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Optimising patient function following elective total hip replacement surgery

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Thesis submitted in fulfilment of the requirements of the degree of Doctor of Philosophy

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Dedicated to Iyé, Roli and Edosa, the rocks on which I build my world.

Abstract

Symptomatic hip osteoarthritis is associated with poor general health status and surgical intervention (total hip replacement; THR) is the most effective treatment for end stage disease. This procedure generally resolves pain, but function usually remains substantially sub-optimal. This protracted disability has detrimental economic, social and health consequences. 'Standard rehabilitation' (SR), (i.e. low intensity exercise, not involving progressive resistance training (PRT)), typically permits patients to regain basic levels of function but fails to resolve the significant muscle wasting and subsequent strength deficits associated with the condition. Supervised PRT following THR produces good results in terms of muscle strength and function. However, delivery of this type of program is expensive due to the high costs associated with supervision, facility provision, and transport of patients. A home-based program featuring relatively high intensity PRT but not requiring a high degree of supervision, would potentially overcome these problems. Before commencing this study, evidence was lacking regarding whether home-based PRT regimes with weekly supervision in the early postoperative period were effective in restoring muscle mass and physical function in THR patients.

Chapter 2 describes the results of a pilot randomised controlled trial comparing a home-based PRT program with weekly supervision in the early postoperative period after THR against SR (control) in terms of improving muscle strength and physical function at up to 1 year follow up. A prospective single blinded study (assessor blinded to results of randomisation) was conducted over a 2 year period (April 2010 to March 2012). Of 50 patients initially recruited (home-based PRT n =26, SR (control) n=24) after informed consent, 26 completed 9-12 months follow up (home-based PRT n=13, SR (control) n=13). There was no effect for treatment (home-based PRT or SR(control)) in terms of the primary outcome measure assessed, i.e. maximal voluntary contraction of the operated leg quadriceps (MVCOLQ in Newtons (N)over the period of follow up. As anticipated, there was a significant effect of time (i.e. improvement) in the primary outcome, with improvements in the secondary outcomes as well. The exception was the lean mass of the operated leg, which showed no improvement over the

period of follow up. Being in the SR(control) group as opposed to the home-based PRT group led to significant improvements in three of the secondary outcomes assessed; GS (estimated effect 0.185m/s; p=0.009), SCP (estimated effect -5.665s, p=0.038), and 6MWT (estimated effect 86.393m, p=0.004) at 9 to 12 month follow up. This study led to the conclusion that early home-based PRT is deliverable and well tolerated but is not successful in providing functional gain beyond that achievable by SR in this population. Due to the large loss to follow up (30%), the results need to be interpreted with caution. As a pilot study the results indicate that there is no need to perform a definitive trial of the home-based PRT intervention due its lack of effect on the primary outcome variable assessed. Centre-based regimes appear to be the only modality that is able to provide additional functional benefits in the early period following total hip replacement surgery, perhaps due to the supervision afforded to patients and hence compliance to higher intensity training.

Although SR was found to confer some benefits over home-based PRT in terms of the secondary outcomes assessed in Chapter 2, SR post-THR is not well defined in the existing literature. Thus, **Chapter 3** aimed to investigate the nature of standard care that exists in the UK post-THR. Questionnaire item development about standard rehabilitation practice was guided by an initial focus group interview (after informed consent) with practising physiotherapists. An online questionnaire was then sent via email to physiotherapists working in the UK from January to May 2011. 106 responses were obtained from a total of 130 physiotherapists' contacted (81.5% response rate), with the physiotherapists considering that the most important muscles to target in all phases of rehabilitation being: the hip abductors (62.2%), followed by the quadriceps (16.9%), and other muscles (21%). Exercise type prescribed revealed no consensus, with weight bearing (42%), functional (45%) and bed-based/bridging/postural exercises (13%) favoured. 83.7% were able to define the basis of progressive resistance training (PRT), but only 33% prescribed it. The study concluded that standard rehabilitation in the UK after THR is variable, and appears to rarely include PRT. This could be a factor contributing to the prolonged poor function in some patients.

An attempt was then made in **Chapter 4** to assess on a molecular level, the changes that occur in the *vastus lateralis* (VL) of patients with end-stage hip osteoarthritis and during the early phase of

rehabilitation following THR. mRNA expression was assessed using reverse-transcriptase polymerase chain reaction (RT-PCR) from VL muscle biopsy samples obtained from patients intraoperatively and at intervals up to 9-12 months postoperatively (6 weeks, 6 months and 9-12 months). The gene panel for RT-PCR was chosen in terms of anticipated activity with regards to the metabolic processes of muscle hypertrophy, atrophy, lipid metabolism and inflammation. It was hypothesised that there would be no effect of biopsy site (proximal versus distal) on gene expression of the VL muscle in patients at the time of THR surgery, and that in patients undergoing early home-based PRT as opposed to SR (control), there would be an increase in genetic markers of hypertrophy and lipid metabolism, with a decrease in genetic markers of atrophy and inflammation. The results of the former analyses showed that hip joint inflammation appeared to have no effect on gene expression on samples taken from 2 sites in the VL, suggesting that for these sorts of analyses, single site muscle sampling is appropriate. With regard to the latter hypothesis; muscle inflammation in the VL of the operated leg at the 6 week time point was reduced. Despite increases in markers of hypertrophy over the period of follow up, these did not reach significance. Significant reductions in markers of lipid metabolism were found (at 6 weeks) and this perhaps warrants further investigation with regards to metabolic efficiency in this group of patients. Participation in the home-based PRT regime did not demonstrate an objective difference in mRNA expression of the genetic panel chosen, confirming at a cellular level, the lack of effect on leg lean mass and objectively assessed function observed (Chapter 2).

Chapters 5 and 6 describe studies performed in order to investigate the effect of psychological distress and behavioural cognitions (issues that can impact on a patient's motivation to participate in an exercise programme) on objective and subjectively assessed physical function of the patients recruited to this study. **Chapter 5** used the DRAM (distress and risk assessment method) to assess the impact of psychological distress on the primary outcome measure of the main study (MVCOLQ) as well as the Oxford Hip Score (OHS) and a reduced version of the Western Ontario and McMasters University Osteoarthritis personal function scale (rWOMAC PF) at 9-12 months follow up (whilst controlling for randomisation into either the home-based PRT or SR (control) groups). The DRAM stratification

('normal' or 'at risk/distressed') was found to be predictive of subjectively assessed function whilst it had no impact on the MVCOLQ at 12 months follow up. Patients who were 'at risk/distressed' had persistently lower function scores (p value range 0.001 to 0.04)), both preoperatively and at all postoperative time points, relative to the 'normal' patients. This investigation was the first in the literature to use the DRAM tool in patients undergoing THR (it is typically administered to patients undergoing spinal surgery) and its routine use in the screening of patients undergoing THR is indicated. However, behavioural cognitions (Recovery Locus of Control, RLOC; Theory of Planned Behaviour Perceived Behavioural Control (TPB PBC)) did not show any impact on OHS nor rWOMAC PF in this population (again with allocation into either home-based PRT or SR (control) groups controlled for; **Chapter 6**). Multiple bivariate associations were found to exist between the behaviour cognitions and the objective measure of physical function (MVCOLQ) as well as subjectively assessed function (OHS and rWOMAC PF) which warrants further investigation. The regression analysis revealed that improvement in behaviour cognitions between 6 weeks and 6 months appeared to have a negative impact on the amount of improvement in MVCOLQ at 9-12 months from pre-operative values. OHS and rWOMAC PF at 9-12 month follow up, as well as the levels of functional gain over time, were best explained by the patients' earlier functional status.

The home-based PRT program was then compared to standard rehabilitation (SR, control) from a health economics (cost consequences) analyses viewpoint (**Chapter 7)**. Client service receipt inventories were available from 20 patients at final follow-up (9 to 12 months; Home-based PRT n=11, SR (control) n=9). The average cost per patient for physiotherapists to implement the home-based PRT programme was £313.95. Home-based PRT was £33 more expensive (bootstrapped 95% confidence interval (CI) -£318, £366) than SR (control) with an incremental benefit of 13.71N in terms of the primary outcome measure (MVCOLQ; bootstrapped 95% confidence interval (CI) -54.64N, 83.83N). There was no difference between the groups in terms of healthcare service utilisation at 12 months or Quality Adjusted Life Years (QALY). There was a significant benefit generically from the THR operation (EQ-5D Health Utility Index (HUI) improved from 0.46 to 0.87 for whole cohort; a value compatible to data published elsewhere). In our investigation, EQ-5D HUI

at final follow up was 10% better than a normal healthy population of age and sex matched individuals in the UK.

In **summary** the main findings from studies conducted for this thesis are:

- Early home-based PRT is not successful in providing additional muscle strength nor objective functional gain beyond that achieved by standard rehabilitation programmes in elective THR patients. However, loss to follow up at final review (30%) for patients enrolled into this pilot study mean that these results should be interpreted with caution
- Standard rehabilitation after elective THR in the UK is variable and appears to rarely include PRT
- Characterisation of the molecular environment of the VL of the affected leg in patients in the early phase of post-THR rehabilitation demonstrates that single site muscle biopsy sampling is sufficient, and processes that reflect protein breakdown (catabolism) appear to persist for 9-12 months following surgery with no obvious impact in favour of participation in the home-based PRT regime
- Psychological distress assessed using the distress and risk assessment method (DRAM) is predictive of subjective outcome in patients undergoing THR independent of participation in an exercise rehabilitation programme
- Behavioural cognitions have no impact on subjective function in this population
- Preoperative functional status appears to be the most significant indicator of post-operative subjectively assessed function
- Participating in the home-based PRT regime as opposed to standard rehabilitation, SR (control), in this population of patients post-THR, costs on average £33 more per patient (bootstrapped 95% CI -£318, £366)
- If home-based PRT were to be reassessed in a further trial, this should be with a different regime to that assessed in this thesis; the current pilot study does not justify performing a full multi-centre randomised controlled trial

Publications and presentations

Original papers

'Methods for optimising patient function after total hip arthroplasty' (Book Chapter).
Okoro T, Lemmey AB, Maddison P, Andrew JG
Publishers 'INTECH' – in 'Recent Advances in Hip and Knee Arthroplasty' Edited by Fokter S. Published Jan 2012. ISBN 979-953-307-647-7

'An appraisal of rehabilitation regimes used for improving functional outcome after total hip replacement surgery'
Okoro T, Lemmey AB, Maddison P, Andrew JG
Sports Med Arthrosc Rehabil Ther Technol. 2012 Feb 7; 4(1):5.

'An assessment of the impact of behavioural cognitions on function in patients partaking in a trial of early home-based progressive resistance training after total hip replacement surgery'
Okoro T, Morrison V, Maddison P, Lemmey AB, Andrew JG
Disabil Rehabil. 2013 Mar 13. [Epub ahead of print]

'What does standard rehabilitation practice after total hip replacement in the UK entail? results of a mixed methods study'
Okoro T, Ramavath A, Howarth J, Jenkinson J, Maddison P, Andrew JG, Lemmey A
BMC Musculoskelet Disord. 2013 Mar 12;14:91. doi: 10.1186/1471-2474-14-91.

Abstracts published

'Do gender, surgical experience and living situation influence perceived control, pain and function in patients awaiting hip surgery'
Okoro T, Lemmey A, Maddison P, Andrew G, Morrison V
A. Oral presentations, Psychology & Health. 2011. 26:sup2, 6-72

'An observational assessment of standard rehabilitation practice after total hip replacement in the UK'
Okoro T, Ramavath A, Howarth J, Jenkinson J, Lemmey A, Maddison P, Andrew JG
Clinical Rehabilitation. 2012. 26(6):570

'Does muscle inflammation influence recovery of muscle strength and function in patients undergoing total hip replacement?'
Okoro T, Stewart C, Al-Shanti N, Lemmey A, Maddison P, Andrew JG
The Lancet, Volume 381, Page S82, 27 February 2013. DOI: 10.1016/S0140-6736(13)60522-X

Manuscripts under review

'Efficacy of an early home based progressive resistance training programme compared to standard rehabilitation for improving patient function following elective total hip replacement; results of a pilot randomised controlled study'
Okoro T, Whitaker R, Maddison P, Andrew JG, Lemmey AB
Submitted to 'Archives of Physical Medicine and Rehabilitation' March 2013

'Home based progressive resistance training in the early post-operative period in patients after total hip replacement: a cost consequences analysis'
Okoro T, Edwards RT, Yeo ST, Maddison P, Lemmey AB, Andrew JG
Submitted to 'Archives of Physical Medicine and Rehabilitation' March 2013

Presentations

Sept 2013 ‘*The effect of muscle inflammation on pain and function in patients with hip osteoarthritis’*
British Orthopaedic Association Annual Congress, Birmingham, UK

May 2013 *‘Effects of early home-based progressive resistance training on objective function after elective total hip replacement – results of a randomised controlled study’*
£200 prize (Runner up –Best Oral Presentation)

‘The distress and risk assessment method of assessing psychological distress predicts poor outcome 2 years following total hip replacement surgery’
Welsh Orthopaedic Society Annual Meeting, Llandudno, Wales, UK

Feb 2013 *‘Does muscle inflammation influence recovery of muscle strength and function in patients undergoing total hip replacement?’*
Spring Meeting for Clinician Scientists in Training, Academy of Medical Sciences, London, UK.

Nov 2012 *‘Do Patient Reported Outcome Measures (PROMS) reflect physical function in patients awaiting hip arthroplasty?’*
Combined 33rd SICOT & 17th PAOA Orthopaedic World Conference, Dubai, UAE.

Sept 2012 *‘The distress and risk assessment method (DRAM) of assessing psychological distress is predictive of short-term functional outcome in patients undergoing total hip replacement surgery’*
European Hip Society Annual Congress, Milan, Italy.

Sept 2012 *‘Can early home-based progressive resistance training improve function after total hip replacement? Results of a randomised controlled study’*

‘Relationship between molecular markers of muscle inflammation and muscle strength in patients undergoing total hip replacement’
£250 prize- Best Poster Presentation

‘Does the Oxford Hip Score reflect objective functional performance in patients undergoing total hip arthroplasty?’

‘Does muscle inflammation affect pain and function in patients with hip osteoarthritis?’
British Orthopaedic Research Society Annual Conference, London, UK.

July 2012 ‘*Effect of muscle biopsy site on gene expression in patients undergoing total hip replacement for osteoarthritis’*

‘Molecular adaptation of skeletal muscle in post-surgical osteoarthritis patients: markers of inflammation, hypertrophy, atrophy and lipid metabolism’
European College of Sports Science (ECSS) Annual Congress, Bruges, Belgium

May 2012 ‘*Are patient reported outcome measures an adequate tool for reflecting functional impairment in patients awaiting total hip replacement surgery?*
Welsh Orthopaedic Society Annual Meeting, Abergavenny, UK
£200 prize (Runner up –Best Oral Presentation)

May 2012 ‘*Use of the DRAM (Distress and Risk Assessment Method) tool in psychological assessment of patients awaiting lower limb arthroplasty’*
European Federation of National Associations of Orthopaedics and Traumatology (EFORT) Annual Congress Berlin, Germany

Feb 2012 ‘*Do PROMS reflect physical function in patients awaiting hip arthroplasty?’*

‘Use of the DRAM (Distress and Risk Assessment Method) tool in psychological assessment of patients awaiting lower limb arthroplasty’

‘*Non-operated hip Kellgren Lawrence score influences preoperative Oxford Hip Score in total hip replacement patients’*
British Hip Society Annual Meeting, Manchester, UK. February 2012

Sept 2011 *‘The influence of gender, surgical experience and living situation on function and perceived control in a cohort of patients awaiting total hip replacement surgery’*
European Society of Health Psychology Annual Congress, Crete, Greece

July 2011 ***‘****An observational assessment of standard rehabilitation practice after total hip replacement in the UK’*
European College of Sports Science Annual Congress, Liverpool
British Society of Rehabilitation Medicine/ Society for Research in Rehabilitation Joint Meeting, Keele
Welsh Orthopaedic Rotation Registrar’s Day, Cardiff

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Abbreviations

6MWT	Six minute walk test
18S	Ribosomal 18S RNA (housekeeping gene)
ADLs	Activities of daily living
ADRB2	Adrenergic, beta-2, receptor
AKT	Serine/threonine specific protein kinase
AF	Annuity factor
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BM	Bone mass
BMI	Body mass index
CAPN1	Calpain 1
CAPN2	Calpain 2
CAPN3	Calpain 3
CAST	Calpastatin
cDNA	Complementary deoxyribonucleic acid
CG	Control group
CHO	Carbohydrates
CI	Confidence interval
CINAHL	Cumulative index to Nursing and Allied Health Literature database
COI	Cytochrome c oxidase I
CONSORT	Consolidated Standards of Reporting Trials
CSRI	Client Service Receipt Inventory
C_T	Cycle threshold
CT	Computed tomography
CTSL1	Cathepsin L1
CTSL2	Cathepsin L2
DNA	Deoxyribonucleic acid
dsDNA	Double stranded deoxyribonucleic acid
DRAM	Distress and risk assessment method
DVs	Dependent variables
EMBASE	Excerpta Medica Database
EPM-ROM	Escola Paulista de Medicina-Range of Motion scales
EQ-5D	Euroqol (5 dimensions) quality of life questionnaire
FA	Fatty acids
FABP3	Fatty acid binding protein 3
FBX032	F-Box protein 32
FOS	FBJ murine osteosarcoma viral oncogene homolog
GS	Gait speed
GSK3A	Glycogen synthase kinase 3 alpha
HADS	Hospital anxiety and depression scale
HAQ	Health Assessment Questionnaire
H-FABP	Muscle fatty acid binding protein
HRQoL	Health related quality of life
HTVP	High training volume participants
HUI	Health utility index
ICC	Intra class correlation coefficient

IG	Intervention group
IGF-I	Insulin-like growth factor-I
IGFBP2	Insulin-like growth factor binding protein 2
IGFBP5	Insulin-like growth factor binding protein 5
IL-6	Interleukin 6
ILOA	Iowa level of assistance scale
IMCL	Intramyocellular lipids
INS-IGF2	Insulin-like growth factor 2 read-through
IVs	Independent variables
JUNB	Jun B proto-oncogene
LPL	Lipoprotein lipase
LTVP	Low training volume participants
MACTAR	McMaster Toronto Arthritis Patient Preference Disability Questionnaire
MAPK14	Mitogen activated protein kinase 14
MEDLINE	U.S National Library of Medicine database
MHS	Mental Health Score
mRNA	messenger ribonucleic acid
MSP	Modified somatic perception
MSTN	Myostatin
MT-CO1	Mitochondrially encoded cytochrome c oxidase 1
MVC	Maximal voluntary contraction
MVCOLQ	Maximal voluntary contraction of operated leg quadriceps
MYOD1	Myogenic differentiation 1
N	Newtons
NFAT	Nuclear factor of activated T cells
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NJR	National Joint Registry
NWORTH	North Wales Organisation for Randomised Trials in Health
OA	Osteoarthritis
OHS	Oxford Hip Score
PBC	Perceived behavioural control
PCR	Polymerase chain reaction
POMS	Profile of mood states
PPARA	Peroxisome proliferated-activated receptor alpha
PPARG	Peroxisome proliferated-activated receptor gamma
PRT	Progressive resistance training
PSMA 7	Proteasome subunit, alpha type, 7
PWB	Partial weight bearing
QALY	Quality adjusted life year
QoL	Quality of life
RAND-36	Research and Development 36-item Health Survey
RCAN1	Regulator of calcineurin transcript variant 3
RLOC	Recovery locus of control
RNA	Ribonucleic acid
ROM	Range of movement
RT	Resistance training
RT-PCR	Reverse transcriptase polymerase chain reaction

rWOMAC PF	reduced version of Western Ontario and McMasters University Osteoarthritis personal function scale
SCP	Stair climb performance
SD	Standard deviation
SF36	Short form 36
SF12	Short form 12
SIRT1	Sirtuin1
SIRT2	Sirtuin2
SR	Standard rehabilitation
ST	Sit to stand (number of repetitions)
STAI-T	Spielberger Anxiety Inventory Trait Form
TGFβ	Transforming growth factor-beta
THR	Total hip replacement
TNF-α	Tumour necrosis factor alpha
TNFRSF1B	Tumour necrosis factor receptor superfamily member 1B
TO	Tosan Okoro, Thesis author
TPB	Theory of planned behaviour
TRIM63	Tripartite motif containing 63
TUG	Timed up and go test (seconds)
UWB	Unrestricted weight bearing
VL	*Vastus lateralis*
WOMAC	Western Ontario and McMasters University Osteoarthritis index
200mFMWT	200m fast walk test

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CHAPTER 1: Introduction

1.1 General introduction

Symptomatic hip osteoarthritis (OA) occurs in 3% of the elderly (Felson 2004) and is associated with poor general health status (Dawson, Linsell et al. 2004). Treatment strategies for hip pain have traditionally involved conservative measures (analgesia, exercise, education, and weight reduction), but for end-stage disease, surgical intervention (joint replacement) is the most effective treatment (Birrell, Croft et al. 2000; Di Domenica, Sarzi-Puttini et al. 2005).

According to the National joint registry, the number of primary total hip replacements (THR) reportedly performed in England and Wales in 2010 totalled 68907, with the average age of patients being 67.2 years (females slightly older than males , average 68.8 years vs. 66.3 years respectively) (National Joint Registry for England and Wales 2011).

As technology and surgical techniques for total hip replacement (THR) improve, patient expectations have also increased, including for an early return to normal physical function and activities (Wang, Gilbey et al. 2002). A reduced time between surgery and mobilisation has been found to have an influence in reducing length of stay and increasing patient satisfaction (Husted, Holm et al. 2008). This is particularly important as initiatives such as integrated care pathways, have rapidly reduced the length of hospital stay following joint replacement with subsequent reduction of inpatient physiotherapy rehabilitation time (National Audit Office 2003).

Whilst THR generally resolves pain, function usually remains substantially sub-optimal (Trudelle-Jackson, Emerson et al. 2002), with patients with low post-operative function five times more likely to require assistance from another person for their activities of daily living compared with those who have high functional status (Fortin, Penrod et al. 2002). Optimising function after surgery is therefore an important part of the rehabilitation process.

1.2 Predictors of outcome following total hip replacement, THR

A recent prospective multivariate regression analysis of factors affecting outcome after THR has shown that the most important factor to influence outcome is the preoperative Western Ontario and McMaster Universities Osteoarthritis (WOMAC) physical function (PF) score (Wang, Wang et al.

1999). WOMAC is one of the most widely used disease-specific outcome instruments for people with osteoarthritis. The study by Wang et al. identified three independent variables; pre-operative WOMAC PF score, gender, and the presence of co morbidities as significantly affecting the WOMAC PF score at 1 year post-operatively. Previous studies have hypothesised that high preoperative functional status has a positive effect on outcome whilst others have suggested that it leaves little room for improvement in functional status (Montin, Leino-Kilpi et al. 2008; Roder, Staub et al. 2007). Not surprisingly, patients with better preoperative functional scores are likely to have higher postoperative scores, whereas patients with poorer preoperative scores are likely to experience greater improvements in function (Wang, Morrison et al. 2010). Greater improvement in functional outcome is generally observed in female patients relative to male patients, which could be due to the fact that women are more likely than men to seek THR at the more advanced stages of their disease (Katz, Wright et al. 1994).

Patients with preoperative co-morbidities are more likely to have a poorer short-term outcome in terms of physical function and this finding by Wang et al. is consistent with more recent results (Lubbeke, Katz et al. 2007; Roder, Parvizi et al. 2003; Wood, McLauchlan 2006). Patients with significant preoperative co-morbidities have more inpatient complications such as hypotension, neuropathy, thromboembolic events, septicaemia, cardiac arrest, myocardial infarction, respiratory failure, and renal failure after THR than those who do not. Whilst hip OA patients who have additional musculoskeletal co-morbidities such as low back pain and osteoarthritis of the non-operated hip, generally have less long term functional improvement after THR (Nilsdotter, Petersson et al. 2003a), a combination of more pain pre-operatively, higher age, and postoperative low back pain predicts a worse outcome after THR in WOMAC PF after 3.6 years of follow-up (Nilsdotter, Petersson et al. 2003a). Function and pain in patients with lower preoperative physical function does not tend to improve postoperatively to the level achieved by those with higher preoperative function (Fortin, Clarke et al. 1999).

