducting a trial of Nordic walking in women with joint pain related to aromatase inhibitor treatment. Specifically, there was a need to determine whether the intervention was acceptable in terms of recruitment, retention and adherence; whether Nordic walking was safe, to test the suitability of trial design and methods, and to look for evidence that Nordic walking may be helpful in women with AIAA.

The findings have shown that it is possible to recruit and retain women to a physical activity intervention despite the presence of joint pain, and that Nordic walking was safe. Whilst adherence to weekly supervised Nordic walking was high (90%); mean adherence to more intensive self managed Nordic walking was only 50%, with most women only managing one session per week, rather than four as prescribed. However, despite suboptimal adherence to self managed Nordic walking, participants in both the control and intervention group managed to increase overall physical activity levels from baseline, demonstrating that increasing physical activity is feasible in women with AIAA. Furthermore, a trend for improvement in self reported pain was observed in both intervention and control groups, which may be related to this increased activity.

As AIAA is a side effect that may be experienced for the whole course of treatment (five years), there is a need to find interventions that women find acceptable to adhere to over the longer term. Considering the above findings together, it is recommended that a fully powered RCT of the Nordic walking intervention in its current format is not conducted, as women are unlikely to adhere to intensive self managed Nordic walking. However, in view of the finding that increasing activity is possible in women with AIAA, together with the observation that there was a trend for improvement in pain and other outcomes, a further trial testing the feasibility of a more acceptable physical activity intervention merits further investigation. Based on results from this study, this should include a supervised group component throughout to maximise adherence. Further findings are discussed below, and it is recommended these are used to optimise the design of a future study.

7.1. Recruitment

Overall, the recruitment strategy was effective, as sufficient numbers of women were recruited who met the eligibility criteria. In the chosen study site which treats 300 women with breast cancer per year, 40 women were recruited over a twelve month period. This was approximately 25% of those screened and eligible (n=40/159). These rates are comparable to other exercise studies in breast cancer populations. For example, the recruitment rate in the largest reported UK based exercise trial for women with breast cancer to date was 12.8% (Mutrie *et al.*, 2007), and the second largest UK trial

reported a recruitment rate of 28.6% (Daley *et al.*, 2007b). Although a recent systematic review (Maddocks *et al.*, 2009) of 65 exercise studies in people with all types of cancer suggests much higher recruitment rates are possible (median 63%; IQR, 33-80%), closer inspection of these studies revealed many to be non randomised small scale studies, and many used convenience sampling methods which can increase apparent uptake.

7.1.1 Suitability of recruitment strategy/screening method

Recruitment via follow up clinics did not achieve population based sampling, as only 50% of the previously estimated population on an AI at the trial centre completed screening in the twelve month recruitment period (377/759; as described in methods section 5.9, table 5.2). Thus recruiting via follow up clinics was not wholly effective. The reasons why can be explained in two ways. Firstly, there was no screening of the non nurse led clinic which was half of those of those unaccounted for. This was due to the limited resources of the researcher during the feasibility study. Secondly, it was decided not to screen women on primary hormone therapy (with letrozole; approximately 250). This was because by nature of this treatment modality (i.e. not suitable for anaesthetic) they would have significant medical co morbidities potentially making them ineligible for an exercise trial.

In order to ensure that screening of women attending all follow up clinics was complete, it would be necessary to dedicate specific resource to this task. For example, one UK based exercise trial for women with breast cancer reported approaching 82% of women attending breast cancer follow up in the recruitment period by employing trained recruitment staff (Campbell *et al.*, 2005).If a future study could secure NIHR adoption, research nurses could be available to dedicate specific time to recruit in clinics where other research staff were not available.

An alternative to clinic based recruitment would be to recruit via cancer registries. This method has been utilised in US based multicentre exercise studies (Irwin *et al.*, 2008a; Cadmus Bertram *et al.*, 2011). Although this strategy aims to offer population based sampling, Cadmus-Bertram et al (2011) argue that that there is still an element of self selection with this method, as in their study non graduates and non whites were under-represented. Furthermore, low recruitment rates are achieved with this method, with Irwin et al (2008a) reporting a recruitment rate of 9.5% and Cadmus Bertram et al (2011) 15.4%. In addition, it is unclear whether this strategy would be transferrable to a UK population. Nevertheless, there is a drive to reduce routine outpatient breast cancer follow up in the UK. Therefore face to face recruitment as undertaken for this study may no longer be possible and cancer registry recruitment would be a viable alternative in any future study.

In terms of identifying suitable women for the trial, the amended CPET screening tool was not specific enough in identifying women fulfilling inclusion criteria. Firstly, it resulted in gathering data on

tamoxifen users as well as AI users, which was unnecessary for this study. In addition, of those screened and taking an AI, a higher than expected percentage had joint pain or stiffness (60%; 227/377). This was because the amended CPET did not differentiate between new and pre-existing pain. This could have led to recruiting women to the study with non AI related joint pain, and consequently the amended CPET cannot be recommended as the sole screening tool for a future study.

A patient reported outcome measure for AIAA is currently being developed and validated by a research group in the US (Castel *et al.*, 2011) which may result in more targeted screening. Alternatively, recruitment staff could screen all women taking AIs by asking the question, 'Do you have joint pain and/or stiffness which is new or worse since commencing your AI therapy?' This method has been used successfully in previous studies (Crew *et al.*, 2007b; Irwin, 2012).

7.1.2. Feasibility of exclusion criteria

The exclusion criteria used in this study resulted in 159 of 227 women who fulfilled the inclusion criteria being invited into the study. A review of the eligibility criteria provided below based on the findings suggests these were suitable for this study.

Despite exclusion criteria being kept to a minimum, a high proportion of women on AIs with joint pain, were excluded by the time of randomisation (30%; 68/227). However, this was less to do with the exclusion criteria and more a problem relating to the duration of recruitment as 14% of (n=32) women had come to the end of their prescribed five years of adjuvant AI treatment by the end of the twelve month recruitment period. A solution to this issue is discussed further in section 7.1.5.

Other exercise studies have more stringent exclusion criteria, and in particular often exclude women over a certain age, and those who are already exercising. Having no age cut off in this study resulted in ten women over 70 being recruited to the study. Although both participants dropping out mid study were over 70, these drop outs were due to recurrent musculoskeletal problems, and therefore it is judged appropriate to offer this study to all ages if they are fit to exercise. It is suggested that more attention be paid to the musculoskeletal section of the PARQ health screen to ensure women with significant existing problems are excluded in any future study.

Women who were already exercising were also allowed in this study unless they were currently enrolled in a Nordic walking programme. Many exercise studies exclude individuals who are already physically active, 'to observe a maximal and independent effect of exercise on outcomes' (Irwin *et al.*, 2008a). It is felt that for ethical reasons it would be hard to justify this when the benefits of exercise in cancer populations are so overwhelming. If there is concern regarding dilution of effect, there is the option to conduct a subgroup analysis stratifying by exercise.

There was no minimum baseline pain level set in order fulfill inclusion criteria. Although other studies investigating AIAA have excluded women with baseline pain levels of three or less, as measured by Brief Pain Inventory worst pain measure (Crew *et al.*, 2010; Irwin, 2012). In this study there was a 30% reduction in worst pain scores between baseline and the end of the study despite not placing such a restriction, thus suggesting this would not be necessary.

7.1.3 Demand for the intervention

There was good demand for the intervention as demonstrated by the level of study uptake (25%, 40/159) similar to other breast cancer exercise studies. This was despite the fact that these women were also experiencing joint pain. Participants were not formally asked to give a reason for declining entry to the study. Asking participants to divulge this information had previously been discussed as a potential barrier to obtaining ethical approval, and therefore was not included in the research protocol. In hindsight, this was a limitation of the feasibility study, and it is recommended that this information be collected in a future study through use of a reply slip. Nevertheless, some women who sent a written response declining participation also provided a reason on the reply slip. Main reasons given were similar to those reported in previous breast cancer exercise studies which include lack of interest, being too busy, other health problems and unwillingness to travel (Mutrie *et al.*, 2007; Irwin *et al.*, 2008a; Penttinen *et al.*, 2009). Based on these factors, an exercise intervention that offers flexibility in timing and proximity to the participants' home might increase chances of participation. One of the reasons for choosing Nordic walking as the exercise intervention was to fulfill these requirements, and allow participants to self manage exercise after a period of training. Therefore providing more clarity and explanation about the flexibility and proximity of the intervention might enhance uptake in the future. This could be achieved by a follow up phone call one to two weeks after sending out the study invitation to non responders. This method has been utilised in the Yale Exercise Study (YES), and Increasing or Maintaining Physical Activity during Cancer Treatment (IMPACT) exercise study (Irwin *et al.*, 2008a; Cadmus Bertram *et al.*, 2011). Alternatively, in the Finnish BREX (BReast cancer and EXercise) Study (Penttinen *et al.*, 2009), eligible women were recruited via telephone as first point of contact, which resulted in a high recruitment rate (58%). This approach would also offer the research team the opportunity to gather data on reasons for non participation.

7.1.4 Recruitment duration

The period of planned recruitment duration was adequate for the method of recruitment employed, i.e. screening women at follow up clinics, as it maximised the number of women screened and invited into the study. However, another advantage of cancer registry recruitment would be that this could shorten the time from invite to randomisation, which might result in fewer women being excluded because they had completed their AI therapy.

7.1.5 Representativeness of sample

Baseline demographic medical details were broadly comparable to previous studies of women with AIAA suggesting that the sample was representative; therefore findings from this study could be generalisable to the wider population with AIAA. (Crew *et al.*, 2007b; Mao *et al.*, 2009; Briot *et al.*, 2010). Comparison with other studies demonstrates that the sample was similar in terms of average age (mean 63). There were more women in the older age group (65+) in my sample which is likely to be because the geographical area of the trial centre has a higher than average population of older people (Poole Borough Council, 2011). However, the sample was racially homogenous (100% Caucasian) due to the geographical location; therefore any results would only be generalisable to this sector of the population. Baseline pain severity was comparable other studies investigating AIAA (Crew *et al.*, 2007a; Crew *et al.*, 2007b; Briot *et al.*, 2010).

7.2 Acceptability of the intervention

Although Nordic walking was enjoyed by the majority of participants, and attrition comparable to other studies, the data collected on adherence demonstrated that the prescribed Nordic walking dose of 30 minutes, four times per week, was not achieved by most. Therefore modifications to the intervention components are warranted to improve acceptability, and thereby increase completion rate and adherence. These are discussed below.

7.2.1. Attrition

Attrition was low (10% of total sample) and compared favourably to other exercise studies in cancer populations. For example, a systematic review of 65 studies examining the acceptability of exercise interventions in people with or cured of cancer (Maddocks *et al.*, 2009) reported a median (IQR) completion rate of 84% (72-93%), in other words, 16% attrition. This suggests that overall the Nordic walking intervention was acceptable and manageable for the participants. Although all drop outs (n=4) were within the intervention arm, two of these occurred before the exercise programme had even commenced. The remaining two that dropped out at six weeks did so due to musculoskeletal problems. It is therefore recommended in a future study that the commitments required are made very clear before randomising participants. This has been found to reduce attrition in past exercise studies (O'Neal and Blair, 2001). Furthermore, there should be careful screening for significant musculoskeletal problems before randomisation.

7.2.2 Adherence to exercise dose

The average weekly frequency of Nordic walking achieved by participants was only 50% of that prescribed (two rather than four sessions per week). Furthermore, for the majority of participants (>75%), only one to two Nordic walking sessions per week was achievable (table 6.3). Women commented in the questionnaire survey that four sessions was difficult to fit in due to commitments at

work, home and to other exercise. However, when other types of aerobic activity was included in the frequency count, participants did manage an average of four sessions of exercise per week and the majority (>75%) managed three (table 6.9). This frequency is comparable to the BREX study (Penttinen *et al.*, 2011), whose participants managed an average of 3-4 sessions of aerobic exercise per week. The data on frequency of both Nordic walking and aerobic activity combined is important to consider when planning a future exercise intervention, as it suggests that three sessions of exercise per week would be feasible for the majority of participants, but only if a variety of aerobic activity was incorporated, rather than a single form of exercise.

The prescribed duration of exercise (120min/week) was also unattainable for most. Throughout the period of self managed Nordic walking, women managed an average Nordic walking duration of 99 minutes per week, which was 82% of that prescribed. Whilst this is lower than national recommendations for the adult population of 30 minutes, five times per week, it is within the exercise dose range found to be effective for improving quality of life in Pastakia et al's (2011) review on exercise interventions for women with breast cancer (as discussed in chapter 4). Furthermore, similar adherence rates are reported in many other breast cancer exercise studies (appendix XIV, table c).

In summary, using the data collected on adherence from this study, it appears unrealistic to expect women to carry out unsupervised Nordic walking four times per week for thirty minutes. In order to increase adherence to the exercise dose in a future study, a combination of aerobic exercise should be allowed, with an exercise dose of thirty minutes, three times per week, provided it is at the correct intensity (measurement of intensity is discussed in section 7.4.4).

7.2.3. Components of the intervention affecting adherence

In chapter 4, a rationale was provided for specific components of the intervention to improve adherence, based on prior research and social cognitive theory. These are reflected on below in light of the study findings, and demonstrate that whilst supervision and group exercise may have improved adherence, other components did not appear to have an effect.

Supervised vs unsupervised

Supervised exercise appeared to encourage adherence as demonstrated by the high adherence rate of 90% to weekly supervised sessions in the first six weeks of the intervention. Furthermore, in the questionnaire survey, participants commented that they found the duration and length of the supervised training programme to be acceptable. There were several comments that suggested participants found the supervised exercise to be more motivating than self managed exercise. As discussed in section 4.2.2, systematic reviews in both chronic musculoskeletal (Jordan *et al.*, 2010) and cancer populations (Husebo *et al.*, 2013) concluded that supervised exercise is better than non supervised exercise at increasing adherence. Increasing the number of supervised sessions might have increased adherence.

However, this would have reduced flexibility of exercise timings, and could have had the reverse effect. For example, in the YES study (Irwin *et al.*, 2008a), more participants were adherent to the two home based sessions per week (96%), than the three gym based sessions (67%). Therefore, it is recommended in a future study that one supervised session per week should continue for the whole twelve weeks of the intervention, but the self managed component should continue twice per week.

Group vs individualised

As the group element of the intervention was also supervised, it was difficult to draw conclusions regarding its independent effect on adherence. However, comments provided by participants in the questionnaire survey suggested that being in a group was a motivating and positive experience. These findings are similar to those reported by Emslie et al's (2007) focus group study of women with breast cancer exercising under group supervision, which found that women valued exercising with others 'in the same boat'. This supports the concept of social modeling described in social cognitive theory, in that group activity may promote adherence by providing an opportunity for participants to see that others like themselves can do it. However, being in group also presented challenges for some, as a few comments suggested the variety of abilities within the group led to individuals feeling the level of exercise was too easy or too difficult. Therefore, in a future study it is recommended that group exercise continue, but with smaller groups to increase flexibility.

Graded activity

Participants did not adhere to the graded exercise prescription set in the first six weeks. As discussed in section 4.2.5, graded exercise was included based on social cognitive theory and prior evidence that gradual increases in activity can increase adherence (Jordan *et al.*, 2010), and also help deconditioned participants acclimatise. However, the diaries revealed that despite the recommendation to gradually increase frequency, on average participants carried out the same volume of Nordic walking throughout the intervention. Therefore, in a future study a static volume would be recommended, as this will reduce the complexity of the exercise prescription.

Type of exercise

Nordic walking was an acceptable and enjoyable form of exercise, as demonstrated by the questionnaire survey in which 75 percent of participants reported they would continue with it, and also the positive comments. However, most only managed one to two sessions per week, and additional exercise performed by participants mainly consisted of normal walking. This suggests that using Nordic walking as the type of exercise did not promote adherence. The warm up was too tiring for some of the older participants. Nordic Walking was chosen as the form of exercise, as it was hypothesised that it might reduce pain more than normal walking by increasing energy expenditure and muscular strength, and reducing load on joints. However, as demonstrated in the review of Nordic

walking in musculoskeletal conditions in chapter 3, this has yet to be proven in randomised controlled studies of Nordic walking in musculoskeletal populations. When participants were asked what type of exercise they would prefer to do in the future, the largest percentage (30%) stated walking was their preferred activity. This concurs with previous research which has demonstrated that walking is the most preferred type of exercise for cancer survivors (Jones and Courneya, 2002; Rogers *et al.*, 2009; Stevinson *et al.*, 2009). To date there is no evidence that one type of exercise is more effective at increasing adherence than another (Jordan *et al.*, 2010). However, the two studies which have examined the effect of exercise on AIAA both employed walking as the aerobic element of the physical activity intervention (Irwin, 2012; Nyrop *et al.*, 2013). In the US based feasibility study by Nyrop et al (2013), only 5% (n=1) dropped out and 50% of participants were able to increase their walking activity to 150 minutes per week. In the HOPE study, drop outs were also low at 8% (5/61). It is therefore likely that by allowing a variety of aerobic exercise with the focus on normal walking, rather than Nordic walking, women would be more likely to adhere to the prescribed exercise dose.

Instructor

As the sample was small, one instructor provided all of the supervised training sessions, with the aim of improving uniformity for all participants. There were many positive comments regarding motivation and quality of instruction which may have had a positive effect on adherence.

Whilst having a single instructor may have helped to homogenize the intervention, it is not known whether the instructor kept strictly to the same protocol. For example, time keeping was identified as a problem, with some sessions overrunning; suggesting that the instructor may have deviated from the protocol. Attention to this would be required in a future trial, by explicitly manualising the Nordic walking intervention. This will include precise details regarding how the Nordic walking technique is taught to participants, the warm up and cool down components, the duration and distance of each walk per supervised training week; and how the instructors encourage and motivate participants. Furthermore, it would be recommended that process evaluation included direct observation of the Nordic walking training sessions, with timely feedback to the instructor regarding any deviations from the prescribed intervention. Additionally, in a bigger trial, multiple instructors would be required, and therefore it would be important to ensure all were adhering to the same content to maintain the fidelity of the intervention. In addition to manualisation, training of the Nordic walking instructors in the behavioural change aspects of the intervention, and the importance of keeping to the protocol would be provided.

Three locations were used, and from the feedback, it would be recommended that future locations should take into account parking, privacy, and condition of walking surfaces.

It is likely that the wet weather encountered during the intervention period reduced adherence to Nordic walking. 2012 was the wettest summer on record, with rainfall for the three months May-July 2012 over twice that normally experienced (322.9 mm vs an average of 148.9 mm; Met office archived data, 2012). In the questionnaire survey women commented that the weather played a big part in reducing opportunities to carry out Nordic walking. During the intervention a couple of women verbally reported that the sticks would slip on wet ground. Any outdoor exercise risks adverse weather conditions and cannot be planned for. However, having the option of a variety of aerobic exercise would enable participants to choose the most suitable form in a future study.

Use of a pedometer may further improve adherence by providing feedback on goals set. A meta–analysis of exercise studies found that the use of a pedometer significantly increased physical activity (Bravata *et al.*, 2007), therefore it is recommended that pedometers be considered to encourage adherence in any future study.

7.3 Safety

In this study Nordic walking was a well tolerated and safe exercise with no new/worsening lymphoedema symptoms, and no new cases of recorded injuries. Furthermore, the risk management strategy (i.e. recording, reporting and management) relating to new pain, injury and lymphoedema was clearly understood and followed by study personnel, and led to early detection of metastatic disease in one participant.

Five participants in the Nordic walking arm on the trial reported non AI related musculoskeletal pain whilst taking part in the study. In four, this predated the commencement of Nordic walking. Although it is possible that Nordic walking made pre-existing non AI related pain worse, it is likely that pain was reported as attention was paid to this very aspect; as they were asked to report any pain experienced during the study straight away. In one participant the pain started after Nordic walking commenced. Physiotherapy concluded this was due to pre-existing OA and could have been related to the intervention, but that Nordic walking would have been less likely to have precipitated symptoms than normal walking.

The low risk of musculoskeletal injury with Nordic walking interventions has been documented in previous trials as discussed in chapter 4. However, it is recommended in a future trial that participants continue to report new musculoskeletal pain so that further safety data can be established. In addition it is recommended that participants with significant chronic musculoskeletal disease are excluded from a future study (participants who are under secondary care management).

All participants in the intervention group with pre-existing lymphoedema had an objective improvement in arm volume during the study. The lack of adverse effects of exercise, and in particular

Nordic walking, on lymphoedema has been previously documented (Jonsson and Johansson, 2009; Malicka *et al.*, 2011). It is recommended in a future study that arm volume is recorded in women with pre-existing arm lymphoedema at baseline, T1 and T2. In addition, any participants reporting new arm aching/swelling should be assessed by the lymphoedema service. Furthermore, due to the improvement seen, it would be recommended that changes in arm volume in participants with lymphoedema be included as a secondary outcome in a future study.

7.4. Suitability of the research methods

As part of the study, aspects of the research methods were tested for feasibility, including the method of randomisation, using a wait list control as the type of comparison group, the response rate to questionnaires and suitability of outcome measures. This testing revealed methodological issues that require attention to reduce bias in a future trial.

7.4.1. Randomisation

Randomising all those eligible at the end of the twelve month recruitment period facilitated assignment to groups but resulted in significant drop out. This was done to facilitate assignment to the group intervention in a single centre study with a small sample. This resulted in fourteen percent of participants coming to the end of their five years' prescribed AI treatment whilst they waited to be invited and randomised. Thus, more women could have entered the study if randomised earlier. Therefore it is recommended that women are randomised in future as soon as there are enough participants for two groups, and also to make group size smaller. Although it is possible in a multi-centre study that recruitment would be quicker, trial centres would have to be close enough geographically that participants from both centres could attend the same location for the intervention.

Permuted blocks randomisation resulted in equal numbers of participants in each group, which was the reason for using this method of randomisation and therefore this objective was achieved. However, at baseline there were demographic and treatment related differences between treatment and control groups, which could have influenced outcomes. These included differences in the average age of the participants (five years); and also differences in the numbers who had received chemotherapy. Previous studies have demonstrated that chemotherapy is associated with an increased risk of AIAA (Crew *et al.*, 2007b; Sestak *et al.*, 2008; Sestak *et al.*, 2009) , as is younger age (Sestak *et al.*, 2009; Honda *et al.*, 2011). In a future study it would therefore be recommended that randomisation was stratified to take into account factors which independently affect AI related joint pain, including age and chemotherapy.

Allocation concealment was not fully implemented in view of the limited resources and staff in this feasibility study. It is recommended in a future study that collection of outcome measures and data analysis be carried by out those blind to group allocation to avoid any potential bias.

7.4.2. Suitability of using waiting list control group receiving enhanced usual care

Using a wait list as control was a feasible means of ensuring all participants had chance to participate in supervised exercise. However, using enhanced usual care, in which the control group had phone contact from researcher every two weeks, and received the exercise diary which contained information about the importance of exercise), resulted increases in self reported walking and vigorous activity in this group from T0 to T2 (table 6.5). This 'exercise contamination' could have led to a treatment effect in the control group.

Based on the evidence that exercise has so many benefits for cancer survivors (Speck *et al.*, 2010), it is unethical and impractical to withhold exercise completely from a comparison group. However, it could be argued that text in the Macmillan exercise diaries encouraged physical activity, based on the concepts of self-regulation and social persuasion in Social Cognitive theory. Therefore, in a future study it would be recommended that participants in the control group were given simple activity recording sheets rather than the Macmillan exercise diaries to eliminate any motivating effect these may have had. In addition there should be minimal routine contact from the research team during the intervention period.

7.4.3 Response rate to questionnaires/burden

Overall response rates to outcome questionnaires were high, as was individual question completion for the majority of measures. However, there were issues identified with individual item completion in the CES-D and GPPAQ, which have implications for a future study. Return of exercise diaries was lower and could have led to response bias.

The high response rate to outcome questionnaires indicates they resulted in minimal burden for participants and that it would be acceptable to use a similar volume of scales in a future trial.

In contrast, the exercise diary had a lower response rate (22.5% not returned). This might have been because participants had them continuously for a twelve week period, and consequently there was more opportunity for them to be mislaid, which was the reason given by 10% (n=4) of the participants for non return. There are only a few studies which report on return rate of diaries. Irwin et al (Irwin *et al.*, 2008a) report a similar return rate (72.5%) in their breast cancer exercise study suggesting return of diaries can be troublesome. However a previous home based exercise study included weekly telephone feedback on exercise recorded in diaries (Pinto *et al.*, 2005). This method would be recommended in a future study to improve data collection on self report of exercise volume.

The questionnaire survey also had a disappointing response rate (22.5% attrition), which might have been because it was administered at the very end of the study and the perceived importance of the

study had receded. This could have led to bias if differences existed between responders and non responders, in their subjective experience of the intervention.

Individual item completion was high on the BPI-SF, PSEQ and SF-36 questionnaires (on average >95%) suggesting that they were user friendly. Completion was slightly lower for the CES-D (but still >90%) and GPPAQ (>85%). Item omissions could have given rise to bias if differences existed between the characteristics of responders and non responders. However, the omissions in these two questionnaires were non-systematic and were probably related to the presentation of these two scales in table format, which made it easier for participants to miss individual items. Additionally, a manual inspection of answers to the CES-D revealed that two participants' questionnaires had been answered with ticks all down one column. This manner of response to questions regardless of content is classified as 'response style bias' (Bowling, 2005). Similar issues have been reported in a previous study of older adults (Carlson *et al.*, 2011) which reported a possible issue with the reverse scored items (i.e. positively worded items) as these 'increase cognitive processing demands' and may lead to measurement problems for older adult respondents. As the format of validated questionnaires cannot be changed (as it would invalidate them), it would therefore be recommended that more attention be paid to checking questionnaires had been completed correctly on their return.

7.4.4. Suitability of outcome and adherence measures

The outcome measures selected for this feasibility study were those expected to most effectively capture the mechanisms by which Nordic walking reduced AIAA, informed by a biopsychosocial model. The BPI-SF, CES-D and SF-36 showed good reliability, validity and responsiveness to change in this cohort of women. However, the PSEQ lacked sensitivity with high baseline scores and ceiling effects. With regard to changes in physical activity, although some of the data recorded with the GPPAQ was superfluous, it provided useful data on changes in physical activity from T0 to T2 in the intervention and control group. The Macmillan physical activity diary was suitable for self report of adherence to exercise frequency and duration; however, intensity was difficult to interpret.