Old age predicts a poor postoperative outcome after THR and this is consistent with the impression that older people with self reported conditions restricting mobility in addition to arthritic pain in the

hip or knee are at higher risk of psychological distress and physical dysfunction (Nilsdotter, Petersson et al. 2003a).

1.3 Muscle strength and its relation to function after Total Hip Replacement

The most common preoperative complaints by patients who elect to have THR are pain and loss of mobility (Trudelle-Jackson, Smith 2004). It therefore follows that the most commonly reported outcomes of THR in the literature relate to pain relief and restoration of mobility (Trudelle-Jackson, Smith 2004). Outcome studies of pain reduction and range of motion restoration, usually conducted 3 to 6 months after THR, indicate an overall satisfaction by patients and physicians (Barber, Roger et al. 1996). However, studies performed at least 1 year after THR reveal that physical impairments and functional limitations persist in the absence of pain. These physical impairments include decreased muscle strength and postural stability on the side of the replaced hip (Trudelle-Jackson, Emerson et al. 2002). The reported deficits in muscle strength of the involved hip after THR are 10-21% when compared to the uninvolved hip at 1 year post-surgery (Rasch, Bystrom et al. 2009; Trudelle-Jackson, Emerson et al. 2002; Shih, Du et al. 1994). Similarly, the muscle atrophic changes that occur about the hip persist up to 2 years following THR (Rasch, Bystrom et al. 2009).

Frail elderly persons with sarcopenia (degenerative loss of skeletal muscle mass and strength associated with aging) often undergo musculoskeletal-related surgery, and some of these patients fail to regain their preoperative level of function and self-care (Suetta, Magnusson et al. 2004).

Gait dysfunctions and asymmetries, both pre-and post-THR surgery, are also evident in patients with unilateral hip osteoarthritis (Madsen, Ritter et al. 2004). This is inherently dangerous because it is well known that gait dysfunctions or lower limb muscular weakness heighten the risk of falls especially when negotiating uneven terrain such as a step or a chair (Madsen, Ritter et al. 2004). Dysfunction can also lead to reduced mobility, living independence, and physical activity levels (Galea, Levinger et al. 2008).

1.4 Impact of aging on muscle

Aging and disuse are two of the main conditions leading to skeletal muscle atrophy in humans (Suetta, Andersen et al. 2008). In both conditions, the loss of muscle mass leads to a decrease in muscle force production. The loss of muscle mass with aging accelerates from the sixth decade onward, partly

owing to a decreased number of muscle fibres and muscle fibre atrophy (Lexell, Taylor 1991). Cross sectional studies generally indicate that type II fibres are more vulnerable to the aging process than type I fibres (Lexell, Taylor 1991), although other studies have found more marked type I atrophy (Frontera, Hughes et al. 2000). Muscle mass has been estimated to decrease by 30% during the life span (Lexell 1995) and maximal muscle strength, as a consequence of aging, is reduced by ~1.5% per year from the sixth decade onwards (Skelton, Greig et al. 1994; Sinaki 2004). Overall, muscle strength has also been shown to decrease by approximately 50% from age 30 to 80 (Sinaki 2004).

1.5 Exercise regimes for improving function

Women above age 60 who perform aerobics twice per week for 12 months have been shown to improve their balance, co-ordination and muscle strength (Lord, Ward et al. 1995). Specifically, muscle strength in the quadriceps muscle improved by 29% and the sway of the body was reduced by 6%. Additionally, there are reports that muscle strength increases of up to 200%, 2-20% increases in muscle volume, and 1-2% increases in bone mass are achieved by octogenarians following a similar training program (Daley, Spinks 2000).

The most commonly used rehabilitation regimes for elderly individuals are based on functional types of exercises without external loading (Suetta, Andersen et al. 2008). However, this type of intervention does not prevent further muscle atrophy (Reardon, Galea et al. 2001). In contrast, resistance training is an effective method to induce muscle hypertrophy and increase muscle strength and functional performance in the elderly (Harridge, Kryger et al. 1999) and using it in the postoperative phase has been shown to be an effective method of restoring muscle function in this group of patients (Hauer, Specht et al. 2002).

Progressive resistance training (PRT) elicits positive performance adaptations by challenging the skeletal muscles with loads that can be lifted repetitively until the onset of neuromuscular fatigue, i.e. the point at which appropriate technique can no longer be maintained (Garber, Blissmer et al. 2011). PRT sessions are optimal when followed by periods of recovery ranging from 48 to 72 h to allow for physiological super compensation (i.e. positive adaptation) (Cheema, Abas et al. 2007). To facilitate continued adaptation, training intensity (i.e. load) and/or volume (i.e. number of exercises x number of sets x number of repetitions) are progressively increased, and exercises are adjusted as indicated

throughout the training regimen to attenuate the onset of a plateau in physiological adaptation. Once the physiological plateau has been reached, performance improvements are maintained with continued training, which may involve periodical manipulations of the PRT variables, including training frequency, training intensity, training volume, types of exercises, and time under tension per repetition (Cheema, Abas et al. 2007).

PRT is a well-established and safe exercise modality for individuals of all ages and fitness levels, including those afflicted with severe chronic illnesses (Garber, Blissmer et al. 2011). It is particularly appropriate for adult and elderly cohorts given its efficacy in counteracting sarcopenia, abating osteoporosis and helping to reverse the physiological and functional impairments that accrue with age (Fiatarone, O'Neill et al. 1994).

1.6 The evidence for preoperative exercise regimes

Appropriate exercise offers many benefits for patients with osteoarthritis (Macera, Hootman et al. 2003). For example, stronger, better-conditioned periarticular muscles, tendons, and ligaments attenuate joint forces during movement (Felson, Lawrence et al. 2000). Additionally, in more severe disease, which often leads to reduced mobility and disuse atrophy, exercise can improve pain, muscle strength, cardiovascular fitness, self-efficacy, and function (van Baar, Assendelft et al. 1999).

Exercise is a cornerstone of rehabilitation following total joint arthroplasty and other surgical procedures (Eyigor, Hepguler et al. 2004), but using exercise in the pre-operative period has variable benefit. For example, although improvement in preoperative functional status has been demonstrated after a 6 week presurgical exercise program (water and land based strength training activities) in patients awaiting total hip and knee arthroplasty in comparison to patients having routine rehabilitation, this improvement was not maintained at 8 and 26 weeks (Rooks, Huang et al. 2006). This finding agrees with those of Wijgman et al (1994) who reported that preoperative physical therapy and instruction failed to improve pain or Harris hip score in 31 patients awaiting total hip arthoplasty. More recent work by Gocen et al (2004) also showed that instruction and pre-operative physiotherapy is of no benefit in terms of improving outcome (measured with the Harris Hip Score and Visual analogue pain scale) after THR surgery.

A systematic review by Ackerman and Bennell (2004) found only two randomised controlled trials involving patients undergoing THR surgery that have demonstrated a benefit of performing pre-operative exercise. Both Wang et al (2002) and Gilbey et al (2003) used a combination of progressive strength and aerobic training. Wang et al (2002) reported a significantly higher mean gait velocity for the exercise group from three to 24 weeks post-operatively, and a greater mean distance walked by the exercise group at 24 weeks post-operatively, whilst Gilbey et al (2003) found that the exercise group achieved greater gains in hip strength, WOMAC scores, and hip ROM from three to 24 weeks post-operatively relative to controls. The systematic review concluded that the major limitation of these studies was the addition of an intensive post-operative exercise program for the intervention group only, so it is impossible to determine which of the pre-operative regimes was responsible for the improvements seen. There is therefore a lack of conclusive evidence to justify the use of pre-operative regimes to optimise function after THR surgery.

1.7 An appraisal of the rehabilitation regimes used for improving functional outcome after THR

In the past, a prolonged hospital stay after THR surgery incorporated a period of supervised rehabilitation to try to achieve restoration of physical function. However, due to the introduction of initiatives such as integrated care pathways and considerations of cost and increasing patient satisfaction, the length of hospital stay over the past decade has been reduced from around 3 weeks to 4 days (Epps 2004; Ogonda, Wilson et al. 2005). Post-discharge rehabilitation is therefore increasingly important following THR. The following section reviews the literature with regards to the highest-level evidence (randomised controlled trials) for studies of rehabilitation programmes for improving physical function after THR.

1.7.1 Methods

Studies were eligible for the review if they met the following criteria: 1) randomised controlled trial of exercise rehabilitation interventions to improve functional outcome in the post-operative period; 2) target population of patients undergoing elective primary total hip arthroplasty for osteoarthritis; and 3) publication in the English language. For the purpose of this review, early interventions occurred ≤1 month after surgery and late interventions were conducted ≥ 1 month after surgery. This distinction is

important as it has been noted that muscle strength declines 4% per day during the first week of immobilisation after major surgery, making it important that rehabilitation is commenced as soon as possible afterwards (Wigerstad-Lossing, Grimby et al. 1988).

Studies were identified from computerized search of MEDLINE (1950 to June 2011). A set was created using the terms: 'total hip arthroplasty' OR 'total hip replacement' and this yielded 22159 articles. The terms 'exercise' OR 'rehabilitation' OR 'physiotherapy' OR 'functional outcome' were incorporated as a unit and nested (addition of the 'AND' term) with the initial set created and this reduced the number of articles to 2748. Restricting the articles to the inclusion criteria described above led to the identification of 23 appropriate studies (Table 1). The studies identified were assessed using the following parameters by the thesis author, TO : 1) whether they were home or centre based, 2) the follow up period used for functional assessment, 3) the interval from surgery to the rehabilitation intervention, 4) the exercise intervention carried out, 5) the outcome measures utilised, and 6) any evidence of dislocation as a complication. For the last parameter listed (dislocation), contact by email was made with the author of any study in which the rate of dislocation was not documented in the article.

Table 1. Characteristics of randomised controlled trials on total hip arthroplasty rehabilitation interventions to improve functional outcome

Article	Number of participants	Site	Follow up period	Interval from surgery to intervention	Exercise intervention	Outcome measures	Dislocation rate	Limitations
Bulthuis, Drossaers-Bakker et al. 2007	Intervention (n=58) Control (n=40)	Centre	1 year	Immediate post-discharge	Intervention group (IG): 1st 2 weeks- two to four supervised training sessions per day (30 minutes per session) involving range of motion exercises for affected joints with angular exercises and mobilizing techniques; strength exercises using graded activity; and hydrotherapy. 3rd week- functional capacity exercises as prioritized by patient Control group (CG): Usual care- Attending physical therapy by local physical therapist	Health Assessment Questionnaire (HAQ) -At 3 weeks more improvement for IG vs. CG HAQ rising : 1.2 vs. 1.4 ($p<0.05$) HAQ walking : 1.6 vs. 1.9 ($p<0.05$) -At 1 year no statistically significant difference between groups. McMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR) -At 3 weeks improvement in IG > CG 34.5 vs. 40.9 ($p<0.001$) -At 13 weeks improvement in IG > CG ; 34.6 vs. 39.4 ($p<0.05$) -At 26 weeks improvement in IG > CG ; 34.1 vs. 40.1 ($p<0.05$) -At 1 year no difference in improvement between groups IG 35.2 vs. 39.5 ($p>0.05$) Escola Paulista de Medicina-Range of Motion scales (EPM-ROM) Statistically significant improvement in IG vs. CG at 3 weeks (2.3 vs. 2.9 ; $p<0.05$), 13 weeks (1.8 vs. 2.7; $p<0.01$), 26 weeks (2.1 vs. 3.0; $p<0.01$) with no difference between groups at 1 year (2.3 vs. 2.6 ($p>0.05$). Research and Development 36-item Health Survey (RAND-36) No statistically significant difference between groups at all time points	None reported	Heterogeneous population including -Patients after knee arthroplasty - Patients hospitalized after a flare-up of rheumatoid arthritis

Galea, Levinger et al. 2008	Home based group (n=12) Centre based group (n=11)	Centre and Home	8 weeks	Immediate post-operative period	All participants: Standard inpatient physiotherapy with functional tasks, instructions to take home and 4 home visits by physiotherapist Centre group: 2 visits /week for 45 minutes each time. 5 bouts of exercise per week Home group: Exercise as above with no advice or further instruction	No differences between groups at final follow up although all parameters improved significantly from baseline in both groups Timed up and go: centre 11.1±2.5s vs. home 11.7±1.5 6 minute walking test: centre 427±78.2m vs. home 457.8±112.2m Stair Climb: centre 3.1±1.8s vs. 2.9±0.5s	None reported	Patients had access to advice and physiotherapist visits. Even though the home group received no further advice (other than the documented instructions), as part of standard protocol these patients could see physiotherapists on a further 3 or 4 occasions if they requested it.
Article	**Number of participants**	**Site**	**Follow up period**	**Interval from surgery to intervention**	**Exercise intervention**	**Outcome measures**	**Dislocation rate**	**Limitations**
Giaquinto, Ciotola et al. 2010	Intervention (n=31) Control (n=33)	Centre	6 months	< 10 days	Intervention group: Hydrotherapy in pool for 40 minutes after 20minutes of passive joint exercises All sessions performed 6x's/week for 3 weeks Control group: Physiotherapy + 'neutral' massage of scar	At 6 months: WOMAC pain subscale: No pain: 45.6% intervention group vs. 23% control WOMAC stiffness subscale: No stiffness: 67.7% intervention group vs. 35.8% control WOMAC function subscale: Score of 0 in function: 19.3% intervention group vs. 2.56% control	None reported	-3 week follow-up data initially reported showed objective improvements in speed and stance for example but no further assessments were made to see if this was maintained at 6 months. -No absolute values of the WOMAC subscales given
Gremeaux, Renault et al. 2008	Intervention (n=16) Control (n=16)	Centre	45 days	Immediate post-operative period	Intervention group: low frequency electrical stimulation of both quadriceps and calf muscles bilaterally. 1 hour session 5 days/week for 5 weeks and conventional physiotherapy (2 hours a day, 5 days/week for 5 weeks (25 sessions)) Control group: Conventional physiotherapy – range of motion exercises, muscle strengthening static and dynamic	Maximal isometric knee extension: Significant ↑ in power of operated limb for intervention vs control (66.7N (77%) vs. 26.7N (23%), $p<0.05$). No significant differences between groups for length of stay nor walking assessment (6MWT and 200mFWT)	None reported	-Small sample size -Absence of a true placebo group -Absence of standardisation for the rehabilitation programme

Article	Number of participants	Site	Follow up period	Interval from surgery to intervention	Exercise intervention	Outcome measures	Dislocation rate	Limitations
Hesse, Werner et al. 2003	Intervention (n=40) Control (n =40)	Centre	12 months	Within 3 weeks post-operatively	All patients: 45 minute individualised treatment on each of 10 consecutive days including passive physiotherapy (massage, heat ultrasound), group therapy in pool. Intervention: Treadmill training after above hip and knee mobilisation (20min days 1-5); days 6-10, 35 minutes treadmill training with 10 minutes physiotherapy Control: Passive hip and knee mobilisation, strengthening of hip abductor and extensor muscles, gait retraining on floor and stairs	Primary outcome: Harris Hip Score: Intervention vs. control significantly higher ($p<0.0001$) at 10 days (13.6 points), 3 months (8.9 points) and 12 months (16.5 points) Secondary outcomes: No change in walking velocity between groups Mean interval to abandon crutches 3.2wks intervention vs 7.9 wks control At end of 10/7 program, for intervention group: Hip extension deficit 6.8º less Gait symmetry 10% greater Affected hip abductor stronger Amplitude of gluteus medius activity 41.5% greater (ALL $p<0.0001$) Above differences persisted at 3 and 12 months	None reported	37.5% drop out rate at 1 year
Husby, Helgerud et al. 2009	Intervention (n=12) Control (n=12)	Centre	5 weeks	Within 1st week postoperatively	Intervention: Above regime and 5 training bouts per week: ~10 minute warm up then stationary cycling at $_{VO2}$max 50%; strength training with 2 exercises: leg press and hip abduction on operated leg only. 4 series with rest periods of 2 minutes Control: Inpatient rehabilitation treatment with sling exercise therapy of hip abduction/adduction, flexion/extension; low resistance exercises for 1 hour, 5 days a week for 4 weeks. Patients discharged before 4 weeks had outpatient treatment 3x's/week and were encouraged to do exercises at home 2x's/week.	Bilateral leg press: 40.9% improvement in intervention vs. control group at 5 weeks ($p<0.002$) Operated leg strength increased by 65.2% vs. control at 5 weeks ($p<0.002$) Abductor strength in operated leg 87% more in intervention vs control at 5 weeks ($p<0.002$) No difference in gait parameters and health related quality of life outcomes (SF36) at 5 weeks between groups For work efficiency, the intervention lowered heart rate by 11.4% relative to the control group at 5 weeks, and also led to 32.3% improvement in work efficiency ($p=0.065$) after 5 weeks	None reported	Lack of adequate sample size to demonstrate significant differences in parameters used to assess work efficiency

Article	Number of participants	Site	Follow up period	Interval from surgery to intervention	Exercise intervention	Outcome measures	Dislocation rate	Limitations
Jan, Hung et al. 2004	Intervention (n=29) Control (n=29)	Home	12 weeks	At least 1.5 years	Intervention group: 12 week exercise program inclusive of hip flexion range of motion, isotonic strengthening of hip flexors, extensors and abductors using ankle weights, walking + weekly telephone calls. Control group: no exercises	Strength measured with an isokinetic dynamometer. Patients in the intervention group who had good compliance (n=13(>50% adherence to protocol)) showed significant improvement in strength of hip abductors, flexors and extensors on both operated and non-operated legs, as well as greater walking speed and functional activity component of Harris hip score compared to low compliance group, n=12 and normal control	None reported	Subjects in the intervention group were not allowed to visit the physiotherapy department but if they raised issues with the program, they were invited to return to the laboratory for further instructions. No detail is given as to what proportion of the cohort required this and how often.
Jesudason, Stiller 2002	Intervention (n=21) Control (n=21)	Centre	7 days	1st post-operative day	Exercise group: Bed exercises; hip, knee, ankle range of movement exercises. Progressed from 5 repetitions once a day to 10 repetitions as tolerated, 2-3x's/day Control group: Standard protocol for mobilisation, progression of mobility as determined by treating physiotherapist	Pain severity: Significant ↓ in pain (p=0.01) in both groups from days 3-7 post-op No significant differences between groups for hip flexion, abduction range of movement, function using the ILOA scale, or length of stay at 3 or 7 days post-operatively	None reported	Short intervention Short period of follow up No objective assessment of muscle strength
Larsen, Sorensen et al. 2008	Intervention (n=45) Control (n=42)	Centre	3 months	Immediate post-operative period	Intervention group (IG): Information day to work on daily preset goals in the areas of information on hospital stay, pain relief medication, nausea control medication, nutrition screening, mobilization with a target of 8 hours per day and elimination using magnesia. Control group (CG): Standard mobilization with physiotherapist in order to reach the discharge criteria	Length of stay -IG > CG 4.9(2.4) vs. 7.8(2.1) p<0.001 Gain in quality of life using EQ-5D change from baseline to 3 month follow up -IG > CG 0.42(0.31) vs. 0.26(0.31) p=0.03	1 dislocation in IG	Heterogeneous study population-included patients undergoing hip or knee arthroplasty, and unicompartmental total knee replacement
Licciardone, Stoll et al. 2004	Intervention (n=30) Control (n=30)	Centre	4 weeks	Up to 1 week	Intervention group (IG): Individualized osteopathic manipulative treatment; 10-30 minute sessions up to 5 times weekly and	Change from rehabilitation unit admission to discharge -Functional independence measure (FIM) IG 26.5(7) vs. CG 26.2(6.5) p=0.86	None reported	-Heterogeneous population of patients including those undergoing knee arthroplasty and internal fixation for hip fracture

					standard rehabilitation care Control group (CG): Sham treatment (range of motion activities and light touch) with standard rehabilitation care	-Analgesia requirement Paracetamol IG (-741(1471) mg/day) vs. CG (-371mg/day (1715) mg/day) p=0.39 -Length of stay IG 15.4(6.6) days vs. CG 12.3 (7.4) days p=0.09 -Rehabilitation efficiency IG 2.0(0.7) vs. CG 2.6(1.1) p=0.01 Change from rehabilitation unit admission to 4 weeks after discharge -Medical Outcomes Study Short form (SF-36) IG -10.0(31.3) vs. CG -15.0(27.2) p=0.55		-No use of condition specific or surgical site specific outcome measures -Trainee osteopaths administered the intervention
Article	**Number of participants**	**Site**	**Follow up period**	**Interval from surgery to intervention**	**Exercise intervention**	**Outcome measures**	**Dislocation rate**	**Limitations**
Liebs, Herzberg et al. 2010	Hip arthroplasty subgroup. Intervention (n=99) Control (n= 104)	Centre	24 months	2 weeks postoperatively	Intervention: Physiotherapist guided sessions with ergometer initially. Sessions 3/week for ≥3 weeks. All patients: standard program of physiotherapy including range of motion exercises, ADL based movements and walking on stairs and uneven surfaces. Control: No ergometer cycling	Primary outcomes: WOMAC function subscale: Intervention group improved more than controls at 3 months (16.4 vs. 21.6, p=0.046)) and 24 months (9 vs. 14.7, p=0.019)) Secondary outcomes WOMAC stiffness subscale: Intervention group improved more than controls at 24 months (13.4 vs. 18.6 (p=0.047)) WOMAC pain: Intervention group improved more than controls at 3 months (11.1 vs. 15.9, p=0.049) Significant improvements also noted in intervention group vs controls in Lequesne hip and knee score (at 24 months), SF36 (6 and 24 months) and patient satisfaction (92% vs. 80%)	1 dislocation in both groups	Mixed hip and knee arthroplasty population 77% follow up at 24 months

Mahomed, Davis et al. 2008	Centre based (n=119) Home based (n=115)	Centre and home	12 months	On discharge from hospital	All patients: standard physiotherapy regimen: deep breathing, coughing, active and assisted bed/chair gait training Centre-regime: 14 day stay in rehabilitation centre with established pathway (regime not specified) Home regime: Referral to community team: nursing, home support etc. Patients discharged when functionally improved as determined by attending therapist	Primary outcomes: WOMAC function subscale: no difference between groups at 3 and 12 months Hip and Knee satisfaction scale: no difference at 3 and 12 months SF36 short form: no differences between groups at 3 and 12 months Impatient rehabilitation more expensive than home based ($14531 vs. $11082	2% dislocation rate in both intervention and control groups	Hip and knee arthroplasty patients included. No specific detail given for hip population
Maire, Dugue et al. 2006	Intervention (n=7) Control (n=7)	Centre	1 year	Immediate post-operative period	Intervention group (IG): 3 sessions per week for 6 weeks of 30min arm exercise. 1 session= 6 consecutive periods of 5 minute arm exercise with 4 minute 'base' work and 1 minute 'peak' work. Increased loads for base and peak (to get corresponding target heart rate) for 6 weeks in addition to standard rehabilitation Control group (CG): Standard rehabilitation program	Six minute walk test (6MWT) IG > CG -2 months 405m (270-508) vs. 259m (218-302); p<0.05 -12 months 486m (343-584) vs. 398m (333-482); p<0.05 WOMAC scores for physical function IG < CG 2 months 15(10-48) vs. 25(15-34) p<0.05 1 year 5 (4-16) vs. 21 (4- 34) p<0.05	None reported	Small number of male participants (x1 in each group). Results may therefore only apply to female elderly patients