Brief Pain Inventory Short Form (BPI-SF)

The BPI-SF was a suitable measure with evidence of reliability and validity in this cohort of women. Baseline scores were comparable with those reported in other studies of AIAA. There was high internal consistency within the -SF (Cronbach's alpha =.94 for pain severity items and .95 for pain interference items at T2), demonstrating reliability of the scale. There was good correlation between the BPI-SF and SF-36 pain subscale in terms of trend and direction of effect, suggesting that the two scales were measuring the same construct. There was support for its responsiveness to change, as scores from T0 to T2 changed by at least 30% in the primary outcome measure, (worst pain in the last 24 hours), and also by at least 20% in pain composite scores. There was no evidence of floor or ceiling effects.

The BPI-SF single item 'worst pain' in the last 24 hours was selected as the primary outcome measure, for the reasons outlined in section 5.10.1; namely that it has been used in several RCTs investigating AIAA (Crew *et al.*, 2010; Irwin, 2012) and thus might aid comparison, and is supported for use in measuring pain in clinical trials by IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) (Dworkin *et al.*, 2005; Turk *et al.*, 2006; Dworkin *et al.*, 2008). In this study, change from baseline to end of the intervention was greater in this single item measure than in the composite pain severity score. This demonstrates greater responsiveness to change and thus its use would be justified in a future study.

Information regarding the location of pain was not recorded in the BPI-SF. Other studies with populations with AIAA have used additional pain questionnaires which capture joint location specific symptoms (Crew et al., 2010; Irwin, 2012; Fenlon et al., 2013). These include the Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH) which assesses pain, stiffness, and functional status in people suffering with hand OA and RA (Sautner et al., 2004); the Western Ontario and McMaster Osteoarthritis index (WOMAC), which is a validated measure for assessing osteoarthritis of the knees or hips (Bellamy et al., 1988); and the Quick DASH, an eleven item instrument for measuring symptoms and physical function of the upper extremities (Hudak et al., 1996). Using such measures could enrich data by adding information on joint specific changes in pain, stiffness and function relating to the intervention, therefore these would be recommended in a future study.

Center for Epidemiological Studies Depression Scale (CES-D)

The CES-D appeared fit for use as it appeared reliable and responsive to change. Good internal consistency was demonstrated in this study (Cronbach's alpha of .9), and was comparable with previous psychometric testing in cancer populations (Hann *et al.*, 1999). The changes seen in the scores from T0 to T2 correlated well with the mental health subscale of the SF-36 in terms of trend and direction of effect, suggesting they were measuring the same construct. The average score for this sample at baseline (median=16) was high compared to norms previously measured in cancer populations (Hann *et al.*, 1999; van Wilgen, 2006), indicating higher psychological morbidity than would be expected .This might be related to high baseline pain levels in this population. In support of this argument, a large epidemiological study involving over 3000 people conducted by the World Health Organisation found a fourfold increase in associated depressive or anxiety symptoms in people complaining of pain persisting after 6 months (Gureje *et al.*, 2001). Both pain scores and depression scores improved from T0 to T2 in this study. This finding may support the use of depression as a useful secondary outcome to evaluate the effect of this intervention on AIAA.

Pain self efficacy questionnaire (PSEQ)

Based on findings from this study, The PSEQ is not considered suitable for use in this population because of high baseline scores and ceiling effects at T2, demonstrating a lack of sensitivity. It had been selected for use after review of several self efficacy questionnaires, as it appeared to be the most relevant for populations with chronic pain (Nicholas, 2007). However, self efficacy scores at baseline for this population with AIAA were much higher than those reported in a large cohort of people with chronic pain in which the scale was validated (median of 47 versus 22; (Nicholas, 2007). Furthermore, there was a ceiling effect in that 25 % (n=10) of the sample scored the maximum score of 60 at T2. Although there is no universally recommended criteria for maximal floor or ceiling effects a figure not exceeding 15-20 percent is suggested in a well known textbook on research methods (Bowling, 2009). The feasibility study in women with AIAA by Nyrop et al (2013) employed the Arthritis Self Efficacy Scale (Lorig *et al.*, 1989). These authors also reported a high baseline value with this scale, and small effect size at the end of the intervention. In spite of these findings, in view of the strong associations between self efficacy and pain (section 2.11.4), it remains an important construct to retain in a future study. Therefore it is recommended that a further review of self efficacy measures with psychometric testing in the cancer populations be carried out before deciding on a scale for a future definitive study. Alternatively further validation studies should be conducted on this scale prior to future utilisation.

Short Form-36 (SF-36)

The SF-36 was found to be suitable, as it was reliable and responsive to change. The scale has been extensively tested in cancer populations previously (section 5.10.4). Here, there were no apparent floor or ceiling effects and the questionnaire appeared responsive in view of the fact scores changed between T0 and T2. Good internal consistency was demonstrated for all subscales except for the pain subscale (alpha of .56). This might have been lower as the subscale consists only of two items and therefore is prone to more variability in consistency. (Indeed at T2 the alpha was higher at .90). Its subscales of pain and mental health correlated well with the BPI-SF and the CES-D respectively, demonstrating convergent validity. Baseline scores were lower than those observed in the general population (Jenkinson *et al.*, 1999) suggesting this sample had a lower quality of life than the general population. Indeed, the scores reported in this feasibility study were similar to those in a previous study comparing joint pain in women with and without breast cancer (Fenlon *et al.*, 2013). This large UK based cross sectional study demonstrated that quality of life was significantly worse for women with breast cancer and joint pain, compared to women with breast cancer who did not have pain. This gives further support for the biopsychosocial model, demonstrating the importance of measuring quality of life in this population.

GP Physical Activity Questionnaire

The GP physical activity questionnaire was useful in showing changes in walking and vigorous activity from baseline to the end of the intervention. It was selected as it is the most widely available questionnaire measuring physical activity for the UK population. Although previous psychometric testing appears to be limited to a sample of 334 people in general practice (Department of Health, 2009a), other physical activity questionnaires also appear to have limited testing (Lowther *et al.*, 1999; Friedenreich *et al.*, 2006). Although all of the data recorded by the GPPAQ was not used in this study, the data on walking and vigorous activity was useful as it demonstrated clearly that the control group increased their walking more than the intervention group. Therefore, in the absence of a simpler measure, the GPPAQ would be recommended for a future study.

Adherence measure: Macmillan physical activity diary.

The Macmillan physical activity diary was suitable for measuring self report of exercise duration and frequency. However, intensity was often difficult to interpret, and therefore an additional objective measure of intensity would be recommended in a future study.

Exercise diaries are one of the most commonly used methods to measure exercise adherence (Jordan *et al.*, 2010), particularly in home based interventions. In this study diaries were used for pragmatism and as they formed part of the model of self regulation within social cognitive theory. Indeed, this was supported by comments from some participants that found the diaries motivating and helped them to reflect on what they had achieved. Whilst there is some evidence that exercise diaries can over estimate physical activity (Yuen *et al.*, 2013), other research suggests that they remain the best measure of adherence (Wilbur *et al.*, 2001).

Only exercise that was reported as moderate to high intensity was included in the data, and although participants had been instructed on how to judge intensity using the BORG rating of perceived exertion, it was sometimes difficult to interpret by the wording used in the diaries, and sometimes it was omitted. This could have led to reporting of a lower (or higher) intensity of physical activity than actually occurred. Therefore, in a future study it would be recommended that an objective measure of intensity be used to supplement self report. Although VO_2 max and accelerometers have sometimes been used to record exercise intensity in breast cancer research (Courneya *et al.*, 2003; Courneya *et al.*, 2007b), these methods are expensive and data collection/analysis is burdensome for researchers (Berlin *et al.*, 2006). The most commonly used objective measure of exercise intensity is the heart rate monitor (Daley *et al.*, 2007c; Mutrie *et al.*, 2007; Demark-Wahnefried *et al.*, 2008; Cadmus *et al.*, 2009) and these have been found to add to the accuracy of self reported intensity. For example, in the SHERBERT study (Daley *et al.*, 2007a), discrepancy was found between heart rate and the participants self rating of perceived exertion, and the authors concluded there should be more than one measure of

intensity to reduce bias. Although this will increase data collection and research costs, heart rate monitors are recommended in a future study for this reason.

7.5 Effect of the intervention

As part of feasibility, evidence of the impact of the Nordic walking intervention on self report of pain and related outcomes was recorded. Importantly, no deterioration was recorded, rather, trends indicative of improvements were observed from baseline of the end of the intervention in pain, depression, health related quality of life and self efficacy. However, these improvements were reported in both the intervention and control groups for nearly all of the measures, making it difficult to determine whether these changes were related to Nordic walking or to increased physical activity levels in general.

Although this study was not powered to detect significant changes in outcomes, the preliminary findings of improvements in pain, mood , quality of life and self efficacy are comparable to previous research examining the effect of exercise in breast cancer populations(Courneya *et al.*, 2003; Daley *et al.*, 2007c; Mutrie *et al.*, 2007; Milne *et al.*, 2008). For example, improvements in health related quality of life, mood (Mutrie *et al.*, 2007) and self efficacy (Phillips and McAuley, 2014) have all been demonstrated in previous studies. However, no prior research has tested the effect of Nordic walking as a specific form of exercise on biopsychosocial outcomes in breast cancer populations. Although the effect of Nordic walking on pain and related biopsychosocial outcomes has been tested in musculoskeletal populations as discussed in chapter three, the findings have been inconclusive.

Pain

The improvement in pain scores from baseline to the end of the intervention suggests that being in this research study may have had a positive effect on participants' pain. The difference observed in worst pain scores at the primary endpoint of twelve weeks:- 40% reduction in control group, and 30% in intervention group; has been demonstrated as a clinically meaningful difference in a meta-analysis of ten trials involving a total sample of 2724 people with chronic pain. The authors of this review (Farrar *et al.*, 2001) compared a ten point rating scale (such as the BPI-SF) to a standard seven point 'patient global impression of change' scale. Findings were that patients' reports of 'much better' or 'very much better', consistently correlated to a change of two , or 30% on the ten point rating scale, regardless of population, study, disease type, age or treatment group. These results have also been replicated in a more recent study (Mease *et al.*, 2011) .

The improvement observed in this study might have been related to the intervention. However, as improvement was reported in both groups, it could alternatively have been related to the increased activity levels observed in both groups; increased attention from study personnel, the information in

the exercise diary which encouraged physical activity; or an awareness of the aims of the study (Hawthorne effect). Another explanation is that participants' AI related joint pain improved independently with the passage of time. However, such dramatic improvements in pain scores over a twelve week period in control group have not previously been demonstrated in longitudinal non-interventional studies of AIAA (Briot *et al.*, 2010; Crew *et al.*, 2010). This suggests the control group as well as the intervention group had a treatment effect.

Improvements in pain scores were greatest in the control group, although differences between groups at T2 were not statistically significant. The biggest improvement in pain scores in the Nordic walking group was seen in the first six weeks of the intervention when Nordic walking was supervised. In view of this, in a future study it is recommended that the supervised element of exercise continue throughout the whole intervention, to assess whether this would have led to a further improvement in pain outcomes. These findings are consistent with those in recent preliminary studies of exercise interventions in women with AIAA, which have found improvements in pain, as reported in section 2.10.1, and provide further endorsement for carrying out a fully powered RCT.

Depression.

Depression as measured by the CES-D and the mental health subscale of the SF-36 improved from baseline to the end of the intervention in both groups but the amount of change was greater in the intervention group. The biggest improvement was seen at midpoint in the study. It is unclear why this occurred, but the effect was seen in both groups and in both measurement scales. Small but significant beneficial effects of exercise on mood have been reported in a recent Cochrane review (Rimer *et al.*, 2012) and in some breast cancer exercise studies. For example, a Scottish study of 203 women with breast cancer randomised to a mixed aerobic and muscle strengthening exercise or usual care found that those in the intervention group had significantly improved mood improved as measured by the Positive and Negative Affect Scale at the end of the intervention (Mutrie *et al.*, 2007). Again, as the greatest effect was seen after the group supervised component, this again suggests supervision should continue throughout the whole intervention.

Self efficacy

Self efficacy as measured by the PSEQ improved in both groups. It is not clear why this should have been; although in this group it may be have been due to high baseline self efficacy scores. This may highlight differences in the women who participated in the study as those who elect to join a walking group of this nature may have different levels of self-efficacy to other groups. It is also possible that improvements in self efficacy were related to an increase in physical activity by both groups. A recent longitudinal study of 1527 women with breast cancer examined the relationship between physical

activity and quality of life, and found that self efficacy was an important mediating factor; i.e., participants who increased physical activity, also increased self efficacy levels, and in turn quality of life improved (Phillips and McAuley, 2014). Although the study had no comparison group, based on the large sample size, it seems likely that exercise frequency and self efficacy are linked, supporting the role of exercise in improving this biopsychosocial outcome.

Quality of life

Health related quality of life improved in all subscales of the SF-36 in the intervention group and in all but the physical function and general health perception subscales in the control group. Improvements in quality of life have previously been demonstrated in several randomised controlled trials of exercise in breast cancer populations (Courneya *et al.*, 2003; Daley *et al.*, 2007c; Mutrie *et al.*, 2007; Milne *et al.*, 2008). The difference in the SF-36 physical functioning subscale scores between intervention and control group at T2 might have been related to greater increases in vigorous activity in the intervention group. It is suggested in a future study that this is more rigorously assessed with the use of an objective measure of physical fitness such as the six minute walk test.

Physical activity

In terms of physical activity, both groups increased vigorous activity over the twelve week intervention period, but to a greater extent in the intervention group (+7 in the intervention group versus +3 participants in the control group). The control group also increased their walking activity from T0 to T2 whereas the intervention group reported a decrease (+9 in control vs -3 participants in intervention group). This finding suggests that being in the study encouraged women to be active. Therefore as both groups increased activity, and pain improved in both groups, it could be that increasing activity in general helps to reduce AIAA.

In summary, no deleterious effect was seen from the Nordic walking intervention and there appeared to be consistent improvements across all measures. However, as both activity increased and outcomes improved in both intervention and control groups, it is difficult to specifically recommend Nordic walking over other forms of activity. In view of the finding that outcomes improved most at six weeks rather than twelve weeks, it is recommended that the design of the trial in the first six weeks, i.e. supervised group activity supplemented with self managed exercise, is continued throughout the intervention.

7.6 Strengths and limitations of the study.

As this was a feasibility study, the aims were to test the acceptability, safety of the intervention and design of the study rather than the effectiveness of the intervention. A strength of the current study therefore lay in the amount of data generated on feasibility which will greatly assist in the design of a future fully powered randomised controlled trial. This includes data on the recruitment strategy, the design of the study, and data collection processes.

However, some limitations were identified. Although the sample was broadly representative of women with AIAA, it was homogenous in terms of geographical location and ethnic background, thus limiting generalisability to the wider population with AIAA. This could be addressed if a future study was multi-centre. Information was missing on reasons for participants declining participation in the study, which could be used to improve uptake in the future. Although uptake was similar to other exercise studies, a rate of 25% implies an element of self selection bias, with only women who enjoyed exercise taking part. The screening method did not achieve population based sampling which again may have introduced bias.

Adherence to self managed Nordic walking frequency was sub-optimal. Without good adherence to the intervention schedule in an exercise trial, the prescribed frequency and duration cannot be properly evaluated. For example, low levels of adherence can lead to a dilution of treatment, and in the case of a non significant effect, it is difficult to determine whether this is due to the poor adherence within the study, or to an ineffective intervention. (Daley *et al.*, 2007a).

Exercise diary return was low and therefore bias might have been introduced regarding exercise volume and adherence achieved. All outcome data were self reported, therefore subject to recall bias. The data collected demonstrated a trend for improvement not only in the intervention but also in the control group; therefore it was difficult to draw conclusions regarding the promise of Nordic walking as an intervention to improve AIAA. Furthermore, as there was exercise contamination in the control group, it is not possible to say whether the improvement seen was due to attention effects from being part of the study, due to increases in activity in both groups, or due to longitudinal change.

7.7 Recommendations for a future study.

The main aims and objectives of this study were to determine the feasibility of a trial of Nordic walking and subsequently make recommendations which would significantly improve a future trial. This next section outlines these recommendations.

7.7.1 Participants and setting

- Women with significant musculoskeletal conditions (under secondary care management) to be excluded from future study.

7.7.2 Recruitment

Although recruitment rates were comparable to previous studies in women with breast cancer, it has been identified that following may improve uptake further:

- Recruitment from all follow up clinics by the allocation of specific staff to recruit such as a research nurse, OR
- Recruitment via cancer registries. Letters to be sent to all women taking aromatase inhibitors as adjuvant treatment for breast cancer, after permission sought from treating clinician
- Use specific screening questionnaire or screen with question: 'Do you have joint pain and/or stiffness which is new or worse since commencing your AI therapy?' as used in previous trials.
- Follow up phone call a week after posting invitation letters to increase uptake and provide more information regarding the flexibility of the intervention.
- Eligibility criteria to remain as for feasibility study, but add exclusion criteria of women with pre-existing musculoskeletal disease managed in secondary care.

7.7.3 Improving acceptability of, and subsequent adherence to the intervention

Nordic walking was too prescriptive a form of exercise for women to adhere to four times per week. Modifications to the intervention components would be recommended to improve acceptability, and thereby increase completion rate and adherence. These would include:

- Reduce exercise dose to 30 minutes, three times per week
- One session per week of supervised exercise throughout the duration of the intervention
- Continue with group intervention for the supervised component
- Recommend a static exercise dose throughout the intervention
- Enhance elements of social cognitive theory to maximise adherence
- Consider use of activity tracker to maximise adherence (pedometer)
- Establish commitment to the intervention before randomisation, to reduce early drop out
- Stricter adherence to exercise training schedule by instructors, and amend locations

7.7.4 Safety

- Use existing risk management strategy to monitor for adverse events
- Record arm volumes of participants with pre-existing lymphoedema at baseline, mid study and at the end of intervention, and on report of new arm symptoms.
- Due to the findings in this study of improvements in lymphoedema, it would be recommended that changes in lymphoedema be included as a secondary outcome.

7.7.5 Research design and methods

Testing of research design and methods revealed methodological issues that require attention to reduce bias in a future trial. Recommendations would include:

- Research design should include continue as parallel group randomised control trial with participants randomised to either intervention or a waiting list control, but comparison group to receive usual care rather than enhanced usual care.
- Randomisation as soon as enough participants recruited for two smaller groups (2 x 5 participants)
- Permuted blocks randomisation but consider stratifying by age and chemotherapy type
- Separate personnel carrying out group allocation and data analysis
- Smaller group size to increase flexibility
- Simple activity recording sheet rather than Macmillan exercise diaries

7.7.6 Data collection

- Data collection points at T0 (baseline); T1 (6 weeks) and T2 (12 weeks) to continue
- Close attention to checking completion of individual items in questionnaires on return
- Maximise return rate/completion of exercise diaries with weekly phone contact
- Use of BPI-SF, CES-D, SF-36 recommended in future study
- Additional pain measures to enrich data on AIAA: WOMAC for lower limb, M-SACRAH for hands
- Alternative self efficacy measure with proven validity and reliability in cancer population
- Simple activity recording sheet to replace Macmillan exercise diary
- Heart rate monitors to increase measurement accuracy of exercise intensity

7.7.7. Future Sample size:

The sample size required for a fully powered definitive study was calculated from the standard deviation of the change score for the primary endpoint (BPI-SF worst pain score), which was 2.1. In order to have 90% power to detect a clinically meaningful change of 2 on the BPI-SF worst pain measure, a future sample size of 24 per group, i.e. 48 would be required.

7.8 Further recommendations for practice education and research

Findings from this study have not only informed recommendations for improving the design of a future study of a physical activity intervention for AIAA, but have also led to further considerations for practice, education and research in this area.

7.8.1 Recommendations for practice

The literature review highlighted the clinical significance of AIAA, including its widespread prevalence, the lack of well tested management strategies, and the effect of arthralgia on AI adherence and early discontinuation. This information should be disseminated to health professionals looking after women after diagnosis and treatment of breast cancer, so that appropriate, informed, and timely support can be provided. This might include more support around the first three months of therapy when onset is greatest; and ensuring women are adequately informed of the likely side effects before commencing therapy.

The diverse benefits that exercise can bring to cancer survivors have also been presented in this thesis. Whilst intensive self managed Nordic walking may not be feasible, women appear to enjoy weekly supervised Nordic walking, and therefore this can be recommended as a general physical acitivity, particularly as safety was demonstrated in this study.

It is likely that the lack of adherence to self managed Nordic walking was due in part to an under-developed behavioural change model underlying the intervention. This indicates that it is not sufficient to implement a physical activity intervention without careful consideration of factors known to promote behavioural change and adherence. Although social cognitive theory appeared to be a useful model in this study, it may be that consideration of all models would further enhance a future intervention. A tool called the Behavioural Change Wheel has been developed from a systematic review and comprehensive synthesis of past behavioural change frameworks (Michie *et al.*, 2011), and may help health care professionals in the future to select and design interventions that will more effectively change target behaviours.

A particular challenge is how to bring about long term changes physical activity behaviour in the current healthcare environment, with increasingly limited resources. Although the use of activity trackers and accompanying online fitness apps may be a solution, these have limited testing and are relatively costly to implement. A recent systematic review has found that physical activity interventions incorporating self regulation were more effective than those which did not (Michie et al.,

2009). In my study, the Macmillan physical activity diaries encouraged reflection and self regulation, which may in part have led to the increased activity levels observed across both groups. Therefore, the provision of these diaries, which are a free resource from Macmillan, should be considered for people following diagnosis and treatment of cancer.

7.8.2 Recommendations for education

Behavioural change theory and models should also be an integral part of the pre-registration nursing curriculum, and recommended as part of post registration area specific training and courses, with a focus on behavioural change techniques which are simple, quick and effective. A recent systematic review has found that motivational interviewing can result in modest improvements in physical activity in people with chronic health conditions (O'Halloran *et al.*, 2014), and therefore this warrants further investigation.

For courses specific to cancer care, the importance of recognizing and managing the long term consequences of cancer and its treatment should be a core component. Macmillan Cancer Support has recently outlined a competency framework for nurses caring for people living with and beyond a diagnosis of breast cancer which highlights these issues, and should be adopted by cancer providers in primary and secondary care. Furthermore, post registration education in cancer/oncology should include information regarding the importance of physical activity.

Finally, this thesis has highlighted the wealth of information that can be gained from feasibility studies to help inform complex interventions, but also the importance of conducting them with fidelity and rigour. It is recommended that training in the design of feasibility studies and complex intervention is provided in research modules for Master's and doctoral level students.

7.8.3 Recommendations for further research

Findings from this thesis have also highlighted areas for further research. As discussed in the introduction, this includes the need to build on existing evidence for effective management of the long term consequences of cancer and its treatment (Macmillan Cancer Support, 2013).

More research is required to clarify the mechanisms underlying AIAA so that interventions can be targeted appropriately. Although these are thought to include local inflammation of tenosynovial structures and alterations in pain processing, further longitudinal research in women at the point of stopping their medication may uncover the relative importance of these two factors. For example, if

pain resolves soon after stopping AIs but local pathophysiological changes persist, it may be that the pain pathways are more important than local changes.

Although there is now considerable data on the prevalence and clinical presentation of AIAA, there is a gap surrounding the lived experience of women with AIAA. Qualitative research of this nature could help to uncover the particular aspects of AIAA that lead to non adherence, which in turn could assist in developing interventions leading to better adherence.

It is recommended that further research be conducted into interventions which may improve the experience of AIAA. This includes RCTs with better methodological design, to determine the role of high dose Vitamin D, and supplements such as glucosamine and chondroitin. As adherence to medication is an overall aim of treatment, it would be interesting to test the effect of a psycho educational intervention on AI adherence. However, it is recognised that adherence can be difficult to accurately measure, and such research would need to be conducted over the longer term.

7.9 Reflections on how the doctorate has impacted on thinking and practice

On reflection, the process of undertaking this professional doctorate has significantly impacted on my thinking and my practice in many areas. Firstly, it has given me confidence in exploring an area of practice in depth; learning how to critically analyse all of the evidence, and synthesize the findings, in order to have an up to date and informed opinion on the subject. This can be used both to provide information for my client group in order to help them with treatment decisions, but also in confident discourse with peers and colleagues. This is particularly important as a nurse working in an advanced clinical practice role traditionally undertaken by medical staff. Furthermore, these skills have developed my authority to present evidence at Network level, in order to have an impact on policy development locally. I now need to develop my national networking skills to have an even broader impact on practice development in my areas of expertise.

In terms of research practice, it has consolidated my knowledge of research methodology and principles, in particular, maximising rigour through a systematic approach to research design, data collection and analysis; acknowledging the effect of preconceived assumptions; the importance of feasibility testing with complex interventions; and optimising fidelity to interventions, all of which aim to reduce sources of bias. For example, I now have more awareness of the impact of preconceived assumptions. In this study I assumed Nordic walking would be acceptable to women, as my past

experience of Nordic walking had been that women with breast cancer enjoyed it, and managed to lose weight and increase activity levels. However, this was based on findings from a service improvement rather than a research study and therefore was not value free. I did not expect that there would be such low adherence to self managed Nordic walking, which subsequently had a big impact on findings in this study.

My findings emphasized to me the necessity of undertaking feasibility studies as part of the research process, particularly when testing complex interventions. Without feasibility testing, I would have been unaware of the adherence problems with self managed Nordic walking, and the exercise contamination in the control group. However, the process of undertaking this research has also demonstrated how to improve the integrity of feasibility testing, for example, by breaking down this process into smaller steps in order to establish which parts of the intervention work and which do not. Furthermore, I have learnt how to improve fidelity in future work, with explicit manualisation of interventions, training of instructors, and direct observation of instructors when carrying out the intervention. In addition, my findings highlighted the importance of using a psychological /behavioural model to underpin complex lifestyle interventions, rather than just testing whether the intervention works or not. In other words, whether or not people will adhere to an intervention is just as important as whether the intervention has an impact.

7.10 Summary and Conclusions.

This thesis has contributed to the body of knowledge surrounding AIAA, by developing and testing the feasibility of a trial of a Nordic walking exercise intervention in this population, based on a theoretical framework incorporating a biopsychosocial pain model and social cognitive theory. From a broader perspective, the findings have added to the evidence base on interventions which may improve the management of long term consequences of cancer treatment.