Munin, Rudy et al. 1998	Mixed hip and knee arthroplasty. Total (n=70) Hip cohort: Intervention (n=14) Control (n=12)	Centre	16 weeks	Immediate post-operative period	Intervention group: Commenced rehabilitation protocol at 3 days post-operation Control group: Commenced rehabilitation protocol at 7 days post-operation	No difference in median length of stay: intervention group, 12.2 days vs. control group, 14.8 days (p>0.05) Cost of surgery and rehabilitation lower for intervention ($28256) than control ($29437) RAND 36 functional self assessment: No difference between both groups through the follow-up period (p>0.05)	1 dislocation each in control and intervention groups	Mixed hip and knee arthroplasty population Analysing both hips and knees together, the intervention group showed more rapid attainment of short term functional milestones such as ambulation, walking distance and stair climbing ability at 6-10 days post-op. No difference in the outcome measures for stratifying patients to type of surgery.
Article	**Number of participants**	**Site**	**Follow up period**	**Interval from surgery to intervention**	**Exercise intervention**	**Outcome measures**	**Dislocation rate**	**Limitations**
Rahmann, Brauer et al. 2009	Aquatic group (n=18) Water exercises (n=19) Control (n=17)	Centre	180 days	From post-op days 4 - 10	All patients: Standard physiotherapy x1/day Aquatic group: Hip abductor/adductor exercises with increasing progression-squat, heel raises in various positions in pool (40 minutes once daily till discharge) Water exercise group: General exercises in water but not targeted at specific functional retraining in the aquatic environment (40 minutes once daily till discharge) Ward control: as above	Hip subgroup: No significant difference across the 3 groups for primary outcomes such as hip abductor strength, 10m walk, WOMAC score and secondary outcomes such as timed up and go, quadriceps strength	None reported	Mixed group of hip and knee arthroplasty patients Small number of participants

Shepperd,Harwood et al. 1998	Intervention (n=36) Control (n=48)	Centre and Home	3 months	Not stated by authors	Intervention group (Hospital at Home, HH): Patients had nursing, physiotherapy, and occupational therapy services at home. Rehabilitation within home but not defined. Control group (In Hospital, IH): Usual inpatient services	Dartmouth COOP chart -↑ Improvement in Quality of life in HH vs. IH at 3 months; 0.97 vs. 0.47 (95% CI of difference 0.13, 0.88) Oxford Hip Score -No significant difference between groups in change from baseline at 3 months HH 4.77 vs. IH 3.13 (95% CI of difference -1.23, 4.50)	None reported	Heterogeneous study population. Study also assessed patients undergoing total knee replacement, hysterectomy, and home therapy for chronic obstructive airways disease.
Smith, Mann et al. 2008	Intervention (n=30) Control (n=30)	Centre	6 weeks	Immediate post-operative period	Intervention group: Gait re-education with programme of bed exercises from day 1 including; active hip flexion, ankle dorsi/plantarflexion, static quads and gluteal exercises. 10 repetitions each, 5 times a day during hospital stay. Patients encouraged to continue same regime on discharge. Control group: Standard gait re-education protocol from post-operative day 1.	Iowa level of assistance (ILOA): Significant improvement from baseline in both groups but no difference between groups at 3 days and 6 weeks SF12: No difference between both groups	At week 6, 1 dislocation in control group; no dislocations recorded in intervention group	No concealed allocation of randomisation so possible selection bias No objective assessment of hip strength performed
Article	**Number of participants**	**Site**	**Follow up period**	**Interval from surgery to intervention**	**Exercise intervention**	**Outcome measures**	**Dislocation rate**	**Limitations**
Stockton, Mengersen 2009	Intervention (n=30) Control (n=27)	Centre	6 days	Immediate post-operative period	Intervention group: 2 physiotherapy sessions per day. Similar protocol to above. Control group: Once daily physiotherapy including mobilisation exercises and transfer practice. Encouragement to perform 4x daily till independently mobile.	Length of stay: No significant difference - Intervention (8.2 days) vs control (8.0 days) Iowa level of assistance (ILOA): Significant difference between groups at 3 days (intervention 28.5 vs control 32.2, p=0.041) but not at 7 days (intervention 18.2 vs control 20.6, p>0.05)	None reported	Length of follow up No objective measurement of muscle strength
Strom, Huss et al. 2006	Intervention (n=17) Control (n=19)	Centre	1 year	Immediate post-operative period	Intervention group: Unrestricted weight bearing (UWB) on affected leg. Supervised intensive	Peak load on operated leg (kg) -1 week UWB > PWB	None reported	-Poor compliance of PWB group to prescribed protocol -No measurement of hip extension

					physiotherapy for 3 months – including ergometer cycling, active exercises in gym Control group: Partial weight bearing (PWB) on affected leg for 3 months, then unrestricted weight bearing	39.9(16.6) vs. 25.8(10.8) p=0.009 -3 months UWB > PWB 70(14.5) vs. 31.7(14.9) p=0.001 -1 year UWB=PWB 75.5(10.4) vs. 73.7(13.0) p=0.47 Isometric abduction muscle strength of operated leg -No difference between groups at all time points -1 year UWB 13.3(3.3) vs. PWB 12.1(3.9) p=0.202 Merle-d'Aubigne Score and Intermalleolus distance in full abduction- No difference between groups		or flexion strength -Patients only underwent uncemented hip arthroplasty
Article	**Number of participants**	**Site**	**Follow up period**	**Interval from surgery to intervention**	**Exercise intervention**	**Outcome measures**	**Dislocation rate**	**Limitations**
Suetta, Magnusson et al. 2004	Total n=36; Standard rehabilitation (SR; n=12) Electrical stimulation (ES; n=11) Resistance training (RT; n=13)	Centre/ Home	12 weeks	Immediate post-operative period	SR: 15 exercises in 2 parts. 1st part 6 bed exercises; 2nd part knee extensions in seated position and hip abduction, knee flexion, step training and calf stretching while standing. The attending physiotherapist added ambulation and transfer during the inpatient stay. Exercise was encouraged in the home setting 2x's/day and attendance was arranged at a physiotherapy department once a week ES: Electrodes placed over quadriceps of operated leg 5cm below inguinal ligament and 5cm above patella. Pulse rate 40Hz, pulse width 250μs, stimulation ~10s with 20s of rest. Total stimulation 1 hour per day for 12 weeks RT: Unilateral progressive resistance training for quadriceps of operated leg. Exercises included knee extension	Length of Stay: RT led to the shortest length of stay compared to ES and SR (10±2.4 days vs. 12±2.8 and 16±7.2 respectively). The difference (37%) between RT and SR was statistically significant (p<0.05) Functional performance: Gait speed: RT ↑ maximal gait speed by 30% at 12 weeks (p<0.001) whilst ES increases it by 19% (p<0.05). No increase was seen in the SR group Sit to stand: RT ↑ 30%, ES ↑ 21% (both p<0.001) at 12 weeks. SR no improvement. Stair Climb: RT↑ 28 % (p<0.005), ES 21% (p<0.001). SR no improvement Quadriceps cross sectional area (CSA): At 12 weeks, CSA of operated leg was ↑12% in RT group, ↑7% in ES group and ↓9% in SR group (all p <0.05). The non-operated leg was	None reported	No assessment of compliance in the SR group No documentation as to whether ES group received additional support for ambulation and transfer Subjective outcome measures not used Length of stay assessed was cumulative, and did not discriminate between acute surgical inpatient stay and rehabilitation centre length of stay

					in seated position with sandbags on ankles, leg presses in supine position, supervised by trained physiotherapist. Intensity increased from 50% of 1RM in week 1 to 65% 1RM during weeks 2-4, 70% 1RM for weeks 5, 6 and 80% 1RM for the last 6 weeks. For each session patients performed 3-5 sets of 10 repetitions during weeks 1-5 and 2-5 sets of 8 repetitions for weeks 6-12	unaffected in all the groups Peak torque on operated leg at 12 weeks was ↑22% in RT group ($p<0.05$) and unchanged in ES and SR groups. No change was noted in any of the groups for the non-operated leg		
Article	**Number of participants**	**Site**	**Follow up period**	**Interval from surgery to intervention**	**Exercise intervention**	**Outcome measures**	**Dislocation rate**	**Limitations**
Trudelle-Jackson et al 2004	Intervention (n=14) Control (n= 14)	Home	8 weeks	4-12 months post-operatively	Intervention: Sit to stand, unilateral heel raises, partial knee bends, 1-legged standing stance, knee raises with alternate arm raise, side and back leg raises in standing, unilateral pelvic lowering and raising in standing Control: 7 basic isometric and active range of movement exercises including the glutei, quadriceps, hamstring sets, ankle pumps, heel slides, hip abduction in supine position and hip internal and external rotation in supine position. Both groups: Progressively increasing repetitions of exercises encouraged 3-4/week for 8 weeks	No difference in fear of falling between both groups. Significant increases ($p<0.05$) in following in the intervention group compared to control at 8 weeks: Hip flexor strength (↑47.8%) Hip extensor strength (↑41.2%) Hip abductor strength (↑23.4%) Postural stability (↑36.8%)	None reported	Not clear whether the intervention and control groups both received the same amount of encouragement to increase repetitions Short follow up period

Unlu, Eksioglu et al. 2007	Intervention Home (n=9) Centre (n=8) Control (n=9)	Centre and Home	6 weeks	12 – 24 months post-operatively	Home Exercise Programme (HEP): Range of motion, isometric and eccentric contractile hip exercises twice daily for 6 weeks Centre based under Supervision (CbS): Same exercise regime as HEP but under direct physiotherapist supervision Control group (CG): No specific intervention	Maximum isometric abduction torque ↑ HEP (30(12) to 38(11) ft.Ib) and ↑CbS (18(10) to 30(9.8) ft.Ib) not CG (18(10) to 19(8) ft.Ib) HEP showed greatest improvement (p=0.006) Gait speed No significant difference between groups in terms of improvement. HEP (67.8(23) to 74.35(24) m/min); CbS (48.53(4) to 56.7(5) m/min); CG 58.01(12) to 59.8(14) m/min Cadence (number of steps in one minute) All improved with no significant difference between groups HEP (97.7(18) to 111(17) steps/min); CbS (90.75(6) to 104.75(7) steps/min); CG (87(16) to 88.22(16) steps/min)	None reported	Short period of follow up No subjective functional score evaluated
Article	**Number of participants**	**Site**	**Follow up period**	**Interval from surgery to intervention**	**Exercise intervention**	**Outcome measures**	**Dislocation rate**	**Limitations**
Whitney, Parkman 2004	Intervention (n=31) Control (n=27)	Centre	3 days	Immediate post-operative period	Intervention group (IG): Standard care and isotonic arm and leg exercises. Sequential protocol for increased ambulation from 1st post-op day to day 3. Control group (CG): Standard rehabilitation	Wound healing responses- Assessed by cellularity, mRNA procollagen, hydroxyproline, and DNA content. No difference between first 3 aforementioned measures between groups but statistically significant↑DNA content for IG vs. CG Subcutaneous tissue oxygen tension: No significant difference between groups	None reported	Short period of follow up No objective measures of function assessed

KEY:
200mFMWT 200m fast walk test
SF12 Short-form 12
SF36 Short-form 36
6MWT Six minute walk test
WOMAC Western Ontario and McMasters University Osteoarthritis scale
RAND 36 Research and Development 36-item health survey questionnaire

1.7.2 Results of review

From Table 1, it can be seen that 17 interventions were performed in a rehabilitation centre, 4 involved a direct comparison between home and centre based interventions, and 2 trials were home based. The data shows that, if early intervention is defined as commencing within a month of surgery, such an intervention is more likely to have a beneficial effect if it is performed in a centre and involves progressive resistance training (PRT; i.e. strength training wherein the resistance (weight) lifted is increased in accordance with improved strength to ensure maintenance of a constant relative intensity) (Tables 1 and 2; 8 out of 9 centre based studies (Suetta, Magnusson et al. 2004; Giaquinto, Ciotola et al. 2010; Hesse, Werner et al. 2003; Husby, Helgerud et al. 2009; Jesudason, Stiller 2002; Liebs, Herzberg et al. 2010; Maire, Dugue et al. 2006; Bulthuis, Drossaers-Bakker et al. 2007) involving resistance training proved beneficial). The only centre based intervention that led to significant improvements in muscle strength without using progressive resistance training utilised electrical stimulation (Gremeaux, Renault et al. 2008), although this modality has been shown to be not as efficacious as PRT (Suetta, Magnusson et al., 2004; Table 1). Another study by Strom et al (2006) demonstrated early benefits of centre-based PRT at 3 weeks and 26 weeks of follow up in favour of the intervention group but this effect was not maintained at 1 year follow up (Table 1). The home based intervention studies identified in this review (Trudelle-Jackson, Smith 2004; Jan, Hung et al. 2004) led to significant improvements in functional outcome parameters after short periods of follow up (8 and 12 weeks respectively), but both were carried out in the late phase of rehabilitation (4-12 months, and at least 1.5 years post-THR, respectively). The other 12 studies reviewed include 4 comparing home and centre based interventions (Galea, Levinger et al. 2008, Mahomed, Davis et al. 2008, Shepperd, Harwood et al. 1998, Unlu,Eksioglu et al. 2007)) and 8 others performed in the early phase in a centre setting but not including PRT(Munin, Rudy et al. 1998; Rahmann, Brauer et al. 2009; Smith, Mann et al. 2008; Stockton, Mengersen 2009; Licciardone, Stoll et al. 2004; Larsen, Sorensen et al. 2008; Whitney, Parkman 2004). The study by Larsen et al (2008) demonstrated a benefit in accelerated perioperative rehabilitation (education seminars for

patients, optimisation of analgesia) on length of stay and quality of life with no PRT prescribed and objective measures of physical function not assessed.

The follow up periods for the centre based studies varied from 3 days to 24 months. In terms of the studies which feature follow up periods longer than the intervention periods used, Liebs et al. (2010) showed that the functional benefits of a resistance program are sustained for 24 months from THR surgery. Although Mahomed et al. (2008) demonstrated that there is not much difference at 1 year between home and centre based post-THR standard physiotherapy interventions in terms of subjective functional outcome (measured with the WOMAC), there was no progressive training included in the prescribed programs used and this may explain the lack of a significant difference between the groups.

Table 2. Timing and effects of rehabilitation interventions following total hip arthroplasty

Article	Timing of intervention: Early (>1month) or Late (>1 month)	Intervention site	Use of progressive resistance training? Yes/ No	Significant effect of intervention on outcomes measured? Yes/No
Giaquinto, Ciotola et al. 2010	Early	Centre	Yes	Yes
Husby, Helgerud et al. 2009	Early	Centre	Yes	Yes
Galea, Levinger et al. 2008	Early	Home/Centre	No	No
Smith, Mann et al. 2008	Early	Centre	No	No
Rahmann, Brauer et al. 2009	Early	Centre	No	No
Liebs, Herzberg et al. 2010	Early	Centre	Yes	Yes
Mahomed, Davis et al. 2008	Early	Home/Centre	No	No
Hesse, Werner et al. 2003	Early	Centre	Yes	Yes
Munin, Rudy et al. 1998	Early	Centre	No	No
Gremeaux, Renault et al. 2008	Early	Centre	No	Yes
Jesudason, Stiller 2002	Early	Centre	Yes	Yes
Suetta, Magnusson et al. 2004	Early	Centre	Yes	Yes
Trudelle-Jackson, Smith 2004	Late	Home	Yes	Yes
Jan, Hung et al. 2004	Late	Home	Yes	Yes
Stockton, Mengersen 2009	Early	Centre	No	No
Licciardone, Stoll et al. 2004	Early	Centre	No	No
Strom, Huss et al. 2006	Early	Centre	Yes	No
Larsen, Sorensen et al. 2008	Early	Centre	No	Yes
Maire, Dugue et al. 2006	Early	Centre	Yes	Yes
Shepperd, Harwood et al. 1998	Not stated by authors	Home/Centre	No	No
Whitney, Parkman 2004	Early	Centre	No	No
Bulthuis, Drossaers-Bakker et al. 2007	Early	Centre	Yes	Yes
Unlu, Eksioglu et al. 2007	Late	Home/Centre	No	Yes

1.7.3 Discussion

'Standard rehabilitation', (i.e. not typically involving resistance training) following major surgery enables most patients to regain basal levels of function but leaves them with significant muscle wasting as it lacks the intensity of exercise required to elicit muscle hypertrophy (Suetta, Magnusson et al. 2004). The most commonly used rehabilitation regimes for elderly individuals are based on functional types of exercises performed without external loading. However, this type of intervention not only fails to elicit increases in muscle mass but fails to prevent further muscle atrophy (Reardon, Galea et al. 2001). In contrast, high-intensity PRT is an extremely effective and safe method for inducing muscle hypertrophy and increasing muscle strength and subsequently improving functional performance in healthy individuals, those with chronic disease (e.g. rheumatoid arthritis; Lemmey, Marcora et al., 2009), and the elderly (e.g. Hauer, Specht et al. 2002). The positive benefits of this method for post-THR rehabilitation are evident from the 8 randomised controlled trials identified in this review (Table 2).

A major disadvantage of programs used in the post-operative period following THR is the need for patients to exercise under the supervision of professional staff at a hospital or rehabilitation centre (Galea, Levinger et al. 2008). This makes program delivery expensive due to the high costs associated with supervision and transport. In addition, some THR patients are excluded because of difficulties with mobility (Barber, Roger et al. 1996). A similar exercise regime that could be performed at home would potentially overcome these cost and logistic implications.

A major concern with orthopaedic surgeons is dislocation of the hip arthroplasty (incidence after primary THR of 2-5%; Khatod, Barber et al. 2006) on patient mobilisation and the instructions patients have to adhere to afterwards take this into account. These include a restriction of hip flexion to less than 90°, no crossing of the legs, and elevation of toilet seats and chairs in the house etc. From this systematic review of 23 randomised controlled trials, the dislocation rate in the pooled sample of patients who underwent the interventions described was 0.007% (5 recorded dislocations in a pooled sample of n = 757) whilst the rate

in patients who were in the normal control groups was 0.008% (6 recorded dislocations in a pooled sample of n = 727). Thus, it is safe to conclude that these exercise programmes are not associated with an increased risk of hip dislocation.

A limitation of the home-based interventions is that follow-up did not extend beyond the end of the exercise interventions. Thus, it is not clear whether the benefits evident at the end of the exercise intervention are maintained in the longer term. A recent systematic review (Di Monaco, Vallero et al. 2009) suggests that a difficulty in THR rehabilitation research is a lack of multicentre clinical trials with large sample sizes to inform the design of optimal physical exercise programs.

1.7.3.1 Study limitations

A limitation of the review performed is that the literature search was limited to published studies in English, which meant that some studies may have been missed. The ideal design for assessment of the studies selected should have included specific quality criteria such as appropriateness, risk of bias, choice of outcome measures, statistical issues , quality of reporting, quality of the intervention and generalisability (Centre for Reviews and Dissemination, 2009). Specific criteria against which the randomised controlled studies selected should have been judged (ideally by at least 2 independent assessors) include an evaluation of the process of randomisation, allocation concealment, blinding of assessors /participants, and rate of drop-outs between groups over the period of follow up (Centre for Reviews and Dissemination, 2009). In this study some specific limitations of individual studies are discussed particularly with regards to heterogeneity of the study populations and the length of follow up. A full description of the populations studied for each study selected, as well as criteria against which each manuscript was judged would have enhanced the findings from this review. Subsequently the RCTs assessed that included PRT have to be interpreted with caution.

1.7.4 Conclusions

This systematic review demonstrates that significant improvements in muscle strength and function are achievable with PRT. Regardless of the timing of the intervention, PRT appears

to have a significant benefit on patient function following THR. Late PRT interventions do work and are safe, and they have been performed mainly in the home setting but the studies done have short periods of follow up and have a further limitation of the pre-existing functional deficit due to the timing post-operatively. Early PRT regimes identified in the studies reviewed have shown the need for a centre-based approach and this has demonstrable benefit but there are issues of transport and supervision costs. Early home based PRT studies that are effective and safe; with adequate follow-up after THR surgery would potentially address these issues.

1.8 Motivators and barriers to improving function through exercise

The benefits of regular exercise (including PRT) are well described and they include reduction in the risk of medical conditions such as coronary artery disease, diabetes, osteoporosis and hypertension (Garber, Blissmer et al. 2011) as well as mental health concerns such as depression (Newson, Kemps 2007). Recent research also suggests that physical exercise plays a role in the maintenance of cognitive vitality in older age (Colcombe, Kramer et al. 2004).

Specific motivators and barriers to exercise differ with age, education, gender, psychological and physical well-being and current level of exercise (Newson, Kemps 2007). People over the age of 75 are more likely to be motivated to exercise purely to maintain an active lifestyle than those aged 63 to 74 years, and medical problems are more likely to prevent them from engaging in exercise compared to their younger counterparts (Newson, Kemps 2007). Men were found to be more likely than women to be motivated to exercise for the challenging nature of exercise. On the other hand, women are more likely than men to report health concerns as a reason to exercise, and they are more likely to blame a lack of exercise facilities and exercise specific knowledge as factors preventing/discouraging them from exercising (Newson, Kemps 2007).

The average age of patients undergoing THR surgery in the UK is 67.2 years (National Joint Registry for England and Wales 2011). Patients in this age group (63-74 years old) view keeping their fitness (feel-good nature of exercise, enjoyment) as the most important

motivator whilst the most significant barrier is situational i.e. “having no one to exercise with”, “disliking exercising alone”, and adverse weather conditions (Newson, Kemps 2007). Psychological distress and behavioural coping mechanisms are also thought to have an impact on the recovery of patients undergoing surgical intervention (Kopp, Bonatti et al. 2003, Hossain, Parfitt et al. 2011). In terms of psychological distress and functional outcome after THR, the evidence is limited and conflicting most likely due to the heterogeneous nature of the assessment tools used (Vissers, Bussmann et al. 2011). Some studies report poor outcomes (Lingard, Riddle 2007) whilst others show no significant impact on functional gain after THR (Hossain, Parfitt et al. 2011).

1.9 Conclusions

Total hip replacement surgery provides good relief for patients' pain but fails to fully restore physical function. Regardless of the timing of the intervention, PRT appears to have a significant benefit on patient function following THR. Home-based PRT interventions work and are safe, but to date have only been performed several months, even years, after surgery. Additionally, these studies have only assessed short periods of follow up. Early PRT regimes identified in the studies reviewed in section 1.7 have shown a demonstrable benefit from centre-based programs, but inherent in this approach are issues of high transport and supervision costs. An early home-based PRT intervention would potentially address these issues. Thus we aimed to assess the efficacy, safety, and cost of a pilot study of an early home-based post-THR exercise intervention, featuring PRT, in improving physical function relative to ‘standard rehabilitation’.

1.10 Aims of study

The aims of the investigations performed in this PhD were the following:

1. To perform a pilot study as a proof of concept, to assess whether a home-based PRT program, with weekly supervision, in the early post-operative phase after total hip replacement surgery, has a benefit in improving muscle strength and patient function relative to standard rehabilitation (SR, control).
2. To assess the current standard of rehabilitation practice after THR in the UK.

3. To investigate the metabolic processes that occur in the *vastus lateralis* muscle of the affected limb in patient undergoing THR
4. To investigate the impact of psychological distress and behavioural cognitions on subjectively assessed functional recovery of patients undergoing THR and partaking in an exercise trial comparing home based PRT to SR.
5. To perform exploratory cost consequences analyses of the home-based PRT program in relation to SR.

CHAPTER 2: Efficacy of an early home-based progressive resistance training programme compared to standard rehabilitation regimes for improving patient function following elective total hip replacement (THR) surgery; results of a pilot randomised controlled study.