The literature review highlighted that aromatase inhibitors increase the incidence of arthralgia compared to the general population, Of clinical significance, studies have reported a 12-20% early discontinuation rate, partly due to this side effect, which has the potential to reduce treatment effectiveness. The review also demonstrated that whilst it is accepted that the profound oestrogen suppression that occurs with AI usage might be the cause of the symptom of joint pain and stiffness, the mechanism underlying this remains unclear. There is preliminary evidence that physiological changes, including an increase in tendon thickness and joint effusions, may be associated with arthralgia, but not all women with AIAA have these changes, therefore the effect may also be related to alterations in pain processing and central sensitisation. Comparison with other chronic musculoskeletal

conditions demonstrates important differences exist between these and AIAA in terms of pathophysiology but that pain mechanisms may by similar. Therefore strategies which help to reduce joint pain in other musculoskeletal conditions might hold promise for this population.

A review of pain models demonstrated the complexities of the pain experience, and that an intervention /strategy for reducing/managing AIAA may work best if targeted at central well as peripheral mechanisms. The biopsychosocial model was chosen as the framework for developing an effective intervention for AIAA, based on the evidence that targeting biological, social and psychological factors is effective in chronic pain management. A literature review demonstrated strong evidence for the role of exercise in reducing joint pain in other musculoskeletal conditions including OA, RA and fibromyalgia, and preliminary evidence for the role of exercise in AIAA.

Evidence was synthesised to provide a rationale for selecting Nordic walking as an exercise intervention as opposed to normal walking, which has been previously identified as the exercise of choice for cancer survivors. However, a review of prior studies in breast cancer and musculoskeletal populations revealed very little research to date, thus demonstrating the need for feasibility testing prior to a full scale RCT. A Nordic walking intervention was subsequently developed based on social cognitive theory, the biopsychosocial model, and evidence from previous research, to maximise effect, acceptability and adherence.

Findings from this feasibility study have demonstrated it is possible to recruit and retain postmenopausal women with breast cancer to a Nordic walking exercise intervention, despite having joint pain and stiffness (AIAA). Nordic walking carried a low risk of injury and did not worsen lymphoedema. There was high adherence to weekly supervised group Nordic walking, giving support to the use of social cognitive theory in understanding factors which increase exercise adherence. Although there was low adherence to intensive self managed Nordic walking, overall physical activity levels improved in both the intervention and control groups, mainly though normal walking. This, together with a trend for an improvement in self report of pain suggests physical activity may be effective for AIAA. High baseline depression and low quality of life scores, which improved after the intervention, gives support to using a biopsychosocial model in understanding pain mechanisms in AIAA and how these might be targeted through exercise.

In view of the low adherence to intensive self managed Nordic walking, there is insufficient evidence to recommend a fully powered trial testing the intervention in its current format. However, the fact that women with AIAA managed to increase activity levels, together with the trend for improved outcomes do justify further testing of a physical activity intervention in this patient population. As AIAA is a side effect experienced for the duration of treatment, i.e. five years; ultimately, an intervention needs to be

developed that can be sustained over the longer term, and therefore walking, rather than Nordic walking may be more suitable, as it appear to be the type of exercise favoured by this population. It is therefore recommended that a further feasibility study is conducted, which employs strategies aimed at increasing adherence to self managed exercise, including a group supervised component throughout the intervention, and based on a robust model of behavioural change.

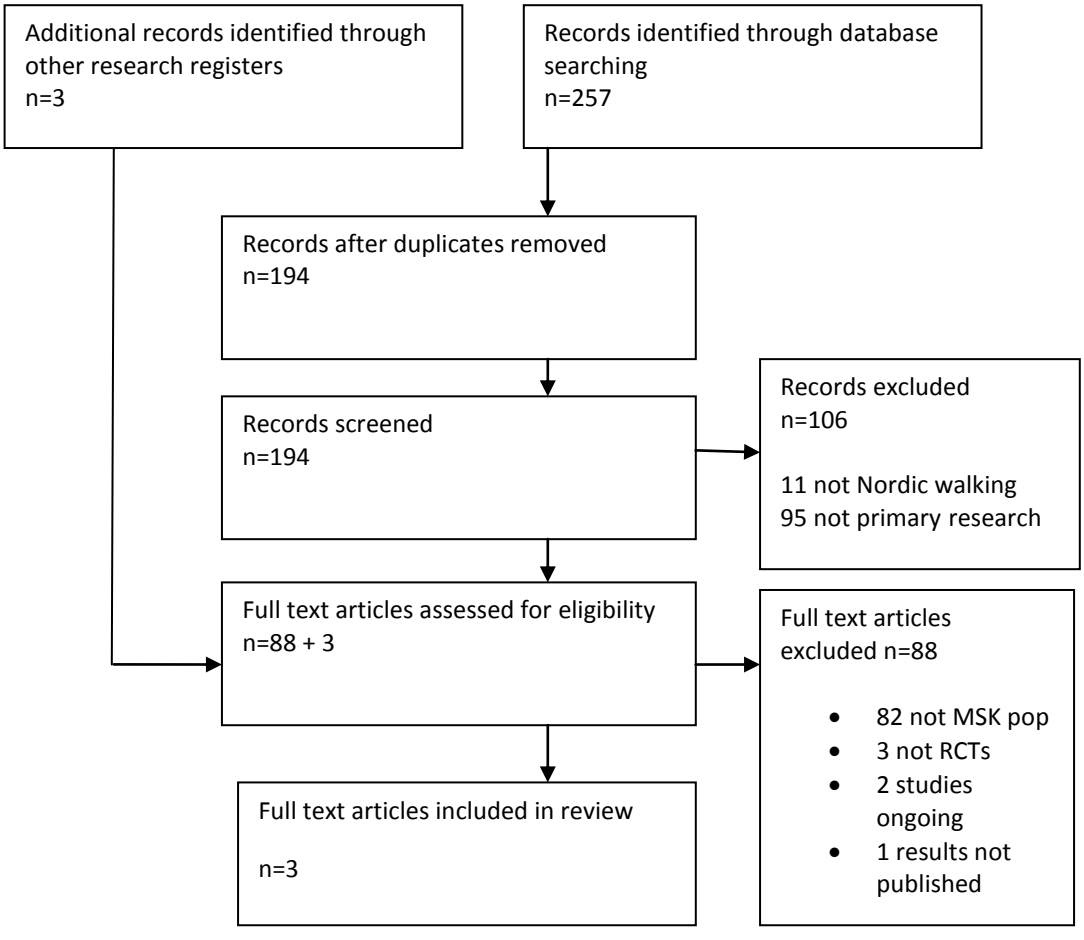
Appendices

Appendix I: Summary of RCTS testing Nordic Walking Interventions in chronic musculoskeletal conditions

Study	Design	Sample	Inclusion criteria	NW intervention	Control group	Outcome measures	Attrition Adherence Safety	Results at T1 Mean change (SD)	Methodology comments
Hartvigsen et al 2010	RCT 3 armed trial	*n*=136 (126 completed) TG =45 CG 1 =46 CG 2 =45	Low back and/or leg pain>8weeks duration with score of at least 3 on pain scale	45 min supervised NW 2 x week for 8 weeks	1) 1 hr NW instruction followed by self managed NW for 8 weeks 2) Advice to remain active	Pain (LBPRS) Function (PSFS) HRQOL (EQ5D) Time points: T1=10 weeks T2= 26 weeks T3= 52 weeks	Attrition: 7% Adherence: not measured No adverse effects of exercise reported	Within group improvements in LBPRS (p=0.009 at 11 wks) TG 8.8 vs CG1 3.4 vs CG2 4.8 No between groups difference Small changes seen in QOL for all groups (no values given)	No difference in activity levels as measured by accelerometer in weeks 5 and 6 in TG and CG1 ITT not performed
Mannerkopi et al 2010	RCT 2 armed trial	*n*=67 (58 completed) TG=34 CG=33	Women with fibromyalgia aged <60	20min supervised moderate to high intensity NW (within 45min exercise schedule) 3 x weekly for 15 weeks	Low intensity walking1 x week for 15 weeks	FIQ pain FIQ Total FIQ physical Time points: T1=12 weeks T2= 26 weeks	Attrition=14% Adherence 62% TG; 50% CG) 1/58 stopped due to chronic trochanteritis	No between gp differences in FIQ pain. Non statistically significant improvements in pain in both groups pre-post test (TG= -4.0; CG=-5.3) p=0.626 Between gp improvement in FIQ physical(TG=-7.9 (12.6) vs1.3 (15.6) p=0.027 No between gp difference in FIQ total -4.8 (12.3) v 1.9 (14.2) p=0.064	High variation in pain scores at baseline Age cut off in inc criteria limits generalisability No control group of no exercise ITT not performed
Strombeck et al 2007	RCT 2 armed trial	n=21 (19 completed) TG=11 CG=10	Women with primary Sjogrens syndrome aged <67	45min Supervised NW 3 x week for 12 weeks	Written instructions for range of motion exercises at home 3 x week over 12 weeks	HRQOL (SF 36) Depression (HADS) Time point: T1=12weeks	Attrition 10% Adherence >90% No adverse effects of exercise reported	Significant between gp improvement in Depression by -2 (SD= -4 to1; p=0.02) No between groups difference in total HRQOL SF-36 phys function subscale within group improvement in intervention gp (+15)	Allocation concealment not performed Lack of long term follow up Small study not adequately powered to detect change

NW= NW; RCT = randomised controlled trial; HRQOL= health related quality of life; VAS = visual analogue scale; FIQ= fibromyalgia impact questionnaire, TG= treatment group, CG= control group, LBPRS low back pain rating scale; ProF= Profile of Fatigue; SF-36=short form 36; FIQ=fibromyalgia impact questionnaire

Appendix II: Flowchart detailing study selection for systematic review of Nordic walking for chronic musculoskeletal conditions



Appendix III: Assessment of bias for systematic review (Higgins *et al.*, 2011)

(Hartvigsen *et al.*, 2010)

Risk of bias	Support for judgment	Authors' judgment
Random sequence generation.	Sealed opaque envelopes arranged in clusters of 15	Medium risk
Allocation concealment.	Distributed by project secretary.	Medium risk
Performance bias.		
Blinding of participants and personnel	Not possible.	High risk
Detection bias.		
Blinding of outcome assessors	Patient reported outcome measures used Therefore not blinded	.High risk
Attrition bias.		
Incomplete outcome data	Attrition reported = 7% ITT analysis not performed	Medium risk.
Reporting bias.		
Selective reporting.	Statistics for EQ-5D not presented in table	Medium risk.
Other bias.		
Other sources of bias.	Baseline data Compliance with intervention not stated Exercise contamination of comparator Data collection time points	

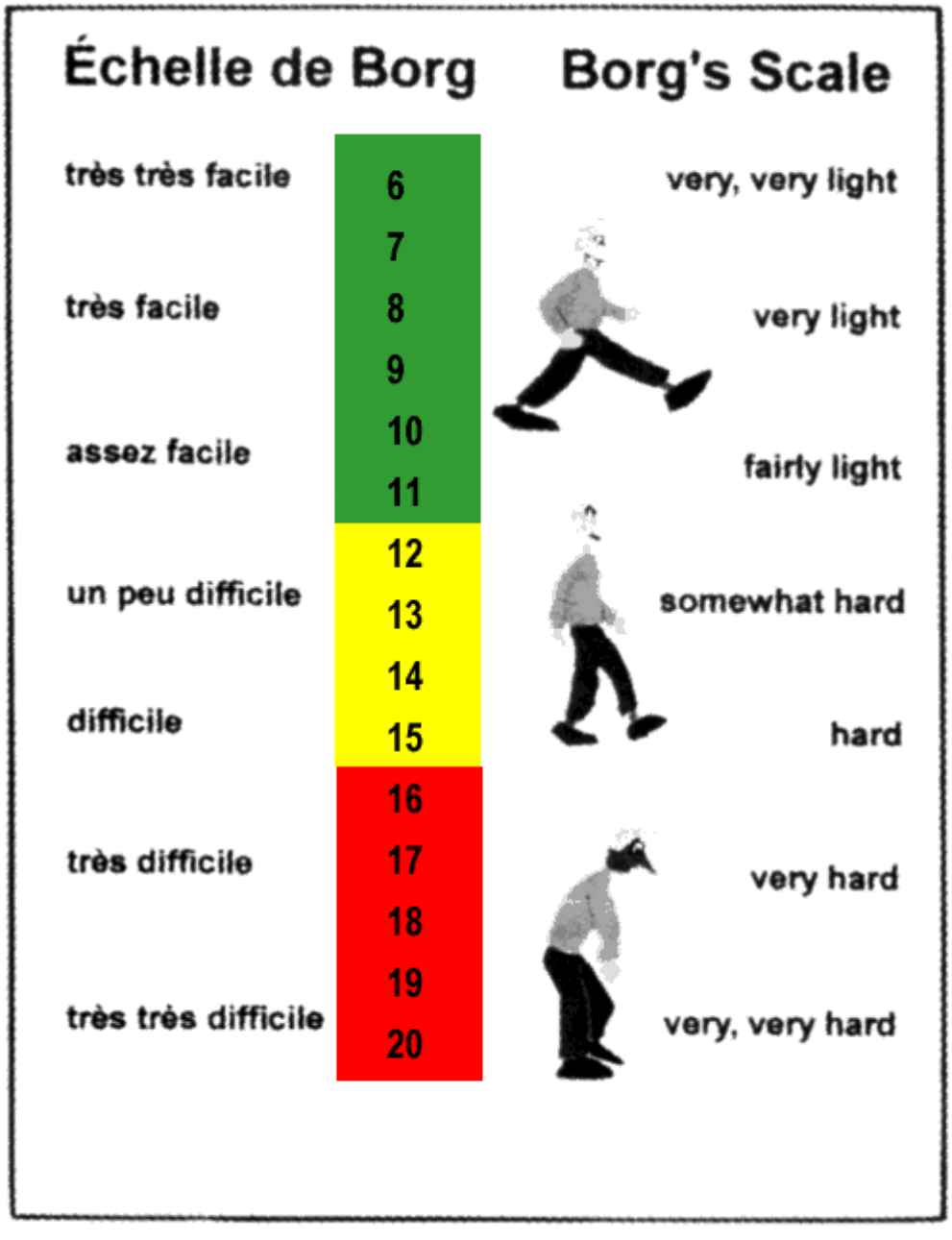
Mannerkorpi et al 2010

Risk of bias	Support for judgment	Authors' judgment
Random sequence generation.	Unclear from paper	Medium risk
Allocation concealment.	Randomisation was performed using concealed envelopes prepared by the statistician. How these were given randomly by participants is unclear	Medium risk
Performance bias.		
Blinding of participants and personnel	Exercise intervention –impossible to blind participants Baseline examiners did not know the group to which participants would be randomised	High risk Low risk
Detection bias.		
Blinding of outcome	No blinding of examiners taking post intervention measures No blinding of participants completing self report outcome measures	High risk High risk
Attrition bias.		
Incomplete outcome data	ITT not carried out	High risk
Reporting bias.		
Selective reporting.	All outcome measures reported on	Low risk
Other bias.		
Other sources of bias.		