2.1 Introduction

Physical impairments that persist in the absence of pain after THR include decreased muscle strength and postural stability on the side of the affected hip (Trudelle-Jackson, Emerson et al 2002). The reported deficits in muscle strength of the involved hip are 10-21% when compared to the uninvolved hip at 1 year post-surgery (Rasch, Bystrom et al, 2009; Trudelle-Jackson, Emerson et al, 2002). Similarly the atrophic changes that occur in the muscles around the hip persist up to 2 years post-THR (Rasch, Bystrom et al, 2009). The most common types of rehabilitation programmes for elderly individuals are based on functional types of exercises performed without external loading but this fails to increase muscle mass and prevent further muscle atrophy (Reardon, Galea et al 2001). In contrast high intensity PRT is an extremely effective and safe method for inducing muscle hypertrophy and increasing muscle strength and subsequently improving functional performance in healthy individuals (Hauer, Specht et al,2002) and those with chronic disease (e.g. rheumatoid arthritis (Lemmey, Marcora et al, 2009)). The positive benefits of this method for post-THR rehabilitation are evident from the 8 randomised controlled trials identified in section 1.7.3 with a significant effect in favour of the PRT regimes on the outcome measures assessed (Table 2).

Centre-based PRT regimes for post-THR patients have been shown to increase strength of the operated leg quadriceps by 22 – 65% (Suetta, Magnusson et al. 2004; Husby, Helgerud et al. 2009), and improve objective measures of physical performance (e.g. 30% higher sit to stand score, 30% higher gait speed and 28% higher stair climb performance (Suetta, Magnusson et al. 2004)). Unfortunately, centre-based regimes inherently require the patients to exercise

under the supervision of staff and this makes program delivery expensive due to the high costs associated with supervision and transport (Galea, Levinger et al. 2008).

Addressing these issues has led to the assessment of home-based rehabilitation programs; which have also been shown to be effective in improving function post-THR. However, at the time the current study commenced, the two home-based interventions in the literature featured programs that had both been initiated between 4 and 48 months following THR, and neither study assessed retention of benefits at follow up (Jan, Hung et al. 2004, Trudelle-Jackson, Smith 2004). Jan et al (2004) demonstrated an improvement in the hip muscle strength of the operated side (~20%), as well as improvement in walking speed (~24%) after a 12 week program, commenced between 18 and 48 months following surgery. Similarly, Trudelle-Jackson et al (Trudelle-Jackson, Smith 2004) showed an improvement in hip flexor and extensor strength (41% and 48% respectively) for patients undergoing their exercise intervention compared to standard regimes after an 8 week program that included PRT, but again the intervention was commenced well after the time of surgery, in this case at least 4 months post-THR. The lack of follow up assessments in both studies means that only the immediate effects of home-based PRT regimes have been described.

After discussions with a research trial methodologist (Mrs Rhiannon Whitaker, MSc CStat CSci) at the North Wales Organisation for Randomised Trials in Health (NWORTH; a registered Clinical Trials Unit based at Bangor University, Bangor, UK), it was decided that the best way to investigate the effects of a home-based PRT programme with weekly supervision in the early post-operative phase post-THR would be to perform a pilot study as a proof of concept. Specifically the aim of this pilot study was to assess if the home based PRT regime was beneficial in improving operated leg quadriceps muscle strength relative to standard rehabilitation at up to 1 year follow-up post-THR. This pilot study was to use a reproducible measurement as the primary end point (operated leg quadriceps muscle strength). The relationship of this primary outcome measure to patient reported outcome measures at the time of commencing this study was not clear, and it seemed likely that a larger trial would need to obtain an indication of the minimally clinically important difference

required on the basis of patient reported outcome measures. Greater preoperative knee extensor strength of the operated site has subsequently been shown by other investigators to be associated with better physical function, measured by using the Western Ontario and McMaster Universities Osteoarthritis Index, subscale Physical Function (WOMAC PF) at 12 weeks postoperatively (Holstege, Lindeboom et al 2011).

Secondary aims of this study were to assess the impact of the proposed PRT regime relative to standard rehabilitation post-THR on objective function with surrogate measures for activities of daily living (ADLs (Jones, Rikli et al. 1999)): sit to stand score in 30 seconds (ST), timed up and go (TUG), gait speed (GS), six minute walk test (6MWT) and stair climb performance (SCP), as well as muscle lean mass of the operated limb.

2.2 Methods

This was a prospective single blinded randomised trial carried out from April 2010 to March 2012. Patients undergoing elective THR surgery for osteoarthritis were recruited after local NHS Research Ethics Committee approval (Ref 09/WNo01/52, APPENDIX 1). The full research protocol used for the ethics application is described in APPENDIX 2, and the trial was appropriately registered (trial registration number ISRCTN13019951).

Patients considered for this study were on the inpatient waiting list for THR at Gwynedd Hospital, Betsi Cadwaladr University Health Board, Bangor, Wales, UK. They were eligible for participation if they had unilateral hip osteoarthritis requiring THR via a posterior approach with a 26mm, 28mm, or 32mm femoral head, with the joint affected being the only severely arthritic joint, and no evidence of inflammatory arthropathy. The exclusion criteria were dementia, neurological impairment, cancer or other muscle wasting illness, unstable chronic or terminal illness, or any co-morbid disease that contraindicated resistance training. A Consolidated Standards of Reporting Trials (CONSORT) diagram (Moher, Schulz et al. 2001) for patients recruited into the study after informed consent is shown in Figure 1, with a corresponding checklist provided in APPENDIX 3. Recruitment was carried out from April 2010 to May 2011. A single patient acted as a pilot for the exercise intervention before subsequent one to one sequential individual randomisation with stratification for age and

gender (Russell, Hoare et al. 2011) was performed for the other 49 study recruits. Randomisation was performed by NWORTH with the results only made available to physiotherapists in contact with the patients in the immediate post-operative period, with TO blinded to the results of randomisation till the end of the study. A total of 25 patients were randomised to the home-based PRT group with 24 randomised to the standard physiotherapy (control) group.

2.2.1 Outcome measures

The primary outcome measure for this study was the maximal voluntary contraction (MVC) of the operated leg quadriceps (MVCOLQ; in Newtons (N)). The secondary outcome measures were the objective measures of function:sit to stand score in 30 seconds (ST), TUG, GS,SCP and the 6MWT, as well as the lean mass of the operated leg as assessed by dual energy x-ray absorptiometry (DEXA) scanning. Assessments of the primary and secondary outcome measures were performed preoperatively, and then at 6 weeks, 6 months, and 9 – 12 months post-operatively by the first author (TO). All data was collected at the laboratories of the School of Sports Health and Exercise Science at Bangor University. The lean mass of the operated leg was assessed at 6 weeks and 9-12 months post-operatively. Final follow-up for the patients assessed was completed in March 2012.

The outcome measures are described below:

Maximal voluntary contraction of the operated leg quadriceps (MVCOLQ; in Newtons (N)): This primary outcome measurement was made using a handheld isokinetic dynamometer (CSD300, Chatillon-Ametek, Largo, FL, USA), which has been shown to have high test/retest reliability (0.97, $p<0.001$; (Wiles, Karni 1983)). For the assessment, subjects sat on a medical table with arms across their chest. The curved push attachment of the dynamometer was positioned over the tibia just proximal to the 2 malleoli, and the subjects were instructed to attempt to straighten the leg as forcefully as they could. Following 2 sub-maximal familiarization trials, subjects were asked to exert force maximally for about 5 seconds. Between all 5

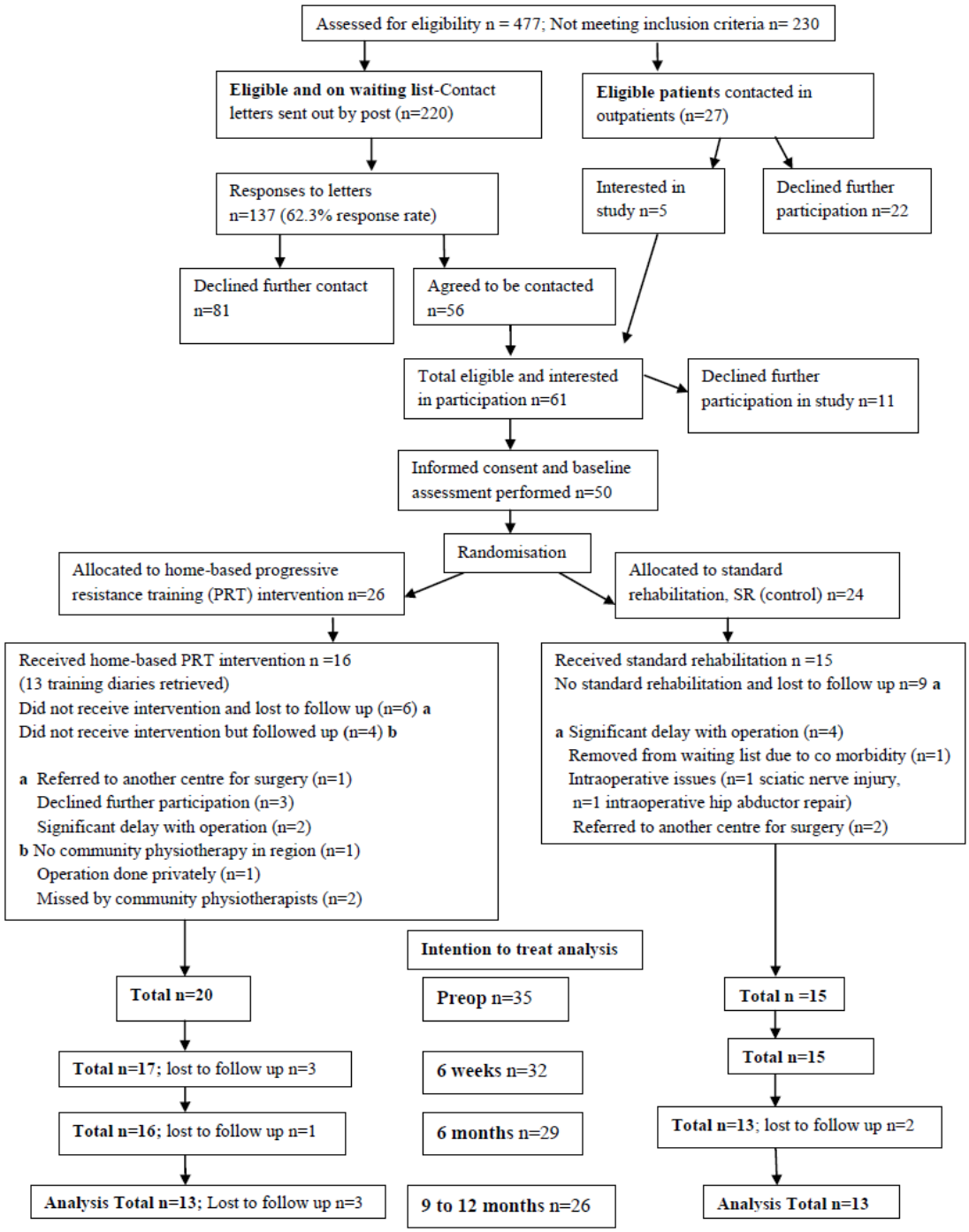
trials, a 1 minute rest was observed. Peak force produced during each of the 3 maximal trials was recorded with the best score noted.

Sit to stand in 30 seconds (ST) score: This is the maximal number of times the subject was able to rise, with arms crossed over their chest, from a standardized chair (seat height 43cm) in 30 seconds, and is a test designed to reflect the ability to perform ADLs (Rikli, Jones 2001). A moderately high correlation exists between ST performance and maximum weight-adjusted leg-press performance for both men and women (r = 0.78 and 0.71, respectively) supporting the criterion-related validity of the sit to stand test as a measure of lower body strength (Jones, Rikli et al. 1999). Construct (or discriminant) validity of the chair-stand has been demonstrated by the test's ability to detect differences between various age and physical activity level groups (Jones, Rikli et al. 1999). It therefore provides a reasonably reliable and valid indicator of lower body strength in generally active, community-dwelling older adults (Jones, Rikli et al. 1999). This test has an intra class correlation coefficient of 0.80 (Ritchie, Trost et al. 2005).

Lean mass of the operated leg: Whole body DEXA was performed using a pencil-beam scanner (QDR1500, Hologic, Bedford, Massachusetts) to determine total and regional (left and right arm, left and right leg, trunk, head) lean fat and bone mass. The lean mass value in grams for the operated leg of the subjects was used to assess if the home-based PRT intervention increased muscle mass in the involved leg compared to standard rehabilitation (SR; control). A calibration standard was scanned daily, and measurement accuracy was measured by scanning a water/oil phantom of known proportions (41% fat) monthly. The coefficient of variation of repeated measurements using the DEXA is between 1-3% (Ellis 2000).

The rationale for the other secondary outcome measures is described in Table 3.

Figure 1. CONSORT* flowchart for a 6 week home-based progressive resistance training intervention study following total hip replacement surgery.



*Consolidated Standards of Reporting Trials (CONSORT) diagram (Moher, Schulz et al. 2001)

Table 3. Description of secondary outcome measures used for assessing efficacy of a 6 week home-based progressive resistance training intervention program relative to standard rehabilitation (control) in patients following total hip replacement surgery

Outcome measure	Characteristics
Timed up and go (TUG)	The time taken in seconds for subjects to rise from a standard armchair, walk at a safe and comfortable pace to a cone 8 feet away, and return to a sitting position (back against the chair). It is a reliable test (Podsiadlo, Richardson, 1991) demonstrating good test-retest reliability for the duration of its subcomponents; time taken for a subject to stand up from a chair, walk 8 feet, turn 180 degrees, walk back to the chair and sit down (Botolfsen, Helbostad et al. 2008). Test-retest reliability estimates of 0.75 (type 2, 1 intraclass correlation coefficient (ICC)) for patients awaiting hip or knee replacement surgery have been demonstrated (Kennedy, Stratford et al. 2005).
Gait speed (GS):	The ratio of the time taken to cover a set distance of 18 metres in m/s. As gait speed has known relationships with overall aerobic capacity and functional status, it can be linked to cardiovascular health and capacity to perform daily activities (Hardy, Perera et al. 2007). It has very high intra class correlation coefficients (ICC) of 0.973-0.977, $p<0.001$ (Ries, Echternach et al. 2009).
Stair Climb performance (SCP)	The time taken to ascend 14 standard steps of 20cm height each in a usual manner and at a comfortable pace. The SCP has test-retest reliability (ICC) of 0.90 (Kennedy, Stratford et al. 2005).
Six minute walk test (6MWT)	The distance covered (metres) in a level corridor over a 6 minute period. Originally conceived as an outcome measure for patients with respiratory problems (Stratford, Kennedy et al. 2010), it has been shown to have high reproducibility in different patient populations (Beriault, Carpentier et al. 2009). It has the advantage of being reflective of patients' ability to perform ADLs (Peeters, Mets 1996). It has a test-retest reliability estimate (ICC) of 0.94 (Kennedy, Stratford et al. 2005).

After informed consent, baseline preoperative assessment, and subsequent THR, patients in the study were randomised to either a home-based PRT intervention or SR (control) for the immediate (6 week) post operative period. These interventions are described below:

2.2.2 Prescribed home-based PRT exercise intervention

This was devised by convening a discussion group of hospital and community physiotherapists (n=5; all with more than 5 years experience of treating patients following THR). The PRT programme is illustrated in APPENDIX 4. For patients randomised to home-based PRT, on post-operative day 2 (whilst they were still inpatients and allowing for complications), the exercises to be performed at home were demonstrated to them by the attending physiotherapist. On discharge home, they were seen by a qualified physiotherapist and, after the home environment had been assessed; the PRT regime was adapted accordingly and initiated between post-operative days 4 to 7. The exercises performed were: sit to stand, stepping up unto and off a block, stair climbing, walking, sitting knee extension against resistance, and weight transfer (APPENDIX 4). Ankle weights and foam blocks were used as inexpensive and adjustable forms of equipment to increase resistance for the knee extension and stepping exercises, respectively. Patients in the intervention group were instructed to perform a range of repetitions (0-3, 4-6, 7-10) depending on their initial physiotherapy assessment and then to progress, when able to, to achieve progressive overload (decisions to progress were reviewed and facilitated by weekly physiotherapy visits during each of the 6 exercise intervention weeks). Subjects were encouraged to exercise at least 5 times a week. Training volume (multiplying the number of sets performed/day by the number of days) was monitored using a simple training diary (APPENDIX 5). Compliance was assessed as a measure of practice ratio i.e. number of days the subjects actually carried out the program divided by the program duration in days (5 days a week for 6 weeks, i.e. 30 days).

2.2.3 Standard rehabilitation, SR (control):

The SR (control) group received routine inpatient and/or outpatient physiotherapy with standard information leaflets provided. The standard rehabilitation provided in this study

typically involved home-based functional exercises that are geared towards getting the patients safely mobile. Whatever care was provided by the local physiotherapy service was accepted as SR (control).

2.2.4 Statistical Analysis

Based on previous research (Suetta, Magnusson et al, 2004) in which resistance training after hip arthroplasty improved isokinetic operated leg quadriceps strength from a mean (± SD) of 71 (± 9.6) Nm to 86.4 (±10.2) Nm, a 21% improvement, at 12 weeks postoperatively, it was hypothesised that the proposed home-based intervention would lead to a 15% increase in the muscle strength (MVCOLQ) of the PRT group relative to the SR (control) group. With an alpha value of 0.05 and power of 0.8, it was determined that 10 experimental subjects and 10 controls would be needed to demonstrate a significant effect. The target of a total of 50 participants (25 per group) was set to allow for potential drop outs during the follow up period (9-12 months post-THR).

A mixed model repeated measures ANOVA was performed with the primary and secondary outcome measures as dependent variables. The null model to fit the grand mean for the outcome variables was run first, and then an unconditional model with no predictors was used to determine whether a model with varying intercepts was suitable as well as determining the variance in the outcome measures between subjects. After the addition of time-point indexing to assess whether the pattern of linear change over time varies, additional predictors (group randomization (fixed, between-subjects effects)) and the effect of the follow up time period (random, within-subjects effects) were added to the model to attempt to explain any overall change over time. An interaction term of randomization group and time was then added to the model and if this was not significant, it was removed from the final model applied. A sensitivity analysis was performed with repeated measures analysis of variance assessment of the primary outcome measure (MVCOLQ) at 9-12 months post-THR. The mixed model analysis was performed with the absolute and change from baseline values of the primary and secondary outcome variables. A further analysis was performed to assess the relationship between the training volume of the exercise regime and the objective measures of physical

function assessed using Pearson's correlation coefficient. A p value <0.05 was considered statistically significant. SPSS version 18 (SPSS for Windows v18, Rel. 30.07.2009. Chicago: SPSS Inc) was used for all analysis.

2.3 Results

Of a total of 50 patients recruited to this study, a total of 15 were lost to follow up preoperatively due to a variety of reasons; see CONSORT diagram (Figure 1). Thirty five patients were therefore included in the final analysis (demographic data are described in Table 4). Three patients were lost to follow up at each of the review time points leaving 26 patients who completed the 9-12 months final assessment. Thus, there was a final follow-up rate of 74.28% (26/35).

The values for the primary and secondary outcome variables preoperatively and at the follow-up intervals for the home-based PRT and SR (control) groups appear in Table 5.

Table 4. Gender and baseline age of total hip replacement surgery rehabilitation trial participants

Characteristic	**Home-based, progressive resistance training (PRT) group** (n=20)	**Standard rehabilitation (control) group** (n=15)
Age in years (mean(SD))	66.20 (8.79)	63.60 (12.40)
Sex Males (n) Females (n)	 9 11	 6 9

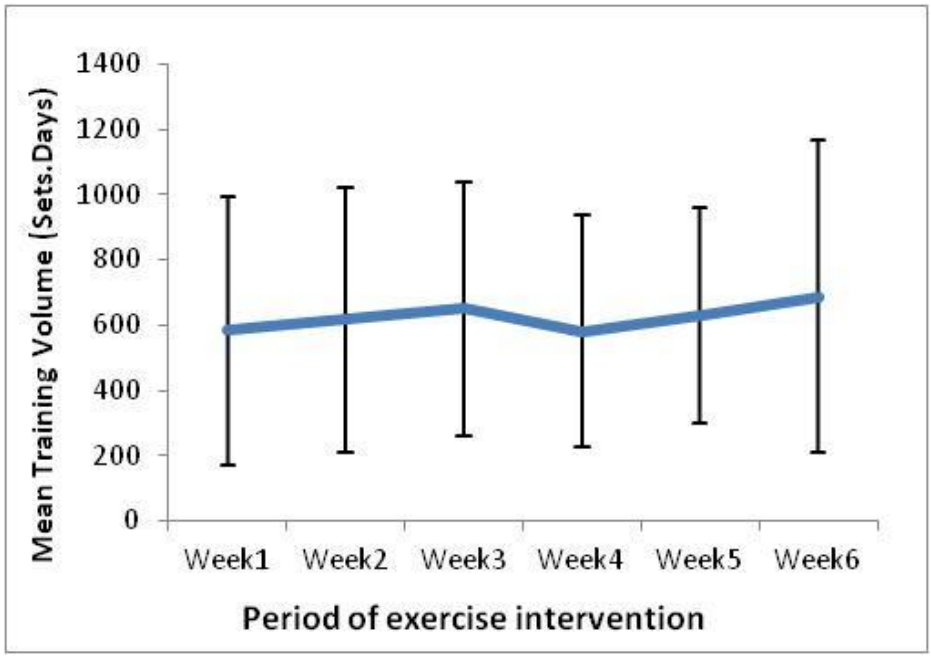
Table 5. Absolute values (mean (SD)) for primary and secondary outcome measures for home-based progressive resistance training (PRT) and standard rehabilitation (control) groups preoperatively and at intervals of up to 12 months following total hip replacement surgery.

	Preoperative [#]		**6 weeks postoperatively**		**6 months postoperatively**		**9-12 months postoperatively**	
Primary Outcomes	Home-based PRT n=20	Standard rehabilitation (control) n=15	Home-based PRT n=17	Standard rehabilitation (control) n=15	Home-based PRT n=16	Standard rehabilitation (control) n=13	Home-based PRT n=13	Standard rehabilitation (control) n=13
MVCOLQ (N)	172.3 (85.1)	174.2 (70.3)	181.8 (49.5)	196.7 (73.4)	233.8 (87.8)	227.5 (101.4)	247.4 (85.1)	240.3 (87.4)
Secondary Outcomes (Exploratory analysis)								
ST	9.30 (4.74)	8.26 (4.84)	9.63 (5.54)	10.25 (5.14)	10.88 (5.70)	14.00 (5.90)	13.21 (5.46)	14.16 (5.47)
Lean mass in grams (g) of the operated leg	8265 (2326)	7601 (1989)	8512 (2309)	7759 (2275)	n.a.	n.a.	8769 (2109)	7889 (2226)
TUG (s)	13.47 (11.06)	12.14 (6.93)	12.94 (7.11)	10.36 (3.43)	9.75 (3.75)	7.74 (1.38)	8.64 (3.23)	7.06 (1.31)
GS (m/s)	0.75 (0.32)	0.70 (0.27)	0.70 (0.28)	0.86 (0.21)	0.89 (0.30)	0.99 (0.21)	1.00 (0.26)	1.04 (0.14)
SCP (s)	13.74 (7.49)	17.80 (10.99)	15.82 (10.55)	13.94 (8.26)	10.99 (5.49)	8.49 (3.21)	8.32 (4.45)	7.64 (2.70)
6MWT (m)	269.8 (115.0)	238.7 (110.5)	250.3 (104.2)	310.0 (76.2)	313.6 (118.1)	358.6 (75.6)	352.4 (109.3)	376.5 (49.9)

Key: MVCOLQ: Maximal voluntary contraction of the operated leg quadriceps
ST: Sit to stand, number of repetitions in 30 seconds
TUG: Timed up and go test in seconds (s)
GS: Gait speed in metres per second (m/s)
6MWT: Six minute walk test in metres (m)
SCP: Stair Climb performance in seconds (s)
n.a.: Not assessed
[#]: No statistically significant differences between groups

Thirteen patients who completed the home-based PRT exercise program returned exercise diaries (Figure 1), with the average training volume over each of the 6 weeks shown in Figure 2. There was a gradual increase in the calculated training volume from (mean (SD)) 583 (409) sets.days in week 1 to 687 (478) sets.days in week 6. Participant 1 (70 year old female) started her program in the 2nd week as the community physiotherapists were not initially aware she was randomized to the home-based PRT intervention, hence the missing value. Participant 8 (60 year old male) had a chest infection in weeks 5 and 6 and was unable to complete the whole program. Participant 3 was 'unwell' during week 4 (training volume recorded 42 sets.days) and did not carry out the intervention as prescribed, and participant 5 only carried out the intervention for 3 days of the final week (training volume recorded 72 sets.days). The average compliance to the prescribed program was 125% (i.e. on average, the home-based PRT subjects completed 37.5 training days rather than the minimal requirement of 30 days), indicating that for the patients from whom training records were retrieved, the intervention was well tolerated (Table 6).