(Strombeck *et al.*, 2007)

Risk of bias	**Support for judgment**	**Authors' judgment**
Random sequence generation.	Not performed. Allocated to groups depending on score for Profile of fatigue	High risk
Allocation concealment.	Not performed	High risk
Performance bias.		
Blinding of participants and personnel	Participants not blinded due to nature of study Personnel not blinded due to nature of study	High risk High risk
Detection bias.		
Blinding of outcome	Participants not blinded as PROMS used Blinding of personnel observing bicycle test	High risk Low risk
Attrition bias.		
Incomplete outcome data	Dropouts= 2 in intervention group (18%) Reasons: (1 = social; 1 wrong diagnosis) 2 in control group could not complete bicycle test, one excluded from analysis, the other given same score as worst score in both groups (? Why disparity) ITT analysis not performed	Medium risk? High risk
Reporting bias.		
Selective reporting.	Pain VAS in baseline measures not reported post intervention No reports on pain measures in SF=36	High risk High risk

Appendix IV: Borg Scale of Perceived Exertion



Borg G.V., 1970. Perceived exertion as an indicator of somatic stress. Scand J Rehab Med; 21:82-98

Appendix V: Physical Activity Readiness Questionnaire

nordic WALKING UK

Physical Activity Readiness Questionnaire

Name:

Address:

Please read carefully:
Circle yes or no. If you circle any of the 'yes' responses below you may need your doctor's consent before you participate in Nordic walking.

1	Has a doctor ever said that you have a heart condition and recommended only medically supervised activity?	Yes / No
2	Do you have chest pain brought on by physical activity?	Yes / No
3	Have you developed chest pain in the past month?	Yes / No
4	Do you lose consciousness or fall over as a result of dizziness?	Yes / No
5	Do you have a bone or joint problem that could be aggravated by physical activity?	Yes / No
6	Has a doctor ever recommended medication for your blood pressure or a heart condition?	Yes / No
7	Are you aware through your own experience or from doctor's advice of any other reason why you should not exercise without medical supervision?	Yes / No

Please outline any other relevant information that may affect your ability to exercise.

Known allergies:

Pre-existing medical conditions:

Current medication:

I realise that my body's reaction to exercise is not totally predictable. Should I develop a condition that affects my ability to exercise, I will inform my instructor immediately and stop exercising if necessary. I take full responsibility for monitoring my own physical condition at all times.

DATE: **SIGNED:**

IN CASE OF EMERGENCY, PLEASE CONTACT:

Name: Phone No:

Address:

Appendix VI: Participant Information Sheet

POOLE BREAST UNIT
Consultant
Miss Abigail Evans MD FRCS
Tel: 01202 442616
Fax: 01202 448720
E-mail: keri.read@poole.nhs.uk

Poole Hospital NHS
NHS Foundation Trust
Longfleet Road
Poole
Dorset BH15 2JB

Participant information sheet. Pilot study to look at the effect of a walking exercise programme (Nordic walking) on joint pain with breast cancer treatment.

What is the purpose of the study? Many women with breast cancer get joint pain as a side effect of treatment with a group of drugs called AIs. These drugs include anastrozole (Arimidex), exemestane (Aromasin) and letrozole (Femara). There is evidence from other joint conditions such as arthritis, that exercise can reduce joint pain. We would therefore like to test whether this is also the case for women experiencing joint pain associated with AIs, using a type of exercise called Nordic Walking. Nordic Walking uses poles in order to add two major benefits to walking:

- The use of poles means the upper body muscles are used as well as the legs
- The poles help to propel the walker along – this means he/she works harder than usual yet the support given by the poles makes it feel easier.

This is a small study which aims to find out whether it is feasible to carry out this research on a bigger group of women in the future, and whether there seem to be any benefits or harm from the exercise.

Why have I been invited? You have been invited as you are taking the above medication and are getting joint pain. The plan is to recruit about 44 women into the study.

Do I have to take part in the study? It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part? If you decide to take part we will randomly allocate you to either the first group of women who will receive exercise training for the first 12 weeks, or the waiting list group, who will receive the exercise training after 12 weeks. The following explains the reason for allocating you in this way. Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly).

What will I have to do during the study? The study involves two stages. The first involves a six week exercise training programme in Nordic Walking, which you will attend once per week with up to ten other women. The trainer will be a fully qualified Nordic walking instructor. Each training session will be an hour long, and by the end of the six weeks you should feel confident in the Nordic walking technique and be able to go Nordic walking independently. The second stage involves a six week period of exercise when we would like you to go Nordic walking four times per week for 30 minutes. You can do this alone, with family/friends, or with other women from the study.

In addition to the exercise we would like you to complete some questionnaires so that we can assess any effect the exercise has. These will include:

a) Basic details about you such as your age, weight, and treatment to date before starting the exercise study
b) Questionnaires on pain, quality of life, self efficacy (confidence in carrying out activities), and mood,
    i. before starting the exercise,
    ii. when you finish your six week training, and

iii. At the end of the 12 week exercises period.

c) A basic exercise diary detailing how often, how long and what type of exercise you undertake each week.

What alternatives are there? Presently there are no other evidence based treatments for joint pain associated with the aromatase inhibitor you are taking. However, if you would like further advice please discuss this with your breast care team. The breast care nurses (Michelle Pidgley and Tracy Acock) are contactable on 01202 442861.

What are the possible disadvantages of taking part? The possible disadvantages of taking part include the time taken to carry out the exercise, and time taken to fill in the exercise diary and questionnaires associated with the study. With any exercise there is a small risk of injury. However, with walking based exercise this is estimated to be an extremely low risk based on previous research.

There is no evidence to suggest Nordic walking will make arm lymphoedema (arm swelling) worse. However, if you currently have lymphoedema and experience any problems with worsening of your lymphoedema during the exercise, then we ask you to contact us so we can arrange for you to see your lymphoedema nurse straightaway.

If you have any other health problems that may put you at any risk during exercise, with your consent we will also need to check with your GP that he/she is happy for you to exercise before you take part in the study.

There is also the possibility that the exercise may make your joint pain worse. However, there is no evidence that this would be the case from the research currently available.

If you were to experience any injury, increased pain or other side effects as a result of the exercise, we would recommend you:

a) Contact the researcher (Jo Neate) on 07984 966433
b) Visit your GP or accident and emergency as appropriate, and

c) Inform the Nordic walking instructor if this happens during training

The research team will contact you every 2 weeks during the training to check you are not experiencing any problems and to answer any questions you may have. You are also free to contact the researcher Jo Neate at any time on 07984 966433.

If you are to experience any new onset or worsening pain that is not typical of treatment or exercise related pain, the researcher may arrange for you to see your clinical team, for further assessment and investigation as appropriate.

What are the possible benefits of taking part? It is possible that taking part in the study may help reduce your joint pain. If this study shows that a nordic walking programme of exercise is feasible, and appears to help with joint pain, it will inform the development of a larger study to test this effect further.

What happens when the research study stops? After both groups of participants have finished the exercise programme you can either carry on exercising, or stop if you wish. It is up to you. If you would like to know results of the study, the researcher will be able to inform you once results are analyzed. Please contact Jo Neate on 01202 442179.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you would like to take part, please read the additional information in Part 2 before making any decision. If you are still interested then

please return the attached consent form in the stamped addressed envelope and the research team will be in contact to arrange a meeting at the hospital when we can provide more information on the study, check you are eligible, and obtain baseline information required for the study.Part 2

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research nurse will tell you and discuss whether you should continue in the study.

What will happen if I do not wish to carry on with the study?

If at any point you wish to withdraw from the study you will be able to do so. Your care will not be affected in any way. Please let your researcher know.

What if there is a problem?

If you have a concern or a complaint about this study you should contact Dr Martina Prude, Head of research Governance, Building 37, University of Southampton, University Road, Southampton, SO17 1BJ; Tel: 023 80595058; email: mad4@soton.ac.uk). If you remain unhappy and wish to complain formally Dr Prude can provide you with details of the University of Southampton Complaints Procedure.

If you still remain unhappy and wish to complain formally, you can do this by contacting Poole Hospital PALS (Patient Advice and Liaison Service) on 01202 448499. In the event that something does go wrong and you are harmed during the research and this is due to someone‘s negligence then you may have grounds for a legal action for compensation against Southampton University Hospital Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in this study be kept confidential? All information which is collected about you during the course of the research will be coded, kept strictly confidential, and stored securely on

an encrypted memory stick and stored in a locked drawer. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised.

What will happen to the results of the research study? Results of the study will be published in the researcher's PhD thesis and possibly in other relevant publications. However, you will not be identifiable in any published articles.

Who is organising and funding the research? The research is sponsored by Southampton University Hospital Trust, and has been funded by Wessex Cancer Trust.

Who has reviewed the study? All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by South Central Research Ethics Committee.

Further information and contact details

For further information about the study, please contact Jo Neate, Nurse Practitioner on 01202 442179.

If you would like further advice as to whether to participate in the research, please contact the breast care nurses Michelle Pidgley or Tracy Acock on 01202 442861

If you are unhappy about any aspect of the study, please contact PALS on 01202 448499

If you need to contact someone in an emergency, please contact your GP out of hours service or emergency services as appropriate.

Appendix VII: Consent form

POOLE BREAST UNIT

Consultant

Miss Abigail Evans MD FRCS

Tel: 01202 442616

Fax: 01202 448720

E-mail: keri.read@poole.nhs.uk

Longfleet Road

Poole

Dorset BH15 2JB

CONSENT FORM

Rec Number: 11/SC/0268

Patient Identification Number for this trial: ☐☐

Title of Project: Nordic Walking for AI related Joint Pain: A Feasibility Study

Name of Researcher: Jo Neate

Please initial box

1. I confirm that I have read and understand the information sheet dated 1.9.11v2 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study and consulted about my medical records. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix VIII: Questionnaire Survey

Now that you have completed the NW programme, please could you fill out the following questionnaire which aims to evaluate

the acceptability of the exercise for joint pain,

your feelings about the study, and

your beliefs about whether the exercise has helped.

As before, all responses will be anonymous and treated as strictly confidential. If you have any questions about the questionnaire or need clarification of any of the questions, please phone Jo Neate on 01202 442179.

Please answer all questions and circle the answer you agree with most.

Questions 1-10 aim to explore the acceptability of the exercise programme.

1. How did you feel about taking part in the Nordic walking programme?

Really enjoyed quite enjoyed ambivalent not really enjoyed not enjoyed at all

Comments.....
.....

2. In relation to the length of NW training sessions, did you feel they were:

Too long about right too short

Comments.....
.....

3.And in terms of the whole training programme (6 weeks length) was it:

Too long about right too short

Comments.....
.....

4. Did you find the physical effort of NW training was :

Too easy about right Too difficult

Comments.....

.....

5.Did you have any problems getting to the venues offered? Y N

Comments.....

.....

6.Were there any other problems relating to the exercise programme that were not addressed?

Yes No

If 'yes' please explain

.....

.....

7.Did you find continuing to exercise for 4 times a week for 30 minutes was

Too much about right too little

Comments.....

.....

8.How likely is it you will continue to exercise regularly (3 or 4 times per week)?

Very likely likely not sure unlikely very unlikely

Comments.....

.....

9.If you are going to continue with exercising will you continue with:

NW other exercise type NW and other exercise type

If other exercise please specific type

.....

10.If continuing to exercise, is this because it has helped with your joint pain? Y N

Comments.....

.....