Figure 2. Mean training volume* (sets.days) for participants in the 6 week home-based progressive resistance training intervention group who returned training diaries (n=13)



* Training volume calculated by multiplying the number of sets performed by the number of training days

Table 6. Compliance (training %), and calculated training volumes for post-operative total hip replacement patients randomly allocated to perform 6 weeks of home-based, progressive resistance training who returned exercise diaries (n=13).

Participant demographics			*Compliance (Training %)	Calculated training volume[#] (sets.days)						
				Week						Total
No.	Age (years)	Sex		1	2	3	4	5	6	
1	70	Female	37/30 (123%)	-	195	448	343	280	287	2667
2	65	Male	42/30 (140%)	434	441	385	1155	606	497	4634
3	67	Female	36/30 (120%)	1540	1491	1652	42	1197	1519	8559
4	63	Female	42/30 (140%)	300	420	392	735	427	399	3793
5	54	Male	36/30 (120%)	329	392	312	413	288	72	2929
6	70	Male	42/30 (140)	1120	1176	1148	1176	1176	1176	8099
7	70	Female	38/30 (127%)	128	136	532	546	539	483	3493
8	60	Male	22/30 (73%)	235	280	505	460	-	-	2689
9	63	Female	41/30 (137%)	744	1064	1029	1029	1029	1029	7135
10	67	Male	42/30 (140%)	686	686	553	441	371	448	4398
11	77	Female	38/30 (127%)	329	434	392	152	392	315	3233
12	77	Male	41/30 (137%)	720	735	525	581	651	1435	5868
13	45	Female	42/30 (140%)	427	560	588	490	588	588	4556
	Mean		37.5/30(125%)	583	616	651	582	629	687	4773
	Standard deviation		-	409	406	389	355	330	478	2032

***** Compliance = Training ratio × 100 (%)
Training ratio = number of days the subjects actually carried out the program divided by prescribed program duration in days (5 days a week for 6 weeks, i.e. 30 days)

[#] Training volume calculated by multiplying the number of sets performed by the number of days (in sets.days)

- Missing data

An intention to treat analysis was performed (Figure 1) and the mixed model repeated measures ANOVA output data for both the absolute values for the primary and secondary outcomes, as well as the change from baseline values for these measures, appears in Tables 7 and 8.

2.3.1 Absolute values of the outcome measures

All the outcome measures (both primary and secondary) showed marked progressive improvements from the baseline measures in terms of absolute values following surgery for both groups (except the lean mass change for the operated leg; estimated effect for being in the standard rehabilitation (control) group 20g, p=0.326).

Table 7 shows that there was no effect of treatment, i.e. no differences between the home-based PRT or standard physiotherapy (control) groups, on the absolute values for any of the outcomes (MVCOLQ, sit to stand (ST) score, and lean mass of the operated leg) at any stage over the 9-12 month period of investigation.

2.3.2 Changes in outcome measures from preoperative values

Superior improvement in 3 of the secondary outcome variables (GS, SCP and 6MWT) at the 9-12 month post-surgery follow-up was observed for patients in the SR (control) group relative to the home-based PRT patients (Table 8).

2.3.3 Sensitivity analysis on the primary outcome variable (MVCOLQ) with repeated measures ANOVA

There was no effect for randomisation into home-based PRT or standard rehabilitation (SR, control) on the MVCOLQ at final follow up on repeated measures ANOVA analysis (F=0.057, df=1, p=0.813), and this confirmed the mixed measures repeated measures ANOVA finding. Significant improvement was noted over time in both groups (F=18.12, df=1, p=0.000) with no significant interaction between change in MVCOLQ over time and randomisation (F=0.008, df=1, p=0.795).

2.3.4 Effect of training volume on change in outcomes (dose response)

The training volumes (dose) were determined for the 13 study participants who completed exercise diaries. The only significant correlation identified was between volume and the

change from baseline for the ST score, with an R value of 0.639 (p=0.019) at 6 weeks, 0.646 (p=0.023) at 6 months, and 0.855 (0.002) at 9-12 months follow up. This indicates that higher training volumes was associated with greater improvement in performance of the ST test, our surrogate measure of lower body function, but not with the other outcome variables (data not shown).

The median training volume was 4398 sets.days. Patients with higher values than this were classified as high training volume participants (HTVP, n=7) whilst those with lower values were classified as low training volume participants (LTVP, n=6). There was a significant effect at 9-12 months for being in the HTVP group compared to the LTVP for improvement in the ST test (mean (SD), 4.83 (2.04) increased repetitions vs. 1.50 (1.00), p=0.010). There was also a significant effect at 9-12 months in the change from baseline values for the MVCOLQ, with the HTVP showing a mean improvement of 121 (84.63) Newtons (N) relative to a reduction of 5.33 (54.12) N in the LTVP (p=0.034). There were no effects of training volume on the other primary and secondary outcome variables.

The compliance scores from the exercise diaries obtained combined with the analysis of training volume in the home-based PRT group indicate that the regime was well tolerated and in those patients who had high training volumes, significantly better improvements in two of the three principal outcomes were achieved and sustained for up to 1 year post-operatively.

Table 7. Results for mixed model repeated measures analysis of variance (ANOVA) modelling for absolute values of primary and secondary outcomes used for randomized study into hip replacement rehabilitation

	Fixed effects			Random effects (within-subjects)		
	Treatment[#]			Effect of time		
Primary Outcomes	Estimated effect (Std error); For being in Standard rehabilitation (control) group compared to home- based PRT	F value	P value	Estimated effect (Std error); For assessment over 9-12 month follow up	F value	P value
MVCOLQ (Newtons,N)	6.01 (23.54)	0.065	0.800	22.22 (6.43)	21.519	0.002*
Secondary Outcomes (Exploratory analysis)						
ST (reps)	-0.825 (1.634)	0.255	0.617	0.963 (0.300)	41.895	0.003*
Lean mass (g) of the operated leg	-702 (762)	0.849	0.364	-69 (90)	0.003	0.954
TUG (s)	-1.48 (2.89)	0.245	0.625	-1.72 (0.66)	12.164	0.001*
GS (m/s)	0.193 (0.096)	0.041	0.841	0.083 (0.014)	82.525	0.0001*
SCP (s)	1.80 (3.20)	0.317	0.579	-2.03 (0.58)	36.357	0.0001*
6MWT (m)	-2.56 (35.59)	0.005	0.943	26.50 (5.84)	61.556	0.0001*

Key:

MVCOLQ: Maximal voluntary contraction of operated leg quadriceps
ST: Sit to stand, number of repetitions in 30 seconds
TUG: Timed up and go test in seconds (s)
GS: Gait speed in metres per second; m/s
6MWT: Six minute walk test in metres (m)
PRT: Progressive resistance training
*: $p<0.05$
[#]: Randomization into either standard rehabilitation (control) or home-based PRT
SCP: Stair Climb performance in seconds

Table 8. Results for mixed model repeated measures analysis of variance (ANOVA) modelling for change from baseline values of primary and secondary outcomes used for randomized study into hip replacement rehabilitation (9-12 month follow up)

	Fixed effects			Random effects (within-subjects)		
	Treatment[#]			Effect of time		
Primary Outcomes ***(Change from baseline)***	Estimated effect (Std error); For being in Standard rehabilitation (control) group compared to home- based PRT	F value	P value	Estimated effect (Std error); For assessment over 9-12 month follow up	F value	P value
MVCOLQ (Newtons, N)	10.38 (23.72)	0.192	0.665	26.50 (8.71)	14.250	0.001*
Secondary Outcomes ***(Change from baseline-Exploratory analysis)***						
ST (reps)	1.43 (1.19)	1.439	0.239	1.37 (0.33)	51.175	0.0001*
Lean mass (g) of the operated leg	280 (419)	0.449	0.508	20 (204)	1.000	0.326
TUG (s)	0.09 (2.64)	0.001	0.972	-1.44 (0.45)	21.242	0.0001*
GS (m/s)	0.185 (0.067)	7.701	0.009*	0.133 (0.016)	78.038	0.0001*
SCP (s)	-5.67(2.61)	4.700	0.038*	-3.41 (0.80)	23.914	0.0001*
6MWT (m)	86.39 (27.94)	9.563	0.004*	45.61 (6.10)	65.626	0.0001*

Key:

MVCOLQ: Maximal voluntary contraction of operated leg quadriceps
ST: Sit to stand, number of repetitions in 30 seconds
TUG: Timed up and go test in seconds (s)
GS: Gait speed in metres per second; m/s
6MWT: Six minute walk test in metres (m)
PRT: Progressive resistance training
*: $p<0.05$
[#]: Randomization into either standard rehabilitation (control) or home-based PRT
SCP: Stair Climb performance in seconds

2.4 Discussion

This study shows no advantage for the 6 week home-based PRT exercise intervention over standard rehabilitation, SR (control) in terms of the absolute values for the primary and secondary outcomes assessed over 9 to 12 months of follow up post-THR. The standard rehabilitation (control) group showed greater improvement at final follow up in three objective measures of physical function, GS, SCP and the 6MWT, relative to home-based PRT patients. All the measures assessed (except the lean mass of the operated leg) improved significantly over time for both treatment groups (Table 5), which would be expected in this patient population as THR provides good pain relief and patients tend to become more physically active following surgery (Wang, Gilbey et al. 2002).

The home-based PRT intervention appeared to be well tolerated, with the participants for whom exercise diaries were retrieved showing compliance rates on average of 125% (i.e. 25% more than the recommended minimum training volume). There was a significant dose response for training, with significant differences observed between patients with high training volumes and those with low training volumes in terms of the amount of improvement at 1 year in ST performance, and MVCOLQ.

A study by Mikkelsen et al (2012), published after our study was undertaken,) also compared a home-based, intensified, early postoperative regime (12 weeks duration) after THR to standard rehabilitation. Consistent with our findings, they also found no differences between groups at their final follow up point (12 weeks). Again, like us, these investigators noted the expected improvement from baseline values in both groups following THR, and the prescribed resistance training regime was well accepted by patients on the basis of pain, compliance, and patient satisfaction (Mikkelsen, Mikkelsen et al. 2012). The authors suggest that the lack of a significant benefit for their home based regime may be because participants' additional training activities could not be controlled for. They also suggest that perhaps not all post-operative THR patients can perform exercises effectively without supervision (Mikkelsen, Mikkelsen et al. 2012). These study limitations are also applicable to the findings of our study.

Home-based interventions in the literature that have demonstrated a beneficial effect on restoration of muscle strength and objective function following THR have all been conducted some time after surgery i.e. 4 to 12 months (Trudelle-Jackson, Smith 2004) and at least 1.5 years (Jan, Hung et al.

2004). Whilst the improvements in the objective measures of physical function assessed in these studies were significantly better in the exercise intervention groups than the controls (routine rehabilitation protocols), a significant level of impairment still persisted in these patients when final function was compared to a population of community dwelling age- and sex-matched adults without hip osteoarthritis. For example, for the high compliance exercise group in the study by Jan et al (2004), the gait speed that was achieved following 12 weeks training was 1.19m/s (±0.19); still a 17% deficit when compared to the matched healthy mean value of 1.43m/s (Steffen, Hacker et al. 2002). Similarly, the average absolute values for gait speed at 9-12 months in the home-based PRT and SR (control) groups in our study were 1.00m/s (±0.26) and 1.04m/s (±0.14), respectively (Table 5); an average functional deficit of 30%.

In contrast, the centre-based rehabilitation intervention conducted by Suetta et al (2004) was able to restore "normal" gait speed (from 1.10m/s (±0.50) to 1.43m/s (±0.60)) following 12 weeks resistance training in patients immediately post-THR. This suggests that gait speed can be fully restored provided that a sufficient intensity of resistance training is applied. As the follow up periods for the centre-based PRT studies in the literature do extend beyond the time frame of the interventions assessed, it remains to be seen whether the substantial functional improvements observed are maintained over a longer period.

For the 6MWT, the values obtained in our study after 9-12 months for the home-based PRT and SR (control) groups were 352 (±109)m and 377 (±50)m, respectively, which again is considerably lower than that for healthy community dwelling match adults without hip osteoarthritis (~527m, (Steffen, Hacker et al. 2002)). This implies an average functional deficit in the present study population at final follow up of around 30%; the same proportional deficit as for gait speed. Once again, this compares poorly to the improvement elicited by the centre-based rehabilitation intervention of Galea et al (2008) in which the values obtained after an 8 week PRT intervention was 427m (an average deficit of 23% from the normal value). These results suggest that centre-based regimes are able to produce better functional improvements.

There was a significant difference in the change from preoperative values at 12 months in 3 of the secondary outcome measures (GS, SCP, 6MWT) in favour of the SR (control) group. This may be

explained by the variability that exists in standard practice across the UK, with the regimes prescribed highly dependent on local resource allocation as well as physiotherapists' preference (see Chapter 3). The only home-based regimes in the literature that have improved functional outcome were performed between 6 months and 4 years after THR and were either for a short duration (8 weeks) with progressive resistance training (Trudelle-Jackson, Smith 2004) or for a long duration (12 weeks) without PRT (Jan, Hung et al. 2004). The longer home-based higher intensity regime (12 weeks, (Mikkelsen, Mikkelsen et al. 2012)) performed on THR patients in the early post-operative period by Mikkelsen et al. (Mikkelsen, Mikkelsen et al. 2012) also provided no additional benefit to patients. The latter result in conjunction with ours appears to suggest that centre-based PRT regimes may be more effective in conferring a functional advantage in the early period following THR perhaps due to the additional supervision and the higher training intensity that is achievable. Additionally, the early period of surgical recovery (limb swelling, pain) may be more restrictive on patients in terms of performing training tasks effectively in the home setting. Undertaking an effective home-based intervention in this population may require the provision of trained home exercise specialists to ensure that sufficiently intense regimes are completed by THR patients to overcome the persistent functional deficits that exist after surgery. This may only be effective in the post-recovery phase (> 4 months) after THR and it may be appropriate to only target patients who have expectations of additional functional gain. The results however may not be generalizable as there was a high number of patients who were eligible and not recruited (Figure 1), hence the results obtained here are best interpreted with caution.

2.4.1 Study Limitations

The participants' additional (not study related) exercise activities (especially relevant for the patients randomised to the SR (control) group) could not be controlled for during the duration of the 6-week intervention period. Another limitation that may have led to the home-based PRT regime not being more effective than standard rehabilitation includes the fact that the community physiotherapists who administered the program were also involved in looking after the patients randomized to the SR (control) group. This may have led to some modification of prescription behaviour in dealing with the control group, in terms of adjustment of exercises prescribed (i.e. inclusion of some of the PRT

exercises). Additionally, our home-based PRT regime concentrated mainly on training the quadriceps, whilst, most of the studies in the literature involved a variety of exercises which included weight bearing progressive resistance working on hip flexors, extensors, and abductors in a variety of positions (Trudelle-Jackson, Smith 2004, Jan, Hung et al. 2004).

2.5 Conclusions

This study demonstrates that home-based PRT is feasible and well tolerated for patients immediately following THR surgery, but that it does not confer additional benefits in terms of physical function or muscle hypertrophy over standard rehabilitation practice. Centre-based regimes may be the only effective way to obtain functional benefits in the early period following surgery, perhaps due to the supervision afforded to patients.

2.6 Chapter summary

The pilot randomised controlled trial carried out compared a home-based PRT program with weekly supervision in the early postoperative period after THR against SR (control) in terms of improving muscle strength at up to 1 year follow up post-THR. Of 50 patients initially recruited (home-based PRT n =26, SR (control) n=24) after informed consent, 26 completed 9-12 months follow up (home-based PRT n=13, SR (control) n=13). There was no effect for treatment (home-based PRT or SR(control)) in terms of the primary outcome measure assessed, i.e. maximal voluntary contraction of the operated leg quadriceps (MVCOLQ in Newtons (N)) over the period of follow up. As anticipated, there was a significant effect of time (i.e. improvement) in the primary outcome, with improvements also noted in the secondary exploratory analysis of objective measures of physical function, as well as the lean mass of the operated leg. Being in the SR(control) group as opposed to the home-based PRT group led to significant improvements in three of the secondary outcomes assessed; GS (estimated effect 0.185m/s; p=0.009), SCP (estimated effect -5.665s, p=0.038), and 6MWT (estimated effect 86.393m, p=0.004) at 9 to 12 month follow up. Due to the high rate of loss to follow up for the patients enrolled at the start of the study (15/50; 30%) the results need to be interpreted with caution. Although the conclusion is that early home-based PRT is not successful in providing functional gain beyond that achievable by SR in this population, it is deliverable and well tolerated. In terms of the pilot study objective, the intervention proposed is not suitable to deliver the

improvement in muscle strength in this cohort, indicating that a definitive multi-centre study assessing the intervention proposed is not appropriate. The following chapters will assess what standard rehabilitation entails in the UK (Chapter 3), as well as investigate the metabolic processes in the muscle of the patients participating in the trial (Chapter 4), with an exploratory assessment of the impact of psychological variables on functional assessment (Chapters 5 and 6). A cost consequences analysis based on the home-based PRT intervention is described in Chapter 7.

CHAPTER 3: What does standard rehabilitation practice after total hip replacement in the UK entail? A mixed qualitative and quantitative study.

3.1 Introduction

Considerable technical efforts have been made towards optimising THR; for example, there are over 100 varieties of hip prostheses, multiple bearing couples, and several surgical approaches. However, the actual health gain for many of these innovations is small in terms of patient function and quality of life (Herndon, Hwang et al. 2007). In tandem with these technical developments, patient expectations, including for an early return to normal physical function and activities, have also increased (Hobbs, Dixon et al. 2011).

The most commonly used rehabilitation regimes that help return older patients to their previous activities are based on functional types of exercises (including passive joint range of movement (ROM) mobilisation, isometric exercise for hip flexors, extensors or abductors, and non-weight bearing ankle and knee joint active ROM exercises), which do not involve external loading.

However, the use of these functional exercises has not been shown to prevent further muscle atrophy (Reardon, Galea et al. 2001). In contrast, progressive resistance training (PRT) is an effective method for inducing muscle hypertrophy and increasing muscle strength and functional performance in healthy and clinical populations, including the elderly (Garber, Blissmer et al. 2011).

PRT in rehabilitation following THR has been shown to significantly enhance muscle strength and function (Suetta, Andersen et al. 2008; Giaquinto, Ciotola et al. 2010; Liebs, Herzberg et al. 2010), with PRT being the main factor in achieving significant functional improvements in rehabilitation regimes used after home or centre based regimes used after THR (Okoro, Lemmey et al. 2012). Although a plethora of studies exist testing different rehabilitation protocols (including PRT) against 'standard' rehabilitation (Di Monaco, Vallero et al. 2009; Minns Lowe, Barker et al. 2009), no explicit definition is made as to what 'standard rehabilitation practice' entails. Thus, this study aimed to investigate 'standard' rehabilitation care undertaken by physiotherapists in the UK after THR and, in view of the evidence attesting to the efficacy of PRT in restoring function following THR, to

determine whether this form of exercise is widely prescribed as part of post-surgical rehabilitation programs.

3.2 Methods

After local NHS Research Ethics Committee approval, a focus group interview with four musculoskeletal physiotherapists (minimum 5 years post-qualification) who regularly treated patients after THR was convened to determine the important areas in postoperative rehabilitation. Of the four physiotherapists recruited: 2 worked in the hospital setting, 1 worked in the community, and the other was outpatient based. After the data obtained was transcribed, familiarisation was undertaken to generate themes, which after indexing and charting, led to the development of questionnaire items important in assessing 'standard' rehabilitation (Gill, Stewart et al. 2008). These items reflected rehabilitation practice in the pre-operative, immediate post-operative, and continuing rehabilitation phases, as defined by the physiotherapy focus group (Table 9). The questions were incorporated into an online questionnaire hosted by a secure survey system (Bristol online survey: URL http://www.survey.bris.ac.uk). A total of 171 hospitals were contacted (128 from England, 27 from Scotland, 10 in Wales, and 7 from Northern Ireland) with a total of 63 email addresses (England n=41, Scotland n=12, Wales n=8, Northern Ireland n=2) obtained from physiotherapists' directly involved in THR care. Each email recipient was also encouraged to forward the online survey link to his or her immediate colleagues with an approximation made (1 colleague for each recipient) of the number of colleagues the survey would be sent to. An online internet link was also posted on the Chartered Society of Physiotherapists website (URL: http://www.csp.org.uk). The online survey was run from January to May 2011. The questionnaire was also tailored to collect demographic information as to the physiotherapists' grade, the type of centre they worked in (NHS or private), and the average number of THR patients managed post operatively per year. The frequency of response (%) to each of the questionnaire items was based on the occupational banding of the physiotherapists' as well as demographic information (Hospital setting, number of THRs performed per year). The survey results were analysed focusing on the exercises the physiotherapists considered most important, as well as the understanding and use of PRT in prescribed rehabilitation regimes.

3.3 Results

106 responses were received from physiotherapists who supervise rehabilitation of THR patients in the UK. Of these, 85% worked in the NHS and 15% in the private sector. 104 out of 106 physiotherapists (98.1%) who responded were Band 5 and above (average of 5 years post-qualification experience, Table 10), and 94% of all respondents worked in centres performing at least 100 THR operations per year (Table 11).

Table 9. Questionnaire items on rehabilitation practice after total hip replacement

Rehabilitation Phase	Question posed with possible responses
Preoperative	In what setting do you see patients in the preoperative period? *Response options:* Orthopaedic Pre-assessment clinic Outpatients Arthroplasty education event Other- Please state……. Which exercise do you personally think is most important in terms of muscular recovery after total hip arthroplasty? *Response options:* Weight-bearing exercises In-bed exercises Bridging exercises Functional exercises Hydrotherapy Which muscle group do you think it is most important to target following total hip arthroplasty for rehabilitation purposes? *Response options:* Quadriceps Hip abductors Spinal Core balance Other-please state What kind of advice do you give? *Response options:* Verbal Trust information leaflet/booklet Video/CD Other…..
Immediate Post-operative	Which healthcare professional mobilises the patient out of bed first? *Response options:* Nurses Physiotherapists Other- Please state…… On average what day do the patients get mobilised? *Response options:* Day 0 Post op day 1 Post op day 2 Post op day 3 What exercises do you prescribe to your patients? *Response options:* Weight bearing exercises In-bed exercises Bridging exercises Functional exercises Hydrotherapy Other- Please state Which one of the following options do you think most underlines progressive resistance training? *Response options:* Progression of frequency of exercises Use of weights Do you build in resistance training routinely into the exercises you prescribe? *Response options:* Yes No
	Which of the following is the average length of stay in your hospital after total hip arthroplasty? *Response options:* 2 days 3 days 4 days >5 days How often is a post-operative hip patient seen routinely by you in a normal day? *Response options:* Once Twice Thrice Four times Other What equipments are your patients routinely discharged from hospital with? *Response options:* Walking aids Thromboprophylaxis e.g. Clexane Other- Please state…….. By what criteria do you discharge your patients from inpatient physiotherapy input? *Response options:* Patient stable on walking aid Compliant with exercises Independent with activities of daily living (ADL) Other- Please state…… Do you routinely refer patients to community physiotherapy on discharge? *Response options:* Yes No
Continuing rehabilitation	What is the reason for referral of patients to your care in the weeks or months after THR in the community? *Response options:* Poor balance Weak hip abductors Frequent falls Recurrent dislocation Other- Please state… What exercises do you prescribe for patients after THR in the community? *Response options:* Weight bearing exercises In-bed exercises Bridging exercises Functional exercises Hydrotherapy Other- Please state By what criteria do you discharge them from your care? *Response options:* Patient stable on walking aid Compliant with exercises Other- Please state…… How many sessions do you on average see the patient in total? *Response options:* 1 2 3 4 5 >5

Table 10. Physiotherapy respondents for survey on standard total hip replacement rehabilitation practice in the U.K., based on occupational banding

Band of Physiotherapist	Number of responses	Frequency (%)
2	0	0.0
3	1	0.9
4	1	0.9
5	10	9.4
6	27	25.5
7	50	47.2
8	17	16
Total	106	100

Table 11. Comparison of physiotherapy respondents based on the number of total hip replacement operations performed per year in their centres of work.

Number of operations per year	Number of responses	Frequency (%)
<100	7	6.6
100-200	18	17
200-300	35	33
>300	46	43.4
Total	106	100

The responses to the questions posed in each of the rehabilitation phases are detailed below:

3.3.1 Preoperative phase:

The majority of the respondents (67.9%) saw patients in the preoperative period; mainly in the pre-assessment clinic (36.1%) or arthroplasty education seminars (33.3%), with general outpatients (8.3%), inpatient ward review and home visits (22.2%) making up the remainder. The advice given preoperatively consisted of a trust booklet (39%), verbal advice (7%), a video/CD (2%), or a combination of these (25%). The hip abductors were considered to be the most important muscle group to target during rehabilitation (62.2%), followed by the quadriceps (16.9%) and others such as the hip flexors, extensors, spinal, and core muscles (21%), Table 12. No consensus existed as to which

form of exercise was most important in the initial phases of rehabilitation; with weight bearing (performed against gravity, 42%) and functional (without external loading, 45%) being the most favoured, and 13% of responses indicating a preference for bed-based (e.g. buttock squeezes, leg sliding and straight leg raise)/bridging (targeting core abdominal muscles as well as lower back and hip)/postural exercises (focusing on strengthening muscles which have become overstretched and weak).

Table 12. Muscle groups felt to be most important to target by physiotherapists' surveyed in the UK with regards to rehabilitation regimes after total hip replacement surgery.

	Actual responses obtained with frequencies (%)				
Band of Physiotherapist	Quadriceps	Hip Abductors	Spinal/Core Muscles	Other	Totals
2	0	0	0	0	0
3	1	0	0	0	1
4	0	0	1	0	1
5	3	6	1	0	10
6	5	15	0	7	27
7	9	35	1	5	50
8	0	10	1	6	17
Totals	18 (16.9%)	66 (62.2%)	4 (3.7%)	18 (16.9%)	106 (100%)

3.3.2 Immediate Postoperative phase:

The length of stay after THR was reported to range between 1 and >5 days with a stay of 4 days eliciting the most frequent response (57.5%). 92% of the physiotherapists who responded to the survey tend to mobilise patients on day 1 with 85% of all respondents using a combination of weight bearing, bed, and functional exercises. 83.7% of respondents knew what PRT entailed, but only 33% routinely included it in the exercises prescribed following THR, Table 13. 74.5% of the survey respondents did not routinely refer patients to community physiotherapy on their discharge from hospital.

Table 13. Responses of physiotherapists surveyed regarding prescription of progressive resistance training in standard rehabilitation after total hip replacement surgery

	Questionnaire Item: Do you build in resistance training routinely into the exercises you prescribe; Actual response (frequency (%))		
Band of Physiotherapist	Yes	No	Totals
2	0	0	0
3	0	1	1
4	0	1	1
5	2	8	10
6	9	18	27
7	19	31	50
8	5	12	17
Totals	35 (33%)	71 (66.7%)	106

3.3.3 Continuing rehabilitation:

A total of 48 (45.3%) respondents saw patients on an outpatient basis after discharge whilst 58 (54.7%) respondents did not. Of the physiotherapists involved in this phase of rehabilitation, 48% considered that weak hip abductors were the most common reason for referral as opposed to poor balance (34%), recurrent dislocation (13%) and frequent falls (5%). The exercises prescribed during this period consisted of functional (62.1%), weight bearing (17.7%), bed exercises (6.9%), and a combination of hydrotherapy, bridging and free active exercises making up the remaining 13.3%. The use of PRT not evident in the responses obtained.

3.4 Discussion

To our knowledge, this is the first study that attempts to quantify the standard practice for physiotherapy rehabilitation following THR surgery in the UK. Recent systematic reviews have looked at programmes and interventions to improve functional outcome in this group of patients (Di Monaco, Vallero et al. 2009; Okoro, Lemmey et al. 2012; Minns Lowe, Barker et al. 2009), and a common observation made is the variety in the 'standard' or control regimes that are used for comparison. With the inpatient stay reduced to an average of 4 days as reported by a majority of the

physiotherapists surveyed in this study, intervening following patient discharge from hospital is increasingly important if the persisting functional deficits typical of these patients are to be resolved.

In the preoperative phase of rehabilitation, 67.9% of the U.K. physiotherapists surveyed had contact with patients in a variety of settings. Preoperative counselling and education reduces unrealistic expectations regarding pain as well as improves patient satisfaction (Wallis, Taylor 2011). Preoperative physiotherapy on the other hand reportedly improves muscle strength and gait, allowing early return to ambulatory function (Minns Lowe, Barker et al. 2009), but its impact on short-term outcome such as gait speed, cadence, walking distance is debatable as the trials performed also include post-operative interventions on the same cohort of patients (Minns Lowe, Barker et al. 2009). The uses of the techniques described (arthroplasty education seminar, trust booklets, etc.) are therefore advantageous and exercise prescription in this phase of rehabilitation did not emerge as a theme from the convened focus group.

Despite 83.7% of the survey respondents being able to ascertain what PRT entailed, only 33% routinely built it into their prescribed rehabilitation programs. 48% of the survey respondents who treated THR patients in the outpatient setting reported that weak hip abductors accounted for the majority of referrals in the 'continuing rehabilitation' phase, with poor balance accounting for 34%. These reasons reflect a lack of muscle strength which is consistent with the established findings after THR as already described (Rasch, Bystrom et al. 2009). This further supports the presumption that the standard prescriptions of functional, weight bearing, and bed exercises fail to sufficiently restore muscle mass and, subsequently, strength. The use of PRT should help address these deficits.

Due to the current financial pressures the NHS is under with staffing levels and patient throughput (Campbell, McNicoll 2011), the primary objective for the majority of physiotherapists may be to mobilise the patients for discharge. Criteria used include stability with a walking aid, compliance with the prescribed exercises, and independence with ADLs. Inherently therefore the objective is to aim for safety on mobilisation, and consequently functional optimisation is not top of the agenda. Possible issues that may hinder physiotherapists in using PRT include time constraints as already described with possibly referral patterns, difficulties in transporting patients to a gym setting, and the demand on inpatient services meaning that the primary objective for the majority of working physiotherapists is

to aim for safety on mobilisation. As intervening to improve function is increasingly difficult to commence in the hospital setting due to the pressures to achieve a short inpatient stay, referral to community physiotherapy to continue appropriate regimes may be what is required. There are inherent difficulties with this approach as 74.5% of the survey respondents did not routinely do this, illustrating the difficulties of adapting practice to reflect the significant evidence base.

From the 8th annual report of the NJR in 2011 (National Joint Registry for England and Wales 2011), 399 centres entered data on the numbers of THR surgery performed up to the year end in 2010. Of the 106 survey respondents, 100 (94%) worked in centres performing ≥100 THR procedures per year (64% (256/399) of centres in England and Wales according to the NJR data). This implies that this survey provides a representative sample of experienced physiotherapists (98% were Band 5 and above) working on a regular basis with the THR patient population.

The use of the focus group to determine the questionnaire items for the survey further validates the findings obtained. This survey aimed to determine 'standard' practice and the 4 physiotherapists used in the focus group were from a mixture of backgrounds (2 worked in the hospital setting; 1 worked in the community, and the other was outpatient based), but all treated THR patients regularly. Since no questionnaire existed to achieve the aim of this study, the focus group ensured that the items obtained helped clarify any underlying assumptions of personal or traditional practice such: as frequency of times patients need to be seen, exercises that should be prescribed, etc. Sources of information and experience as well perspectives and viewpoints of the professional group to be studied are also better integrated using this method of qualitative research (Edmunds, Brown 2012). The focus group participants in this instance were more likely to feel a sense of community and belonging which makes them more comfortable and willing to express opinions, therefore ensuring that the items obtained for the questionnaire reflect the standard practices in the operative, post-operative and continuing rehabilitation phases.

A limitation of this study is that no analysis of regional variations in practice was performed. This was in part due to an effort to anonymise the data obtained in order to preserve the confidentiality of respondents as required by the ethics committee. Another limitation of this study is that only one focus group was performed. Thus, key topics may have been excluded from the final questionnaire.

We sought to address this by running a trial pilot with locally based physiotherapists to identify any additional issues omitted from the initial questionnaire before the online survey was set up. No further items were added to the final questionnaire after this exercise. Further information may also have been gleaned from content analysis of the preoperative advice and instructions given to patients in the form of booklets, videos and CDs. Such an undertaking was not feasible in this instance but perhaps can be part of a future study to further clarify what standard THR rehabilitation regimes entail.

3.5 Conclusions

This survey demonstrates that standard rehabilitation practice for THR patients in the UK rarely includes progressive resistance exercise; and this may be a factor contributing to the prolonged poor function in some patients.

3.6 Chapter Summary

This study aimed to investigate the nature of standard care that exists in the UK post-THR. The questionnaire developed after an initial focus group interview was used to survey practising physiotherapists. 106 responses were obtained, with the physiotherapists considering that the most important muscles to target in all phases of rehabilitation are: the hip abductors (62.2%), followed by the quadriceps (16.9%), and other muscles (21%). Exercise type prescribed revealed no consensus, with weight bearing (42%), functional (45%) and bed-based/bridging/postural exercises (13%) favoured. 83.7% were able to define the basis of progressive resistance training (PRT), but only 33% prescribed it. Thus, standard physiotherapy rehabilitation in the UK after THR is variable, and appears to rarely include PRT. Although no benefit in favour of the PRT intervention was demonstrated on a macroscopic level (MVCOLQ), an attempt was made to quantify the effects on a cellular level (quadriceps muscle biopsies) in patients participating in the trial. Hence, the metabolic environment of the vastus lateralis of the patients participating in the trial is investigated in Chapter 4.

CHAPTER 4: The expression of genetic markers of muscle hypertrophy, atrophy, lipid metabolism and inflammation in the *vastus lateralis* muscle of patients undergoing total hip replacement surgery

4.1 Introduction

Skeletal muscle is derived at approximately six weeks of gestation in the human embryo (Stewart, Rittweger 2006). Embryonic mesodermal stem cells originating from the myotome of the somites migrate into adjacent embryonic connective tissue, where they become precursor skeletal muscle cells or myoblasts (Stewart, Rittweger 2006). After a period of proliferation, which in humans occurs between weeks 7 and 9 of gestation, these differentiate to multi-nucleated myotubes (Stewart, Rittweger 2006). The synthesis of actin and myosin (contractile proteins) as well as cross-striation and innervation occur around this period (Stewart, Rittweger 2006). The muscle gradually responds to contractile activity by converting to adult-type myosins and by 11 weeks the fibres grow in circumference and length, but by 24 weeks gestation it is believed that the fibre numbers are set. Further cross-sectional muscle growth at this stage is thought to occur as a consequence of hypertrophy not hyperplasia (Rowe, Goldspink 1969).

Increased muscle cross sectional area (hypertrophy) and altered neural recruitment patterns represent the typical adaptations to repeated bouts of heavy exercise (Hakkinen 1989). Hypertrophy following resistance training occurs when the rate of protein synthesis (anabolism) is greater than that of protein degradation (catabolism) (Chesley, MacDougall et al. 1992, Phillips, Tipton et al. 1997). The hypertrophic adaptation to resistance training includes increased protein synthesis via regulatory changes in transcriptional and translational mechanisms, and, when the demand for de novo protein synthesis outweighs the supply by resident myonuclei, the recruitment of muscle cells that are added to existing myofibres or combine to form new contractile filaments (Coffey, Hawley 2007). Thus the hypertrophic adaptations provide additional contractile machinery with which to generate greater force (Rennie, Wackerhage et al. 2004, Rennie, Wackerhage et al. 2004, Rennie, Wackerhage et al. 2004). In addition, while a degree of protein degradation is required for muscle remodelling,

resistance training may also decrease long-term activation of atrophy pathways, resulting in supplementary net protein synthesis (Figure 3; Marimuthu, Murton et al. 2011).

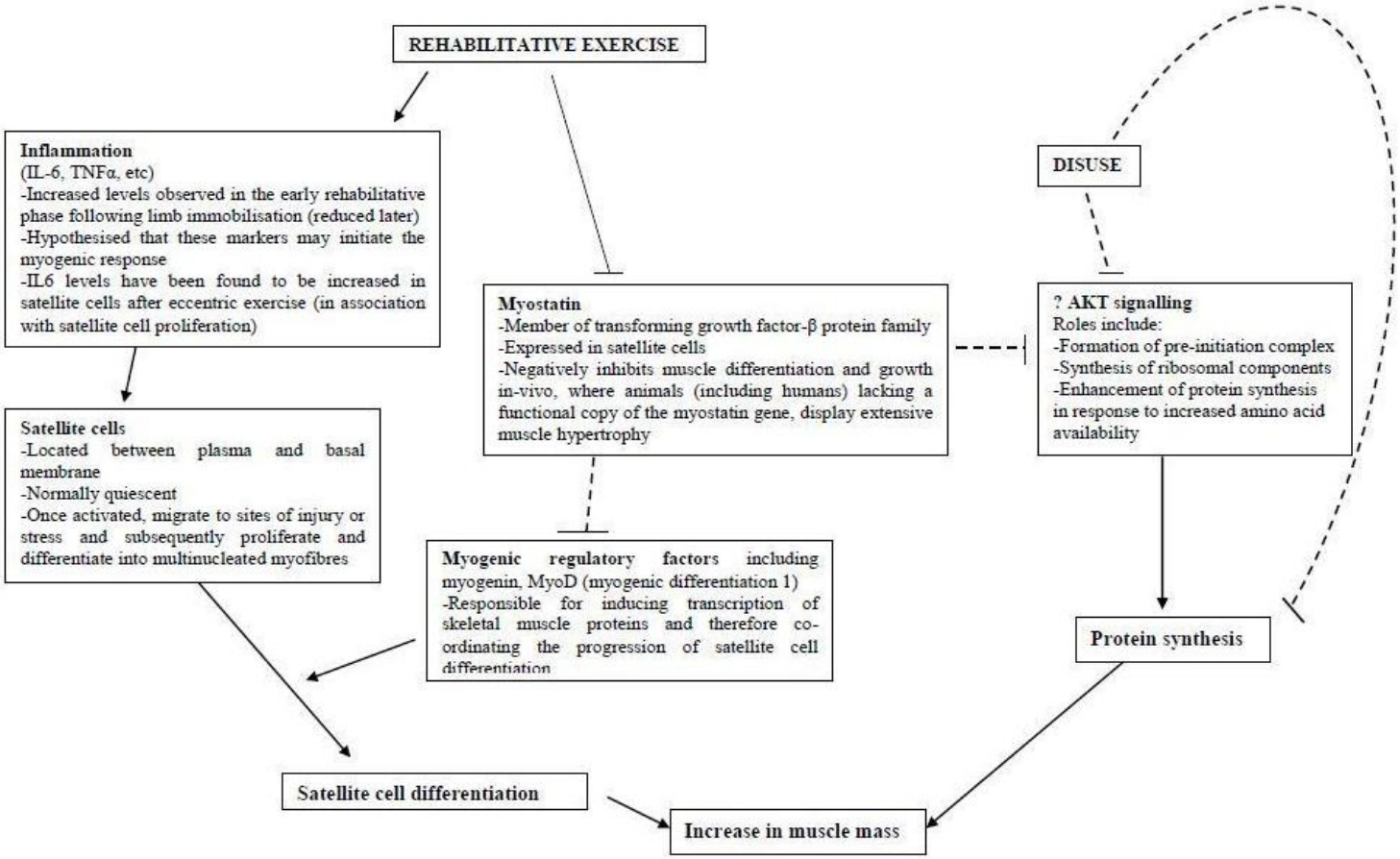
The early adaptive changes in skeletal muscle during increased loading are probably also due to enhanced translation of existing mRNAs with such increases being significant enough to increase protein production after a few days of overloading (Booth, Chakravarthy et al. 2002). The type of exercise stimuli governs the intricate balance by which signalling pathways are turned on or off, thereby providing a mechanism for a regulation of phenotypic outcomes. For example, endurance exercise does not lead to phosphorylation of kinase enzymes involved in the AKT (serine/threonine protein kinase) pathway whilst high resistance loading exercise does (Bodine, Stitt et al. 2001). This suggests a differential regulation of signalling by the type of exercise and the possibility of different phenotypic outcomes.

Little is understood about the molecular muscle related changes that occur in patients undergoing total hip replacement (THR). Measures that are used to assess muscle change range from subjective assessment at the time of surgery (Teratani, Naito et al. 2010) to radiological assessment using magnetic resonance imaging (MRI, (Bal, Lowe 2008)) and computed tomography (CT, (Rasch, Bystrom et al. 2009)).

Previous muscle biopsy related studies have demonstrated that there is significant Type 2A and 2B muscle fibre atrophy present intra-operatively in the quadriceps muscle of THR and that these changes are exacerbated during the early post operative recovery period (Reardon, Galea et al. 2001).

In a centre based intervention carried out by Suetta *et al* (Suetta, Clemmensen et al. 2010), gene expression was characterised in the *vastus lateralis* (VL) of THR patients. The authors showed that progressive resistance training administered immediately after THR for 12 weeks led to marked increases in expression of genetic markers of muscle hypertrophy (Insulin-like growth factor-I (IGF-I), in comparison to electrical stimulation therapy or standard physiotherapy rehabilitation (Suetta, Clemmensen et al. 2010).

Figure 3. Diagrammatic representation of main mechanisms responsible for regulating skeletal muscle mass following a period of disuse and subsequent rehabilitation in humans* (Marimuthu, Murton et al. 2011)



Key: AKT : Serine/threonine specific protein kinase IL6: Interleukin 6 TNFα: Tumour necrosis factor alpha
* The role of the AKT signalling pathway remains unclear. Processes promoting gain of muscle are denoted by black lines; events associated with loss of muscle mass are represented by broken lines

Muscle wasting is associated with many chronic severe illnesses, including osteoarthritis (OA). This reduction in mass is associated with a reduction in strength and ultimately in functional ability and quality of life (QoL). In unilateral hip osteoarthritis, there is a general deficit in muscular strength along the affected limb as compared to the contra-lateral (healthy) side and related muscles such as the abductors, vastii, rectus femoris and psoas show marked atrophy (Rasch, Bystrom et al. 2009). This is evidenced by reduced cross sectional area and an infiltration of non-contractile components; an average of 10% increased fatty infiltration occurs in the affected limb compared to the healthy one (Rasch, Bystrom et al. 2009). Fatty infiltration of muscle (myosteatosis) increases with age and results in reduced muscle strength and function, and increased fall risk (Lang, Cauley et al. 2009).

Metabolism of carbohydrates (CHO) and fatty acids (FA) provides the primary means for energy production in working skeletal muscle, whereby selection of these substrates depends primarily on exercise intensity (Brooks, Mercier 1994). During endurance exercise at lower intensity and of long duration, metabolic demand relies more on FA oxidation than CHO metabolism (Horowitz, Klein 2000). Extramyocellular FA from the adipose tissue is available as metabolic fuel throughout prolonged exercise (Horowitz, Klein 2000) and the content of intramyocellular lipids (IMCL) in human muscle can almost completely be exhausted after exercise of several hours duration (Johnson, Stannard et al. 2003).

Successfully aligned transport, storage and conversion steps are involved in the metabolism of FA in skeletal muscle (Horowitz, Klein 2000). Endothelial lipoprotein lipase (LPL) and several facilitative transport proteins are involved in transporting FA from the vasculature through the interstitium into the myocellular compartment where FA may be stored as IMCL or transferred to the mitochondria (through action of muscle fatty acid binding protein, H-FABP) for immediate oxidation (Glatz, Storch 2001; Jeukendrup 2002). Oxidative phosphorylation is achieved in the mitochondria though the action of cytochrome c oxidase I (COI). In a study of trained and untrained male participants, from whom tibialis anterior muscle biopsies were obtained, the mRNA levels of LPL, H-FABP, and COI were significantly higher in trained individuals (Schmitt, Fluck et al. 2003). This study also showed that mRNA levels of LPL and peroxisome proliferator-activated receptors (PPARA), which encode factors involved in import of FA from the vasculature and in transcriptional regulation of lipid metabolism,

showed a trend to be higher in trained than in untrained participants (Schmitt, Fluck et al. 2003). It can therefore be hypothesised that these markers of lipid metabolism will be expressed more highly in patients after surgery, especially after undertaking an exercise intervention program. Post-THR, because of the reduction in pain, activity levels in all patients should also increase.

The aims of this study in particular were therefore to characterise the metabolic adaptations of the VL muscle in patients undergoing a trial comparing home-based PRT to SR (control) after THR.

4.1.1 Objectives

The key objectives of this study were the following:

1. To characterise the local and distal effects of hip osteoarthritis on skeletal muscle gene expression in the VL muscle of patients at the time of total hip replacement (THR) surgery.
2. To assess the changes in the genetic markers of muscle inflammation, hypertrophy, atrophy and lipid metabolism in the VL of patients after THR and in the early phase of rehabilitation.

4.1.2 Hypotheses

1. There is no effect of biopsy site on gene expression of the VL muscle in patients at the time of THR surgery.
2. In the VL muscle of the affected leg of THR patients, an early home-based PRT intervention will cause an increase in genetic markers of hypertrophy and lipid metabolism, with a decrease in genetic markers of inflammation and atrophy, in comparison to standard rehabilitation (SR; controls).

4.2 Methods

Information regarding the trial comparing the home-based PRT programme to SR (control) after THR is provided in Chapter 2. Following ethical approval *(Ref. 09/WNo01/52)* and informed consent, intra-operative muscle biopsies were obtained from the proximal portion of VL at the distal end of the surgical wound of patients undergoing THR for osteoarthritis.. From consenting patients, a further sample was retrieved from the distal VL in the mid to distal portion of the lateral thigh intra-operatively, and 6 weeks, 6 months and 9-12 months post-operatively.

The distal VL samples were taken at a constant depth- standardised from the point of entering the muscle tissue- from the mid-portion of the VL (anterolateral aspect of the middle third of the thigh)

under local anaesthesia (2% lignocaine) using a bioptic gun with a 14 gauge needle (TruCore® II Biopsy Instrument, Angiotech Gainesville, FL, USA) (Bergstrom 1962). The tissue was snap-frozen in liquid nitrogen. The follow up samples at 6 weeks, 6 months and 9-12 months were taken ~1cm away from the first biopsy site.

Seventeen proximal and 15 distal VL samples were obtained at surgery, whilst 10 distal VL samples were obtained at 6 weeks, 3 at 6 months and 4 at 9-12 months. Each muscle sample underwent gene expression array analyses for the following candidate pathways: inflammation, hypertrophy, atrophy and lipid metabolism; with selected genes described in Table 14. Gene expression in this study was assessed by quantifying messenger RNA (mRNA) using the real-time reverse-transcriptase polymerase chain reaction (real time RT-PCR). Total RNA (50ng was converted into cDNA in 20µl using the Taqman Arrayscript™ UP Reverse Transcriptase (Applied Biosystems, Austin, TX, USA) according to the manufacturer's protocol. For each target mRNA, the amplification was monitored using the 7900HT Real-Time PCR system (Applied Biosystems, Austin, TX, USA). The rationale for real time PCR as well as the protocol for RNA extraction and quantification is described fully in APPENDIX 6. The rationale for real time RT-PCR is illustrated in Box 1. The $2^{-\Delta\Delta CT}$ method (section 4.2.1) was used for relative quantification of mRNA expression.