Questions 11-16 aim to evaluate your feelings about the study process.

11. Did you understand the information sheet inviting you to enter the study? Y N

Comments.....
.....

12. Did you have enough information about the study before agreeing to take part?

Yes No

Comments.....
.....

13. Did you have any problems understanding the questionnaire booklet (which asked about pain mood, quality of life etc)? Y N

comments.....
.....

14. How long on average did it take you to complete the questionnaire booklet (in minutes) 5 10 15 20 25 30 35 40

15. How did you feel about completing the exercise diary?

.....
.....

16. Were there unacceptable costs to you in taking part in the study? Y N

If answering yes, what were these?

.....
.....

Questions 17-20 aim to evaluate whether you think the exercise programme has helped with your joint pain.

17.In the last 3 months do you think your joint pain is :

Much better slightly better not changed slightly worse much worse

Comments.....
.....

18. Do you think this is related to the exercise programme (NW)?

Yes, definitely possibly unsure probably not no, very unlikely

Comments.....

.....

19. If not related to the exercise, what else do you think has affected your joint pain?

.....

.....

20. Following your participation in the study, how likely are you to stop your hormone therapy because of joint pain?

More likely neither more nor less likely less likely

Comments.....

.....

Many thanks for taking the time to complete this questionnaire. Please return in the envelope provided by..... . If you have any questions please ring Jo Neate on 01202 442179

Appendix IX: Amended CPET

Checklist for Patients on Hormone Therapy (Amended C-PET)

Hormone treatment for breast cancer sometimes causes side effects. Please go through this list and tick boxes that apply to you, leaving the other boxes blank. This information will help in your consultation.

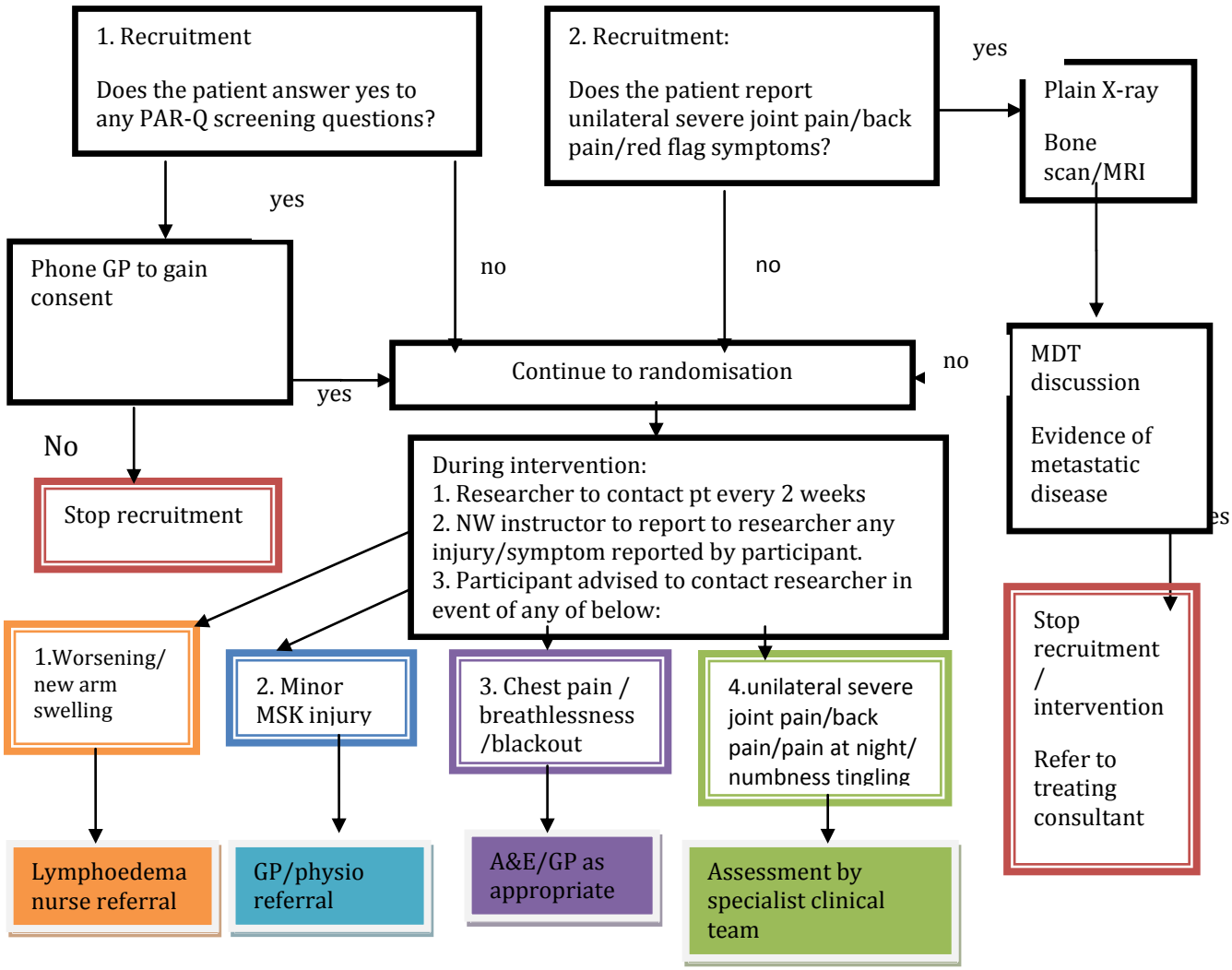
To be completed by doctor or nurse:
Name
Hospital Number
Date

	I am currently experiencing this symptom	I would like to talk to the nurse about this symptom	Comment from medical professional
Hot flushes			
Weight gain			
Nausea			
Low energy			
Fluid retention			
Irritability			
Loss of libido			
Joint pain			
Joint stiffness			
Bone pain			
Muscle pain			
Muscle stiffness			
Hair thinning			
Vaginal dryness			
Vaginal discharge			
Vaginal bleeding			
Other			

Amended from Hopwood (1996) A checklist for patients on endocrine therapy. Eur J Cancer Care 1996;5(suppl. 3):7–8.

Appendix X: Managing Safety/Adverse Events within Study

Flow diagram demonstrating risk management strategy



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Office use only: Trial number

Nordic Walking for Aromatase Inhibitor Related Joint Pain: A Feasibility Study

Rec no: 11/SC/0268

How to fill in this questionnaire

Thank you for completing this questionnaire.

This questionnaire will ask you about your health. We need to ask at the beginning of the study, in the middle of the study, and then at the end, to see if there have been any changes in that time which could be due to you taking part.

Section A asks about pain you may have had in the last 24 hours. Section B asks about how confident you are in certain activities, despite the pain you might be getting. Section C asks about your mood, and section D is about your health in general. Finally there is a questionnaire on physical activity levels.

This questionnaire should take about 15 minutes to complete. There are no right or wrong answers. If you are unsure about how to answer a question please put the best answer you can. If you make a mistake, then please shade in the box completely and then mark the correct one.

Your answers will be treated as strictly confidential. No names will be used in the reports we write.

If you have any questions about filling in this questionnaire please contact Jo Neate (Researcher) on 07984 966433 or the breast care nurses on 01202 442861.

Poole Hospital NHS
NHS Foundation Trust

WESSEX CANCER trust

Section A

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1 YES **2** NO

2. Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can

3. Please rate your pain by circling the one number that best describes your pain at its LEAST in the last 24 hours

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can

4. Please rate your pain by circling the one number that best describes your pain on AVERAGE

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can

5. Please rate your pain by circling the one number that tells how much pain you have RIGHT NOW.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can

6. What treatments or medications are you receiving for your pain?

.....

7. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0 1 2 3 4 5 6 7 8 9 10

No Relief — Complete Relief

8. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely

D. Normal Work (Includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely

Section B

Please rate how **confident** you are that you can do the following things <u>at present</u>, **despite the pain**. To indicate your answer circle **one** of the numbers on the scale under each item, where 0 = not at all confident and 6 = completely confident.

For example:

0	1	2	3	4	5
	6				
Not at all					Completely confident

Remember, this questionnaire is **not** asking whether or not you have been doing these things, but rather **how confident you are that you can do them at present, <u>despite the pain</u>.**

1. I can enjoy things, despite the pain.

0	1	2	3	4	5
	6				
Not at all confident					Completely confident

2. I can do most of the household chores (e.g. tidying-up, washing dishes, etc.), despite the pain.

0	1	2	3	4	
5	6				
Not at all					Completely confident

3. I can socialise with my friends or family members as often as I used to do, despite the pain.

0	1	2	3	4	5
	6				
Not at all confident					Completely confident

4. I can cope with my pain in most situations.

0	1	2	3	4	5
	6				
Not at all confident					Completely confident

5. I can do some form of work, despite the pain. (“Work” includes housework, paid and unpaid work)

0	1	2	3	4	5
Not at all confident					Completely confident

6. I can still do many of the things I enjoy doing, such as hobbies, or leisure activity, despite the pain.

0	1	2	3	4	5
Not at all confident					Completely confident

7. I can cope with my pain without medication.

0	1	2	3	4	5
Not at all confident					Completely confident

8. I can still accomplish most of my goals in life, despite the pain.

0	1	2	3	4	5
Not at all confident					Completely confident

9. I can live a normal lifestyle, despite the pain.

0	1	2	3	4	5
Not at all confident					Completely confident

10. I can gradually become more active, despite the pain.

0	1	2	3	4	5
Not at all confident					Completely confident

Section C

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way during the **past week**. Please respond to all items.

Place a tick in the appropriate column. **During the past week….**	**Rarely or none of the time (less than 1 day)**	**Some or a little of the time (1-2 days)**	**Occasionally or a moderate amount of time (3-4 days)**	**All of the time (5-7 Days)**
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor				
3. I felt that I could not shake off the blues even with help from my family and friends.				
4. I felt that I was just as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people disliked me.				
20. I could not "get going."				

Section D

The following questions ask for your views about your health: how you feel about your health, and how well you are able to do your usual activities. If you are unsure about how to answer any question, please give the best answer you can and make any comments in the space available after the final question.

Please tick ONE box per question

1. In general, would you say your health is:
   - Excellent ☐
   - Very good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. Compared to one year ago, how would you rate your health in general now?
   - Much better than one year ago ☐
   - Somewhat better than one year ago ☐
   - About the same ☐
   - Somewhat worse now than one year ago ☐
   - Much worse than one year ago ☐

HEALTH AND DAILY ACTIVITIES

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

   Please tick ONE box per question

   a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
      - Yes, limited a lot ☐
      - Yes, limited a little ☐
      - No, not limited at all ☐

   b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.
      - Yes, limited a lot ☐
      - Yes, limited a little ☐
      - No, not limited at all ☐

c. Lifting or carrying groceries.

Yes, limited a lot	☐
Yes, limited a little	☐
No, not limited at all	☐

d. Climbing several flights of stairs

Yes, limited a lot	☐
Yes, limited a little	☐
No, not limited at all	☐

e. Climbing one flight of stairs

Yes, limited a lot	☐
Yes, limited a little	☐
No, not limited at all	☐

f. Bending, kneeling or stooping

Yes, limited a lot	☐
Yes, limited a little	☐
No, not limited at all	☐

g. Walking more than a mile

Yes, limited a lot	☐
Yes, limited a little	☐
No, not limited at all	☐

h. Walking half a mile

Yes, limited a lot	☐
Yes, limited a little	☐
No, not limited at all	☐

i. Walking 100 yards

Yes, limited a lot ☐

Yes, limited a little ☐

No, not limited at all ☐

j. Bathing and dressing yourself

Yes, limited a lot ☐

Yes, limited a little ☐

No, not limited at all ☐

4. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down on the amount of time you spent on work?

Yes ☐ No ☐

b. Accomplished less than you would like?

Yes ☐ No ☐

c. Were limited in the kind of work or other activities?

Yes ☐ No ☐

d. Had difficulty performing the work or other activities?

Yes ☐ No ☐

5. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling anxious or depressed?)

a. Cut down on the amount of time you spent on work?

Yes ☐ No ☐

b. Accomplished less than you would like?

Yes ☐ No ☐

c. Didn't do work or other activities as carefully as usual?

Yes ☐ No ☐

6. During the past 4 weeks to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Not at all ☐
Slightly ☐
Moderately ☐
Quite a bit ☐
Extremely ☐

7. How much bodily pain have you had during the past 4 weeks?

None ☐
Very mild ☐
Mild ☐
Moderate ☐
Severe ☐
Very severe ☐

8. during the past 4 weeks how much did pain interfere with your normal work (including work both outside the home and housework?)

Not at all ☐
Slightly ☐
Moderately ☐
Quite a bit ☐
Extremely ☐

YOUR FEELINGS

9. These questions are about how you feel and how things have been with you during the past month (for each question please indicate the one answer that comes closest to the way you have been feeling).

Please tick ONE box per question

a. Did you feel full of life?

All of the time	☐
Most of the time	☐
A good bit of the time	☐
Some of the time	☐
A little of the time	☐
None of the time	☐

b. Have you been a very nervous person?

All of the time	☐
Most of the time	☐
A good bit of the time	☐
Some of the time	☐
A little of the time	☐
None of the time	☐

c. Have you felt so down in the dumps that nothing could cheer you up?

All of the time	☐
Most of the time	☐
A good bit of the time	☐
Some of the time	☐
A little of the time	☐
None of the time	☐

d. Have you ever felt calm and peaceful?