Table 14. Description of genes used in characterising *vastus lateralis* of the operated leg in patients undergoing total hip replacement (Coffey, Hawley 2007; Jones, Hill et al. 2004; Schmitt, Fluck et al. 2003; Raffaello, Milan et al. 2010; Lecker, Jagoe et al. 2004; MacNeil, Melov et al. 2010; Jackman, Kandarian 2004; Adams, Caiozzo et al. 2002; Bickel, Slade et al. 2003; Kopple, Wang et al. 2007; Wagner, Liu et al. 2005; McNally 2004; Reisz-Porszasz, Bhasin et al. 2003; Sng, Taniura et al. 2004; Trenerry, Carey et al. 2007; Coletta, Balas et al. 2008; Black, Packer et al. 1991; Buford, Cooke et al. 2009; Crul, Spruit et al. 2007; Kandarian, Jackman 2006; Dunn, Chin et al. 2000; Yu, Auwerx 2009; Obata, Brown et al. 2000)

Anticipated metabolic activity	**Gene**	**Characteristics**
↑ in ***Hypertrophy***	ADRB2 (Adrenergic, beta-2-, receptor)	Activation of mitogen activated protein kinase (MAPK) activity, important in transcription of prohypertrophic genes
	CAPN1 (Calpain1)	Mediation of skeletal muscle myofibrillar disassembly, cleavage of actinomyosin, and the initial remodelling
	CAPN2 (Calpain2)	
	CAST (Calpastatin)	
	FOS (FBJ Murine Osteosarcoma viral oncogene homolog)	Immediate early response gene and member of the AP1 transcription factor complex. Its abundance increases transiently and abundantly in response to mitogenic stimuli. Levels have been shown to increase in response to eccentric exercise
	IGFBP2 (Insulin-like Growth Factor Binding Protein 2)	Part of the binding protein family for insulin-like growth factors (IGFs) as above. IGFBP2 mRNA levels have been shown to increase after exercise training
	INS-IGF2 (Insulin-like Growth Factor 2 read-through product)	
	JUNB (Jun B proto-oncogene)	Belongs to a class of immediate early genes that are rapidly activated, usually transiently, in response to cytokines, growth factors, stress signals, infection or oncogenic stimuli. In a mouse model, JunB over-expression induced hypertrophy without affecting satellite cell proliferation, and stimulated protein synthesis independently of the Akt/mTOR pathway (main intracellular signalling pathways involved in IGF-induced hypertrophy) and without reducing basal protein degradation. JunB expression can be regulated by exercise or insulin and mRNA increases during cardiac hypertrophy induced by increased workload
	RCAN1 (Regulator of calcineurin transcript variant 3)	Calcineurin is a Ca^{2+}-calmodulin-dependent phosphatase that is probably activated in overloaded muscles via the chronic increases in intracellular calcium that occurs under overloaded conditions as a result of a doubling of nerve-mediated muscle fibre activation and load-related increases in IGF-I. Once activated, calcineurin may signal downstream genes involved

		in regulating muscle fibre size via dephosphorylation of its substrate transcription factors, nuclear factor of activated T cells (NFAT). RCAN1 plays a role in calcineurin regulation and has been shown to be significantly expressed in the recovery phase following eccentric exercise in humans, using DNA microarray analysis
Anticipated metabolic activity	**Gene**	**Characteristics**
↑ in ***Atrophy***	CAPN3 (Calpain 3)	Regulation of muscle cell fate, as it has been shown to be down-regulated following skeletal muscle damage induced by eccentric exercise
	CTSL1 (Cathepsin L1)	Degradation of membrane proteins such as receptors, channels and transporters
	CTSL2 (Cathepsin L2)	
	FBX032 (F-Box protein 32)	Activity of ATP-dependent ubiquitin proteasome pathway, a process involving the interaction of multiple enzymes regulating 'ubiquitin-tagging'of proteins for destruction bv the proteasome
	GSK3A (Glycogen Synthase Kinase 3 alpha)	Increased by stretch and contraction, has been shown to increase after 2 weeks of disuse atrophy. Plays a role in deactivating glycogen synthase and reduced levels after atrophy may reflect promotion of glycogen breakdown
	MAPK14 (Mitogen activated Protein kinase 14)	Stress-activated protein kinase that responds to a variety of stimuli, including oxidative stress and TNF-α, and has been identified as a likely mediator of catabolic signalling in skeletal muscle
	MSTN (Myostatin)	Transforming growth factor-beta (TGF-β) family member that functions as an inhibitor of muscle hypertrophy. The role of myostatin as a negative regulator of hypertrophy is highlighted by the extraordinary increase in muscle mass of myostatin-deficient animals and humans. Transgenic expression of myostatin has also been shown to reduce muscle mass, fibre size and myonuclei number, suggesting that increased myostatin expression may have the capacity to exacerbate atrophy
	PSMA7 (Proteasome Subunit, Alpha type, 7)	Is a ubiquitin protein coupled to myofibrillar protein substrates prior to proteasome degradation, ∴ involved in increased activity of ATP-dependent ubiquitin proteasome pathway
	TRIM63 (Tripartite Motif containing 63)	E3 ubiquitin ligase Regulates proteasomal degradation of cardiac troponin and probably of other sarcomeric-associated proteins. Associated with activation of FOXO transcription factors crucial in

		progression of muscle wasting in catabolic states
↓ in ***Atrophy***	IGFBP5 (Insulin-like Growth Factor Binding Protein 5)	IGF-I has been shown to stimulate anabolic and myogenic processes associated with the development of skeletal muscle hypertrophy. In muscle, the IGF-I axis consists of locally expressed IGF-I and mechano growth factor (MGF), the type I IGF-I receptor, and a number of binding proteins which increase IGFI half life. IGFBP5 mRNA levels have been shown to be reduced after increased muscle loading in animal studies
↓ in ***Atrophy***	MYOD1 (Myogenic Differentiation 1)	A member of the muscle-specific gene family, and transcriptionally controls local IGF-I production within muscle. Involved in muscle differentiation and has been shown to be decreased in hospitalised patients compared to healthy controls.
Anticipated metabolic activity	**Gene**	**Characteristics**
↑ in ***Lipid Metabolism***	FABP3 (Fatty Acid Binding Protein 3)	Transfer of fatty acids from the vasculature to the mitochondria for immediate oxidation (intramyocellular transport)
	LPL (Lipoprotein Lipase)	Facilitative transport protein involved in transport of fatty acids from vasculature through interstitium into myocellular compartment for storage as intramyocellular lipids (IMCL) of transfer to mitochondria for immediate oxidation
	MT-CO1(Mitochondrially encoded Cytochrome C Oxidase I)	Oxidative phosphorylation of fatty acids transported into the mitochondria from the vasculature through the action of FABP3
	PPARA (Peroxisome Proliferator-Activated Receptor Alpha)	Encode factors involved in import of fatty acids from the vasculature and in transcriptional regulation of lipid metabolism.
	PPARG (Peroxisome Proliferator-Activated Receptor Gamma)	
	SIRT1 (Sirtuin 1)	Is activated by nutrient deprivation and shown to increase mitochondrial fatty acid oxidation, electron transport, and oxidative phosphorylation. Improves insulin sensitivity in a mice model Plays a role in myogenesis, with over-expression of SIRT1 causing repressed muscle specific gene transcription and retarded myogenesis
↓ in ***Lipid Metabolism***	SIRT2 (Sirtuin 2)	Cytoplasmic sirtuin Inhibits pre-adipocyte differentiation Function not well characterised

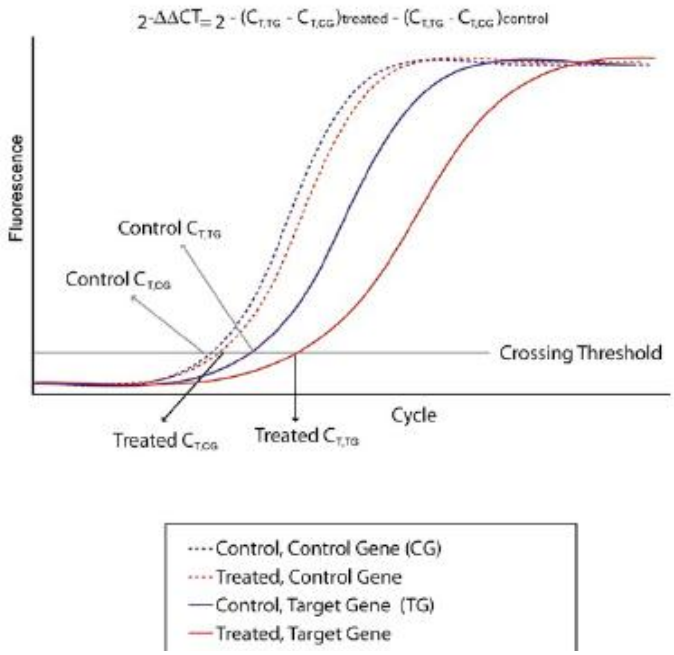
Anticipated metabolic activity	**Gene**	**Characteristics**
↑ in ***Inflammation***	IL6 (Interleukin-6)	Inflammatory cytokine. Is produced by skeletal muscle and levels are not altered in serum as opposed to locally in muscle after resistance exercise. mRNA levels have been shown to increase following exercise in skeletal muscle
	TNF-α (Tumour Necrosis Factor-alpha)	Inflammatory cytokine (TNF-α) and its receptor (TNFRSF1B) whose mRNA expression has been shown to be stimulated early in the muscle repair process after acute resistance exercise.
	TNFRSF1B (Tumor Necrosis Factor receptor Superfamily, member 1B)	
Equivalence	ELF1 (E26 Transformation Specific Domain Transcription factor1)	The encoded protein is primarily expressed in lymphoid cells and acts as both an enhancer and a repressor to regulate transcription of various genes. Chosen in this instance as a housekeeping gene
	18S (RNA, **18S** ribosom-al 1)	RNA, 18S ribosomal 1; Manufacturer's (Applied Biosystems, Austin, Texas, USA) housekeeping gene

4.2.1 Data analysis in RT-PCR

Analyses of real time PCR data can either be of absolute levels (i.e. numbers of copies of a specific RNA per sample) or relative levels (i.e. sample 1 has twice as much mRNA of a specific gene as sample 2) (Van Guilder, Vrana et al. 2008). In absolute quantification, an RNA standard curve of the gene of interest is required in order to calculate the number of copies. In this case, a serial dilution of a known amount (number of copies) of pure RNA is diluted and subjected to amplification (Van Guilder, Vrana et al. 2008). The unknown signal is compared with the curve so as to extrapolate the starting concentration. The primary limitation to this approach is the necessity of obtaining an independent reliable standard for each gene to be analysed and then running concurrent standard curves during each assay (Valasek, Repa 2005).

The most common method for relative quantification is the $2^{-\Delta\Delta CT}$ method (Livak, Schmittgen 2001) which relies on the assumptions that the reaction is occurring with 100% efficiency (i.e. with each cycle the product doubles), and that there is a gene (or genes) that are expressed at a constant level between samples (therefore, the choice of endogenous control is important) (Van Guilder, Vrana et al. 2008). The C_T is the number of cycles that it takes each reaction to reach an arbitrary amount of fluorescence. Once the C_T value is collected for each reaction, it can be used to generate a relative expression level (Figure 4). For each sample, the difference in C_T values for the gene of interest and the endogenous control is calculated (ΔC_T). Next, subtraction of the control-condition ΔC_T yields the $\Delta\Delta C_T$. The negative value of this subtraction, the $-\Delta\Delta C_T$, is used as an exponent of 2 in the equation and represents the difference in 'corrected' number of cycles to threshold. The exponent conversion comes from the fact that the reaction doubles the amount of product per cycle. For example if the control sample ΔC_T is 2 and the treated sample is 6, computing the $2^{-\Delta\Delta CT}$ (which becomes $2^{-(6-2)}$) yields 0.125, a value referred to as the RQ, or relative quantity value (Livak, Schmittgen 2001). This means that the level of the gene of interest in the treated sample is only 12.5% of the level of that gene in the control sample or there is a reduction of 87.5% in the level of the gene in the treated sample compared to the control sample.

Figure 4. Mathematical basis of the $2^{-\Delta\Delta CT}$ method (VanGuilder, Vrana et al. 2008)



4.2.2 Analyses performed

The following analyses were performed as per the aims and objectives of this study using the Data Assist Software (v3.0, Applied Biosystems, Austin, TX, USA):

1. Characterisation of the preferential local and distal effects of known hip osteoarthritis on gene expression in the VL of patients at the time of THR. This was based on the hypothesis that there would be more muscle wasting in VL proximally as opposed to distally. A comparison of distal (comparator n=17) vs. proximal (control n=15) muscle biopsy gene expression with anticipated changes distally – i.e. increased (↑) gene expression for markers of hypertrophy and lipid metabolism with decreased (↓) gene expression for markers of atrophy and inflammation, was performed.
2. Assessment of changes in the genetic markers of muscle inflammation, hypertrophy, atrophy, and lipid metabolism in VL of THR patients after 6 weeks of early home-based PRT relative to patients receiving standard physiotherapy rehabilitation (controls).

   2 a Comparison of all distal (6 week) muscle biopsies (comparator n=10) versus pooled proximal and distal intra-operative samples (control n=32 total). This was based on

the hypothesis that there would be an element of generalised muscular recovery in VL in the early post-operative period with ↑ gene expression of markers of hypertrophy and lipid metabolism and ↓ gene expression of markers of inflammation and atrophy.

2 b Comparison of distal (6 week) home-based PRT group (comparator n=6) versus 6 week SR group (control n=4). This was based on the hypothesis that the home-based PRT intervention would result in ↑ gene expression of markers of hypertrophy and lipid metabolism and ↓ gene expression of markers of inflammation and atrophy in the VL muscle of patients recovering from THR.

2 c Comparison of distal (6 week) home-based PRT group (comparator n=6) versus pooled proximal and distal intra-operative samples from the same subjects (control n=17 total). This was based on the hypothesis that the exercise intervention would result in ↑ gene expression of markers of hypertrophy and lipid metabolism and ↓ gene expression of markers of inflammation and atrophy in the VL muscle when compared to intra-operative levels in the same population.

2 d Comparison of distal (6 week) SR group (n=4) versus pooled proximal and distal intra-operative samples from the same subjects (control n=15 total). This was based on the hypothesis that not being in the home-based PRT group would result in ↓ gene expression of markers of hypertrophy and lipid metabolism and ↑ or no difference in gene expression of markers of inflammation and atrophy in the VL muscle when compared to intra-operative levels in the same population.

The results for the comparison of the distal 6 month (comparator n=3) and 1 year (comparator n=4) VL samples versus the pooled proximal and distal intra-operative samples (control n=32 total) are described in APPENDICES 7 and 8 respectively.

4.3 **Results**

4.3.1 Characterisation of the preferential local and distal effects of known hip osteoarthritis on gene expression in the VL of patients at the time of THR (APPENDIX 9)

At the time of surgery, there appears to be no single dominant metabolic process occurring in the distal VL compared to the proximal VL according to the genes assessed in this population. In terms of hypertrophy, 5 out of 11 genes were expressed more distally than proximally as anticipated (%fold increase/decrease (p value); CAPN1 +63.2% (p=0.7154), CAPN2 +110% (p=0.6489), CAST +130% (p=0.6399), RCAN1 +172% (p=0.6257), and TNFα +17% (p=0.7154)), but significance was not achieved. The same was true for atrophy with 4 genes also out of the 11 specified expressed in the manner hypothesised (CAPN3 -16.4% (p=0.7154), MSTN -27% (p=0.5499), PSMA -18.44% (0.6489), MYOD1 -16% (p=0.7154)); again, however, significance was not achieved. The majority of the genes for lipid metabolism show a reduction in expression distally compared to proximally. There was also an increase in markers of inflammation but none of the expression levels noted attained statistical significance. In summary, distal versus proximal VL analyses revealed little impact of biopsy site on gene expression. Therefore for the rest of the analyses performed, the proximal and distal samples were pooled if comparisons were made to the initial intra-operative samples taken.

4.3.2 Assessment of changes in the genetic markers of muscle inflammation, hypertrophy, atrophy, and lipid metabolism in VL of patients after THR and in the early phase of rehabilitation

2 a. At 6 weeks when comparing the pooled postoperative 6 week samples (n=10) to all the intra-operative proximal and distal samples (n=32), there was a significant increase in FOS (+1463% (p=0.0158)) with a reduction in ADRB2 (-60.68% (p=0.0003)), TNFα (-29.64% (p=0.0228)), and TNFSRF1B -35.71% (p=0.0039) expression. IGF2, IGFBP2, JUNB, and RCAN1 all had reduced expression, but significance was not achieved. In terms of atrophy, there was a significant reduction in PSMA7 (-44.70% (p=0.0158)) with CTSL2, FBX032 and MSTN also decreased as predicted but not significantly (APPENDIX 10). SIRT1 and SIRT2

showed increased and decreased expression, respectively at 6 weeks postoperatively (+108% (p=0.0039) and -33.45% (p=0.0376)). FABP3 (-43.47%, p=0.0755) and CAPN2 (+129.24%, p=0.0867) showed a trend towards significant changes with no other genes indicating an effect. There was a significant reduction in expression of the initially proposed housekeeping gene, ELF1 (-63.74%, p=0.0158) therefore this was not used, as initially planned as a calibrator in these experiments.

2 b. In comparing the distal VL samples obtained at 6 weeks from the home-based PRT group (n=6) to those of the subjects that underwent the SR regimen (n=4), a minority of the genes coding for hypertrophy showed increased expression as would be anticipated but no significance was evident; JUNB +258.71% (p=0.7545), RCAN1 +5616.90%(p=0.7545), TNFα +182.88% (p=0.7545). In terms of atrophy, none of the genes showed significant changes, but CTSL2 and GSK3A showed increased expression without significance (+857.22% (p=0.7545) and +195.60 (p=0.7545) respectively). There was an increased fold expression of IL-6 in terms of inflammation (+1791.41% (p=0.7545) but this was also not statistically significant (APPENDIX 11).

2 c. In comparing the distal VL samples obtained at 6 weeks (n=6) for patients in the home-based PRT group to their own intra-operative samples (n=17), the only genes that were altered (albeit not significantly) were CAPN1 (+81.67% (p=0.3916)), CAPN2 (+122.64% (p=0.2622)), CAST (+54.87% (p=0.6296)), FOS (+2507.88% (p=0.1187)), and RCAN1 (+359.93% (p=0.1187)) for hypertrophy, with SIRT1 increasing significantly (+139% (p=0.0026)), as anticipated in terms of lipid metabolism. Significant reductions in expression were observed at 6 weeks for ADRB2 (-62.96% (p=0.0131)), whilst CAPN 3 was increased (+107.14% (p=0.0457)). PPARA showed a reduction in expression (-80.25% (p=0.0702)) which trended towards significance, APPENDIX 12.

2 d. For the distal VL samples (n=4) of patients in the SR group compared to their own intra-operative pooled samples (n=15), there were significant reductions in RCAN1 (-91.60%, p=0.0303), LPL (-46.88%, p=0.0435), PPARA (-74.55%, p=0.0303) and a trend to

significance for IL6 (-93.99%, p=0.0506). There was a marked increase in FOS but this did not reach significance (+556%, p=0.371), APPENDIX 13.

The fold changes that were reported above as being statistically significant, showed a trend to significance, or changed markedly with no significance, for all the analyses performed during the early rehabilitation phase following THR are illustrated in Figure 5.

4.4 Discussion

The presence of inflammation in the hip joint appears to have no statistically significant effect on expression of the genes assessed in the VL muscle in this population, with no differences observed in the genes assessed in terms of the sampling being performed on the proximal or distal VL. This suggests that for these analyses, single site muscle sampling is appropriate for subsequent analyses of training effects, with inflammation of the hip not altering expression of genes identified as coding for hypertrophy, atrophy, inflammation and lipid metabolism. Repeated muscle biopsy sampling is often necessary to elucidate muscular adaptation to different modes of exercise, as adaptation is thought to occur as the result of transient changes in gene expression (Hoppeler, Klossner et al. 2007). Repeated muscle biopsy sampling from the same muscle region has also been previously shown to influence the expression of marker genes such as IL-6 and IGF-I after an acute bout of resistance exercise (Friedmann-Bette, Schwartz et al. 2012). IN the context of this study however, at the time of THR, no differences were found to exist between the distal and proximal muscle biopsy samples in terms of the gene expression analysis.

For the anticipated metabolic responses in the VL for the early phase of rehabilitation in this population, the genes which demonstrated significant, a trend to significance or markedly increased/decreased levels without significance (Figure 5) are discussed below:

4.4.1 Hypertrophy

1. *FOS (FBJ Murine Osteosarcoma viral oncogene homolog)*: showed significantly increased expression as anticipated for the analysis of the pooled 6 week distal VL samples vs. all the pooled intra-operative VL samples (2a). It showed a marked increase without reaching significance for the analysis comparing the distal VL samples for the home-based PRT group at 6 weeks to their own intra-operative samples (2c) and the comparison of the distal VL

samples for the SR group at 6 weeks to their own intra-operative samples (2d). For 2d, the anticipated change was a reduction in FOS expression. There was a differential expression of ~2000% in favour of the home-based PRT group (comparing 2c and 2d), with no direct evidence of an effect when distal VL samples at 6 weeks for the home-based PRT group were compared to those obtained from the SR group at the same time point (analysis 2b). FOS is known as a transient marker of eccentric exercise (MacNeil, Melov et al. 2010) and may perhaps be related to the physical activities performed just before each muscle biopsy was taken. The only significant change in FOS was for the pooled analysis comparing the samples obtained from the distal VL to those obtained intra-operatively (2a). This may indicate that for this population, the relief of pain as a result of surgical intervention may have led to increased physical activity and therefore an increase in this marker of eccentric exercise.

2. *RCAN1(Regulator of calcineurin transcript variant 3):* showed increased expression (+5616%) as anticipated without statistical significance when the distal VL samples for the home-based PRT group at 6 weeks was compared to the SR group at the same time point (analysis 2b). A similar result in terms of the direction of expression was obtained when the distal VL samples from the home-based PRT group at 6 weeks were compared to their own intra-operative samples (analysis 2c; +360%) with no statistical significance achieved. RCAN1 plays a role in calcineurin regulation and it is thought that calcineurin (a calcium-calmodulin-dependent phosphatase) may signal downstream genes involved in regulating muscle fibre size (MacNeil, Melov et al. 2010). RCAN1 therefore can be expected to increase after eccentric exercise that leads to muscle hypertrophy and this was mainly evident when the distal VL samples at 6 weeks for the home-based PRT group was compared to those obtained from the SR group at the same time point (analysis 2b).
3. *CAPN2 (Calpain2):* acts in the initial muscle remodelling phase and is thought to be important in subsequent myofibrillar hypertrophy (Du, Wang et al. 2004). CAPN2 in this study was postulated to increase in an anabolic response to the home-based PRT regime. For this analysis, in comparison of the distal VL samples at 6 weeks for all patients vs. the pooled intra-operative samples (analysis 2a), CAPN2 showed increased expression (+129%) with

only a trend to significance (p=0.0867). This suggests perhaps that the initial recovery process after THR leads to an attempt at muscle remodelling in both the home-based PRT and SR groups but that this is not sufficient to attain significance in the subsequent analyses especially when comparing the home-based PRT and SR groups to each other at 6 weeks.