All of the time ☐
Most of the time ☐
A good bit of the time ☐
Some of the time ☐
A little of the time ☐
None of the time ☐

e. Did you have a lot of energy?

All of the time ☐
Most of the time ☐
A good bit of the time ☐
Some of the time ☐
A little of the time ☐
None of the time ☐

f. Have you ever felt downhearted and low?

All of the time ☐
Most of the time ☐
A good bit of the time ☐
Some of the time ☐
A little of the time ☐
None of the time ☐

g. Did you feel worn out?

All of the time ☐
Most of the time ☐
A good bit of the time ☐
Some of the time ☐
A little of the time ☐
None of the time ☐

h. Have you been a happy person?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

i. Did you feel tired?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

j. Has your health <u>limited your social activities?</u>

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

HEALTH IN GENERAL

10. Please choose the answer that best describes how true or false each of the following statements is for you.

Please tick ONE box per question

a. I seem to get ill more easily than other people

- Definitely true ☐
- Mostly true ☐
- Not sure ☐
- Mostly false ☐
- Definitely false ☐

b. I am as healthy as anybody as I know

- Definitely true ☐
- Mostly true ☐
- Not sure ☐
- Mostly false ☐
- Definitely false ☐

c. I expect my health to get worse

- Definitely true ☐
- Mostly true ☐
- Not sure ☐
- Mostly false ☐
- Definitely false ☐

d. My health is excellent

- Definitely true ☐
- Mostly true ☐
- Not sure ☐
- Mostly false ☐
- Definitely false ☐

General Practice Physical Activity Questionnaire

Date……

Name……..

1. Please tell us the type and amount of physical activity involved in your work.

		Please mark one box only
a	I am not in employment (e.g. retired, retired for health reasons, unemployed, full-time carer etc.)	
b	I spend most of my time at work sitting (such as in an office)	
c	I spend most of my time at work standing or walking. However, my work does not require much intense physical effort (e.g. shop assistant, hairdresser, security guard, childminder, etc.)	
d	My work involves definite physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter, cleaner, hospital nurse, gardener, postal delivery workers etc.)	
e	My work involves vigorous physical activity including handling of very heavy objects (e.g. scaffolder, construction worker, refuse collector, etc.)	

2. During the *last week*, how many hours did you spend on each of the following activities? *Please answer whether you are in employment or not*

Please mark one box only on each row

		None	Some but less than 1 hour	1 hour but less than 3 hours	3 hours or more
a	Physical exercise such as swimming, jogging, aerobics, football, tennis, gym workout etc.				
b	Cycling, including cycling to work and during leisure time				
c	Walking, including walking to work, shopping, for pleasure etc.				
d	Housework/Childcare				
e	Gardening/DIY				

3. How would you describe your usual walking pace? Please mark one box only.

Slow pace (i.e. less than 3 mph)		Steady average pace	
Brisk pace		Fast pace (i.e. over 4mph)	

This is the end of the questionnaire. Please hand this form in to Ladybird reception once completed.

Thank you very much for your assistance. We greatly appreciate the time you have taken to complete this questionnaire. Your participation is very helpful to us.

If you have any questions or concerns after filling in this questionnaire, please ring Jo Neate (Researcher, Ladybird Unit, Poole Hospital NHS Trust) on 07984 966433 or the Breast Care Nurses on 01202 442861.

Appendix XII. Histories of participants with new/pre-existing musculoskeletal pain and. Physiotherapy reports (where available).

1. Participant 6 reported lower back pain and stiffness with right sided sciatica in week 6 of the trial following a long haul flight to the US. Radiological tests within the preceding 6 months had excluded metastatic disease and thus were not repeated. This symptom was recurring from an old injury and she had been treated for the same symptom earlier in the year by physiotherapy. She received 6 sessions of therapy with an improvement in symptoms.

2. Participant number 3 reported pain in and clicking/sticking of right 4th finger in week 11 of NW programme, present for 12 weeks but worsening during trial. She had visited her GP who arranged a plain X-ray which was normal; GP diagnosed trigger finger (stenosing tenosynovitis) Treatment administered corticosteroid injection and splint with improvement in symptoms.

3. Participant 5 reported right shoulder pain in the last 2 weeks of NW and was referred to physiotherapy. Impingement syndrome was diagnosed and she received 3 therapy sessions after which she described a 90% improvement in symptoms.

4. Participant 7 reported a four month history of bilateral knee pain which actually predated commencement of the NW training but was referred to the physiotherapist who diagnosed bilateral knee OA. Treated 10.7.12-27.09.12 with 8 sessions of manual therapy and acupuncture with 80% improvement in symptoms according to physiotherapy report and continue in the programme. At the end of the 12 week course she reported an improvement in her knee symptoms.

5. Participant 9 reported onset of right medial compartment knee pain in week 11 of the NW programme. Plain X ray changes were noted in the left knee only. Assessed and treated once only – successful abolition of symptom. OA as underlying issue suggests that walking might have precipitated symptom – in either knee. Nordic Walking would have benefited this condition over normal walking – in the opinion of the physio.

6. Participant no.18 reported upper back pain in week 4 of the trial. Equivocal findings on CXR and normal bone scan led to chest CT which demonstrated lung metastases. By the time she commenced palliative chemotherapy the trial period had finished, however the patient was keen to continue NW with the agreement of her treating oncologist.

7. Pt no. 29 c/o left hip pain for 5 weeks in week 3-4 of trial. A pelvic X-ray was reported as normal and bone scan was arranged, which the patient cancelled at week 7, reporting an improvement in symptoms. The patient stopped NW and at week 11 reported the pain was no better or worse but declined further investigation. Treating oncologist was made aware.

Appendix XIII. Histories of patients with lymphoedema, participant contact sheets, and copies of lymphoedema notes

1. Participant no. 5 felt her arm may be more swollen at week 11 of the programme and was referred back to the lymphoedema service. Measurements taken on 1/10/12 found no significant increase in arm lymphoedema (non significant 7mls excess compared to pre NW measurement). Pitting oedema was noted in the upper right posterior chest wall? cause ?related to NW. Note 3 months following completion of NW pitting oedema still noted in posterior quadrant between bra edging ? Garment related.

2. Participant no 6 felt her lymphoedema may be worse in week 3 and was referred to LN and seen 8.5.12 lymphoedema clinic (week 3). Arm measurements not available in medical notes but written comment that arm volume reduced from pre-NW measurement.

3. Participant 36 had pre-existing lymphoedema in left arm and breast. No self report of increase, measurements in lymphoedema clinic pre NW to post NW report 'in status quo'.

4. Participant no 37 (intervention group; JS) reported aching of her affected arm in week 5-6 of programme and was referred back to LN. Measurements reported on scan by lymphoedema nurse showed reduction in arm volume pre-post NW (verbal report from LN 20.5.13).

5. Participant no 24 self reported an improvement in arm and chest wall lymphoedema during the NW study. She had no arm measurements but clinical examination in lymphoedema clinic in week 9 of study found stable lymphoedema.

6. Participant 22 (control, NW 24.7-9.10.12): no self report of worsening lymphoedema. However, lymphoedema clinic arm measurements increased from July to November 2012. However, had increased prior to NW also after completion of MLD with therapist in early 2012. Also patient had stopped wearing sleeve, had stopped self massage and thus difficult to ascertain what had led to increased arm lymphoedema.

Appendix XIV Summary tables of breast cancer exercise studies.

Table a. Breast cancer exercise studies: Intervention, and measures used

Author/ date	n=	Mean age	Primary aim	Intervention
Cadmus Bertram 2009 (IMPACT study)	50	54	QOL during adjuvant tx	Home based aerobic 30min 5 x week
Courneya et al 2007	242	49	aerobic vs resistance QOL during adjuvant tx	Supervised Aerobic supervised resistance 3 x wk 18 weeks duration
Courneya et al 2003	53	59	QOL + fitness	Graduated supervised aerobic (cycle ergometers) 15-35min/wk 3 X wk
Daley et al 2007	102	51	QOL post tx	supervised aerobic exercise 50min 3 x wk
Demark Wahnefried et al 2008	90	42	Body composition	Home based aerobic 30min 3 x week strength training alternate days
Irwin et al 2013 (HOPE study)	121		AIAA	moderate aerobic 30min 5 x wk plus twice weekly supervised resistance
Irwin et al 2008 (YES study)	75	56	QOL post tx	Supervised and home based aerobic exercise 30min 5 x wk
Ligibel *et al.* (2008)	101	52	Bio-markers	2 x 50min supervised strength training plus 90min home based aerobic exercise weekly vs usual care
Milne, Courneya et al 2007	58	52	QOL bcs	12 weeks of supervised aerobic(20min) and resistance exercise three times per week
Mock et al 2005	119	52	Fatigue during adjuvant tx	Home based walking exercise during adjuvant therapy 15-30min 5-6 x week
Mutrie et al 2007	203	52	During tx	Supervised group exercise 45min mixed aerobic and muscle strengthening 2 x wk plus 1 x home per wk
Penttinen et al (2009) and Saarto *et al.* (2012)	413	52.8	QOL BMD	Supervised and home based aerobic exercise 60 min 1 x wk and home 3 x wk
Pickett et al 2002	52	48	Adherence to home based exercise	Home based walking exercise during adjuvant therapy 15-30min 5-6 x week
Pinto et al 2005	86	53	Effects of telephone based counselling on adherence	home based aerobic exercise 3 x wk with weekly counselling

Table b: Breast cancer exercise studies: Recruitment: eligibility, duration, rate, sampling method

Author/ date	n=	eligibility criteria	Recruited over (mths)	Mean age	Study length (mths)	Recruitment rate/sampling method
Cadmus Bertram 2009 (IMPACT study)	50	Newly diagnosed undergoing adjuvant tx 35-75yrs	22	54	26	15.4% Population based
Courneya et al 2007	242	Undergoing chemotherapy age.>18	29	49	18	33% Population based
Courneya et al 2003	53	Post menopausal aged 50-69	18	59	15	16% Population based
Daley et al 2007	102	Breast ca diagnosed 1-3 yrs previous 'not regularly active' 18-65yrs	30	51	8	28.6% Population based
Demark Wahnefried et al 2008	90	Willingness to be randomised to trial Premenopausal	30	42	26	81% convenience sampling)
Irwin et al 2013 (HOPE study)	121	AIAA Taking AI>6m Sedentary (<60min/wk worst pain measure >3 <75y	3 2		52	16.6% Population based
Irwin et al 2008 (YES study)	75	1-10 yrs post diagnosis Sedentary (<90min) Postmenopausal <75y	22	56	12	9.5% Population based
Ligibel et al 2008	101	BMI>25 Sedentary (<40min/wk) No age limit	25	52	16	51% Convenience
Milne, Courneya et al 2007	58	Post treatment No age limits (but must pass PARQ) No previous exercise trials in last 6m	3	52	12	44.3% Convenience
Mock et al 2005	119	Medical co-morbidity Sedentary <70y	36	52	6w 12-24w	51% (convenience sampling)
Mutrie et al 2007	203	'No regular exercise' No age limit (but must pass PARQ)	12	52	12	17.74% Not described
Penttinen et al (2009) and Saarto et al (2012)	413	35-68y	31	52.8	52	53.8% (413/768) 31% of all screened
Pickett et al 2002	52	No age limit*	Not described	48	6w 12-24w	Not described
Pinto et al 2005	86	Willingness to be randomisedto exercise study Sedentary No age limits*	Not given	53	12	20%

Table c. Breast cancer exercise studies: Adherence and attrition

Author/date	Attrition	Adherence measured by	Defined as	Adherence
Cadmus Bertram 2009 (IMPACT study)	10%	HR monitor diaries	Minutes per week %meeting prescribed ex volume % returning all logs	144min 64% 72%
Courneya et al 2007	8%	Blood gases Diaries	% total supervised sessions	72% (AET) 68?% (RET)
Courneya et al 2003	2%		% total supervised sessions	98.4% 44.3 out of 45 sessions
Daley et al 2007	11%	HR and RPE Exercise logs	% attending 70% supervised sessions	78% 89%
Demark Wahnefried et al (2008)	8.8%	HR monitor Physical activity logs	% achieving prescribed exercise volume	34.5%
Irwin et al 2013	-	Pedometer 7 day PAQ	%total supervised sessions	82%
Irwin et al 2008	11%	HR monitor diaries	Minutes per week %meeting prescribed ex volume % returning all logs	123 min 33% at 150min/wk
Ligibel et al 2008	18%	Phys activity log	% tot supervised sessions Minutes per week	73% 114 mins
Milne, Courneya et al 2007	2%		% total supervised sessions	61%
Mock et al 2005	9%		Min per week % adhering to >60min /wk	127min 72% NB Adoption of regular exercise by 39% control gp
Mutrie et al 2007	12.8%	HR monitor 7 day PAL	Not reported	Not reported
Penttinen et al (2009) and Saarto et al (2012)	12.8%		% tot supervised sessions Minutes per week Frequency per week	58% pre-men 63% post-men 196 pre men 210min post men 3.3 4.3
Pickett et al (2002)	8%	Exercise logs pedometer	% increasing activity levels	67%
Pinto et al 2005	5%	Exercise logs pedometer	Percentage reaching weekly goal Minutes per week	53-91% 43-128min

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