4. *ADRB2 (Adrenergic, beta-2-, receptor):* was hypothesised to increase in a hypertrophic response to the home-based PRT regime but demonstrated an inverse response. A statistically significant reduction in its expression (~ -60%) was demonstrated in the comparison of the pooled distal VL samples at 6 weeks vs. all the intra-operative samples (analysis 2a). A further significant decrease in expression (~ -63%) was also observed in the analysis comparing the distal VL samples at 6 weeks from the home-based PRT group to their own intra-operative samples (2c), perhaps suggesting that this gene may not be an appropriate marker for the hypertrophic response, or that there were insufficient mitogenic (cell division initiating) stimuli (as regards the home-based PRT regime undertaken) to initiate activation of mitogen-activated protein kinase activity (noted to be important in terms of prevention of skeletal muscle atrophy (Kramer, Goodyear 2007)). It is important to note, however, that MAPK activation itself was not assessed.

Figure 5. Significant fold changes obtained on follow-up analyses of gene expression in the *vastus lateralis* muscle of patients after total hip replacement (THR) surgery.

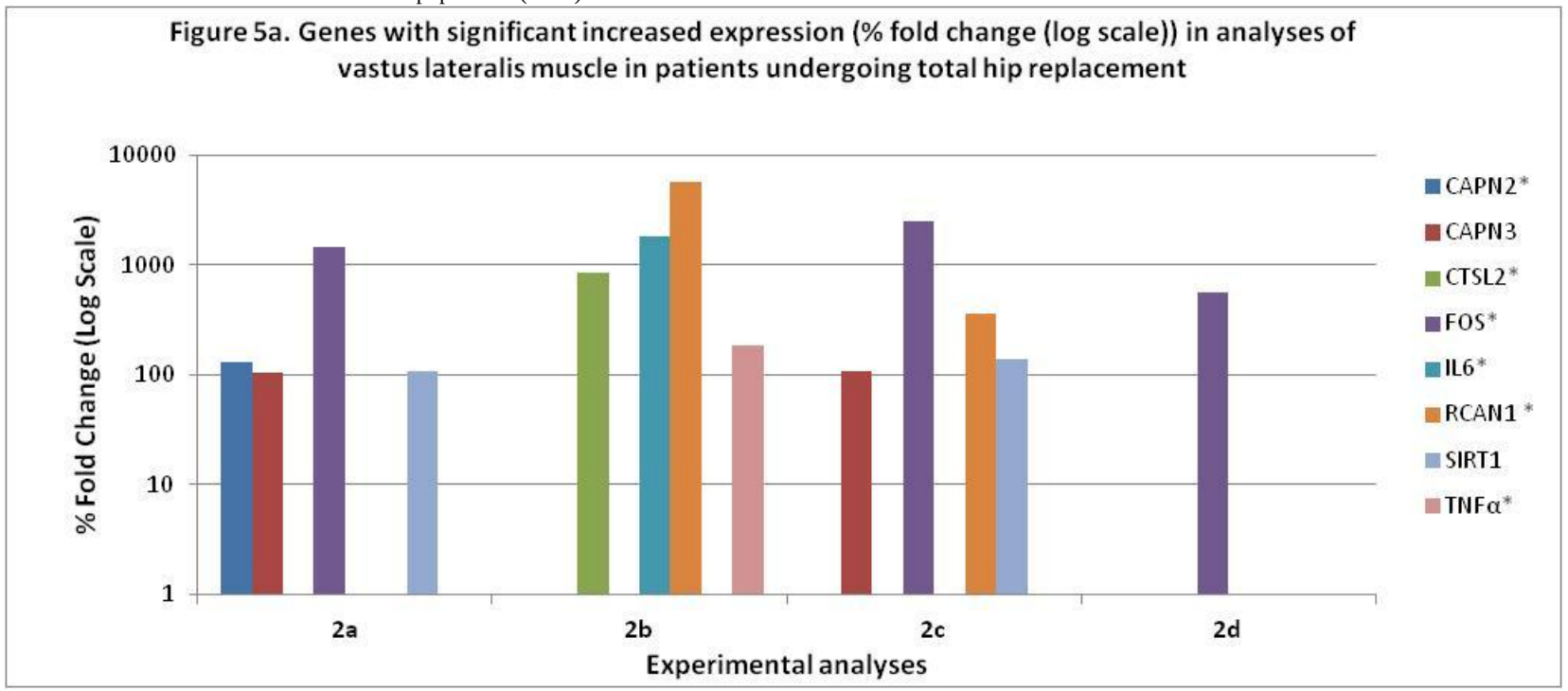
Figure 5a. Genes with significant increased expression for analyses:

2a -Comparison of distal *vastus lateralis* gene expression at 6 weeks (n=10) postoperatively versus pooled preoperative proximal and distal *vastus lateralis* muscle biopsies (n=32)

2b -Comparison of distal *vastus lateralis* gene expression at 6 weeks postoperatively for the exercise intervention group (n=6) versus the standard rehabilitation group (n=4)

2c -Comparison of distal *vastus lateralis* gene expression at 6 weeks postoperatively for the exercise intervention group (n=6) versus pooled proximal and distal *vastus lateralis* samples obtained at baseline from the same population (n=17)

2d -Comparison of distal *vastus lateralis* gene expression at 6 weeks postoperatively for the standard rehabilitation group (n=4) versus pooled proximal and distal *vastus lateralis* samples obtained at baseline from the same population (n=15)



KEY

CAPN2- Calpain 2 | *CAPN3*- Calpain 3 | *CTSL2*- Cathepsin L2

FOS- FBJ Murine Osteosarcoma viral oncogene homolog | *IL-6*- Interleukin-6 | *RCAN1*- Regulator of calcineurin transcript variant3

SIRT1- Sirtuin 1 | *TNF*α- Tumour necrosis factor alpha

*- Increased gene expression without statistical significance:
RCAN1: 5616% and 359% for analyses 2b and 2c respectively; FOS : 2507%, 556% for analyses 2c and 2d respectively;
CTSL2: 857% for analysis 2b; IL6: 1791% for analysis 2b; TNF: 182% for analysis 2b; CAPN2: 129% for analysis 2a

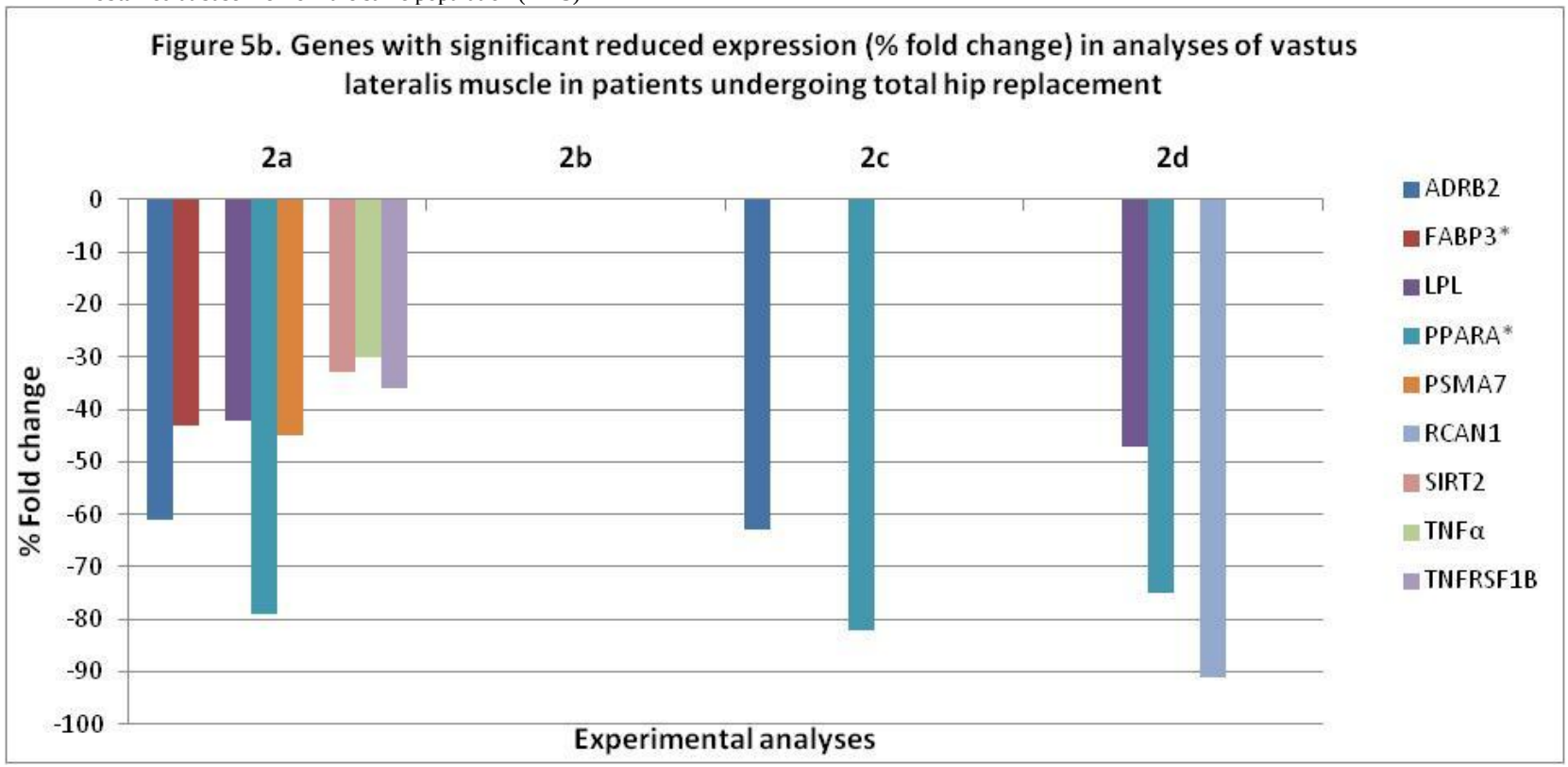
Figure 5b. Genes with significant reduced expression for analyses:

2a -Comparison of distal *vastus lateralis* gene expression at 6 weeks (n=10) postoperatively versus pooled preoperative proximal and distal *vastus lateralis* muscle biopsies (n=32)

2b -Comparison of distal *vastus lateralis* gene expression at 6 weeks postoperatively for the exercise intervention group (n=6) versus the standard rehabilitation group (n=4)

2c -Comparison of distal *vastus lateralis* gene expression at 6 weeks postoperatively for the exercise intervention group (n=6) versus pooled proximal and distal *vastus lateralis* samples obtained at baseline from the same population (n=17)

2d -Comparison of distal *vastus lateralis* gene expression at 6 weeks postoperatively for the standard rehabilitation group (n=4) versus pooled proximal and distal *vastus lateralis* samples obtained at baseline from the same population (n=15)



KEY

ADRB2- Adrenergic, beta-2-receptor
FABP3- Fatty Acid Binding Protein 3
LPL- Lipoprotein lipase
PPARA- Peroxisome proliferator-activated receptor alpha
PSMA7- Proteasome subunit, alpha type 7
RCAN1- Regulator of calcineurin transcript variant 3
SIRT2- Sirtuin 2
*TNF*α- Tumour necrosis factor
TNFRSF1B- Tumour necrosis factor superfamily member 1B
*- Trends to significant reduced expression obtained:
FABP3: -43% (p=0.0755) for analysis 2a; PPARA -80% (p=0.0702) for analysis 2c

4.4.2 Atrophy

1. *CAPN3 (Calpain3):* was postulated to show a decrease in RNA expression as it was anticipated that the home-based PRT regime would result in less muscle catabolism and hence atrophic processes. CAPN3 is thought to be down-regulated following skeletal muscle damage induced by eccentric exercise (Feasson, Stockholm et al. 2002) but in this instance, it showed significantly increased expression when all the distal VL samples obtained at 6 weeks were compared to the pooled intra-operative samples (analysis 2a), perhaps indicating that the period following surgery did not modulate catabolic processes that pre-existed preoperatively.
2. *CTSL2 (Cathepsin L2):* was also expected to show a reduction in expression, as its activity is mainly in the degradation of membrane proteins (Jackman, Kandarian 2004). It was hypothesised that in the early rehabilitation phase following surgery, an anabolic (hypertrophic) process would dominate due to the home-based PRT regime, in addition to the relief of existing arthritic pain, and improved physical activity. The response obtained however for CTSL2 was the converse however, with RNA expression showing a marked increase (+857%) in expression, when comparing the distal VL samples obtained at 6 weeks from the home-based PRT group to the SR group at the same time point (2b), but this was not statistically significant.
3. *PSMA7 (Proteasome Subunit, Alpha type, 7):* is an ubiquitin protein, which is coupled to other substrates prior to proteasome degradation, as part of the ubiquitin-proteasome dependent pathway (UDP) (Kandarian, Jackman 2006). The UDP is one of the pathways known to be responsible for protein catabolism that occurs in skeletal muscle, in conjunction with lysosomal, calcium dependent, and caspase dependent pathways, none of which have been found to be the major pathway for muscle loss (Lenk, Schuler et al. 2010). It was anticipated that PSMA7 RNA expression would reduce with participation in the home-based PRT regime, particularly in the early period of rehabilitation, reflecting the effects of a reduction in protein catabolism. In the analyses performed, PSMA7 RNA expression in the the distal VL samples at 6 weeks vs. all the intra-operative samples (2a) was reduced significantly, perhaps indicating that this period did lead to less muscle breakdown and

catabolic processes were suppressed. There was no significant difference however in the comparison of the distal VL samples at 6 weeks for the home-based PRT group to the SR group at the same time point (analysis 2b), indicating that intervention (home-based PRT) may not be responsible for the changes observed.

4.4.3 Lipid metabolism

It was postulated that genes primarily involved in the transport of fatty acids from the vasculature to the mitochondria for metabolism, LPL (lipoprotein lipase), PPARA (Peroxisome Proliferator-Activated Receptor Alpha), and FABP3 (Fatty Acid Binding Protein 3), would show increased RNA expression in the period following surgery (Schmitt, Fluck et al. 2003). The home-based PRT intervention was intended to be tolerable for the patients and this was achieved as demonstrated by the average compliance to the program in patients who returned exercise diaries of 140% (Chapter 2). As the exercise program was initiated shortly after THR, it was necessarily performed at relatively low intensity. Lipids provide the majority of energy substrate used during exercise performed at low intensity, with this substrate derived mainly from the blood (Pendergast, Meksawan et al. 2011). No increases in the RNA expression of LPL, PPARA or FABP3 were observed for the analyses performed, perhaps reflecting that the metabolic efficiency in the patients assessed does not lean towards lipid metabolism. There was a significant reduction in LPL and PPARA RNA expression in analyses comparing the pooled distal VL samples at 6 weeks to the pooled intra-operative samples (2a) and that comparing the distal VL samples from the SR group at 6 weeks to their own preoperative samples (2d). FABP3 showed a trend to significant reduction in analysis 2a (pooled distal VL samples at 6 weeks vs. pooled intra-operative samples).

SIRT1 (Sirtuin 1): RNA expression of this gene increased significantly in analyses comparing the pooled distal VL samples at 6 weeks vs. all the intra-operative samples (2a) and in comparison of the home-based PRT group at 6 weeks against their own intra-operative samples (2c). This was in the direction as anticipated. SIRT1 is thought to play a role in reduction of myoblast death especially in unfavourable environments *in-vitro* (Saini, Al-Shanti et al. 2012), and is also thought to increase mitochondrial activity, fatty acid oxidation, and insulin sensitivity in skeletal muscle (Yu, Auwerx

2009). The increase in SIRT1 may demonstrate a protective effect for the muscle cells in terms of the catabolic environment that exists in the muscle before surgery.

SIRT2 (Sirtuin 2): showed reduced expression, as anticipated, in the analyses of the pooled distal VL samples at 6 weeks vs. all intra-operative samples (2a). SIRT2 is thought to inhibit pre-adipocyte differentiation with other functions not well characterised (Yu, Auwerx 2009). Its reduced expression in the early phase of rehabilitation may perhaps be an important indicator of the cellular changes that could be occurring as a precursor to the inhibition of fat deposition. This may be the case as patients in this phase of recovery may perhaps be less sedentary as they move around in less pain.

4.4.4 Inflammation

The effects of the home-based PRT regime were anticipated to result in increased expression of genetic markers of inflammation. Short term inflammation is thought to be a necessary part of muscle repair after bouts of exercise (i.e. it promotes muscle anabolism), whilst chronic inflammation induces protein catabolism (Buford, Cooke et al. 2009). TNFα (Tumour necrosis factor) and TNFSRF1B (Tumour necrosis factor super family member 1B) showed a reduction in RNA expression when comparison was made between the pooled distal VL samples at 6 weeks and all the intra-operative samples (analysis 2a). IL6 (interleukin 6) on the other hand, showed a trend to significant reduction in RNA expression in the assessment of the distal VL samples for the SR group at 6 weeks vs. their own intra-operative samples (analysis 2d). Both TNF and IL6 showed increased levels without statistical significance in the analysis of the distal VL samples at 6 weeks of the home-based PRT group vs. the SR groups at the same time point (2b), suggesting that although inflammation was reduced overall, it appears to be more so in the SR (control) group as opposed to the home-based PRT group. These inflammatory cytokines (TNF, IL6) are necessary components of the muscle repair process following mechanical stretch (Buford, Cooke et al. 2009). The inflammatory process as measured by these markers may not have been sufficiently activated to demonstrate the presence of any ongoing muscle repair processes. It may therefore be inferred that perhaps the administered home-based PRT regime was not intense enough to elicit an acute inflammatory response or that a response was elicited but the biopsy sampling time (6 weeks) may have been too late.

The most evident metabolic explanation for muscle decline is an imbalance between protein catabolism and anabolism (Lenk, Schuler et al. 2010). There is a prevalence of sarcopenia (degenerative unintentional loss of skeletal muscle mass and strength associated with aging) of approximately 25% in community dwelling older adults (Carmeli, Coleman et al. 2002, Baumgartner, Koehler et al. 1998). Loss of muscle mass of 5% per decade of life from the fourth decade onwards also occurs, with the rate of loss increasing after the age of 65 years (Lenk, Schuler et al. 2010). The average age of patients undergoing THR in the UK is 67.2 years (National Joint Registry for England and Wales 2011) and the associated deficits in muscle mass and strength associated with hip osteoarthritis have been shown to persist up to 2 years following surgery (Rasch, Bystrom et al. 2009).

Previous attempts to assess the genetic expression in the VL in patients after THR and undergoing an exercise program have demonstrated that prolonged resistance training after surgery (12 weeks) led to substantial hypertrophy in both types 1 and 2 fibres and these adaptations were accompanied by gains in mRNA expression of IGF-I splice variants (Suetta, Clemmensen et al. 2010). The supervised nature of the regime prescribed (centre-based) as well as the duration (12 weeks) are two important differences in relation to this study (home-based, 6 weeks, relatively low intensity) and may explain why there were no significant changes observed, especially with the comparison of the home-based PRT to SR groups at 6 weeks (analysis 2b).

A limitation of this study is that the analysis was performed on the VL of the affected leg only. Distal VL biopsies from the contra-lateral leg, as well as having an age and sex matched population with no previous history of hip osteoarthritis, may have provided a better comparison of the RNA expression levels observed for the genes chosen. This study's aim was to assess recovery post-THR so focusing on the operated leg was appropriate.

In terms of the early rehabilitation phase following surgery, the same limitations as previously listed apply (assessment of the contra lateral leg and use of an age and sex matched healthy population for comparison). With underlying sarcopenia and added muscle loss due to underlying osteoarthritis, there appears to be an underlying catabolic state that exists in the patients intra-operatively with some evidence at the 6 week time point of an attempt by the VL to adapt by increasing transcription activity (↑FOS), with an attempt at myofibrillar hypertrophy (↑CAPN2), all in the context of possibly

suboptimal mitogenic (exercise) stimuli (↓ADRB2). The evidence for the stimuli not being sufficiently effective is reinforced by the fact that the genetic markers of atrophy or protein catabolism were increased in the case of CAPN3 (indicating no muscle damage) but decreased as anticipated in the case of PSMA7, indicating perhaps that ubiquitin-proteasome dependent pathway activity (↑ in atrophy) may be suppressed in the early recovery period.

Significantly reduced inflammation for all the pooled samples in the early phase of recovery when compared to the intra-operative samples (analysis 2a) can be said to also accentuate the point that perhaps the exercise regime was not of sufficient intensity to result in activation of an inflammatory cytokine response. The relative quotient (RQ) in terms of mRNA expression for TNF at 6 weeks for all the patients (n=10) showed a trend to a significant negative correlation with the improvement in the maximal voluntary contraction of the operated leg quadriceps (MVCOLQ) in Newtons (N) (R=-0.626, p =0.053; data not presented). This further lent credence to the theory that a reduction in TNF mRNA expression is to be expected in the early period of recovery post-THR. The associated improvement in muscle strength may be a consequence of the improvement in pain in all patients post-THR.

Metabolic efficiency in this context is also important to address. Substrate utilisation differs based on the level of exercise performed with lipids from the blood being the main energy source utilised for low intensity exercise, intramuscular stores of fat and carbohydrates being the principal substrate for moderate exercise, and intramuscular glycogen the primary source for high intensity exercise (Pendergast, Meksawan et al. 2011). The home-based PRT regime did not lead to increases in strength (assessed as the MVCOLQ in Newtons (N)), muscle mass (lean mass of the operated leg quadriceps in grams (g)), or improvements in objectively assessed physical function (sit to stand measure, gait speed, timed up and go, stair climb performance and six minute walk test) relative to standard rehabilitation in the clinical effectiveness study in which context this muscle biopsy analysis was performed (Chapter 2). The home-based PRT regime may not have been sufficiently intense to demonstrate an objective difference and at a molecular level, it appears it was not also able to show any increased activity for genes coding for the transport of fatty acids from the vasculature to the mitochondria for metabolism (LPL, PPARA, FABP3 all reduced).

4.5 Conclusions

In summary, this study has shown that single site biopsy sampling of the VL is sufficient to study exercise training effects in patients undergoing THR. Characterisation of the molecular environment in the phase of early rehabilitation (in terms of the processes that reflect protein catabolism and anabolism) seems to indicate that catabolism appears to persist following THR with no obvious impact in favour of the home-based PRT intervention. Further exploration of the underlying mechanisms with examination of the post-transcriptional effects of the genes identified is required.

4.6 Chapter summary

An attempt was made in this chapter to assess on a molecular level, the changes that occur in the *vastus lateralis* (VL) of patients with end-stage hip osteoarthritis and during the early phase of rehabilitation following THR. The analyses performed showed that preoperative hip joint inflammation appears to have no effect on gene expression on samples taken from 2 sites in the VL, suggesting that for these sorts of analyses, single site muscle sampling is appropriate. Muscle inflammation in the VL of the operated leg at the 6 week time point was found to be reduced. Despite increases in markers of hypertrophy over the period of follow up, these did not reach significance. Significant reductions in markers of lipid metabolism were found (at 6 weeks) and this perhaps warrants further investigation with regards to metabolic efficiency in this group of patients. Participation in the home-based PRT regime did not demonstrate an objective difference in mRNA expression of the genetic panel chosen, confirming at a cellular level, the lack of effect on muscle strength (MVCOLQ) and objective measures of physical function (Chapter 2).

As previously stated (section 2.1), preoperative operated leg quadriceps strength is predictive of self-reported subjective function post-operatively after THR (Holstege, Lindeboom et al, 2011). Self-reported functional measures are the primary tools utilised in assessing THR as a surgical intervention (Ahmad, Xypnitos et al, 2011) and the impact of psychological factors on outcome following THR is not well described due to the heterogeneity of the measures used (Vissers, Bussmann et al, 2011). Chapters 5 and 6 investigate the impact of psychological distress (using the distress and risk assessment method) and behaviour cognitions (recovery locus of control, perceived behavioural control) on objective and subjective function in the cohort of patients recruited in Chapter 2. This is as

previous evidence suggests that psychological well-being is important in performance of exercise (Newson, Kemps 2007), and it also has an impact on the recovery of patients undergoing a surgical intervention (Kopp, Bonatti et al, 2003).

CHAPTER 5: The impact of psychological distress, assessed by the distress and risk assessment method (DRAM), on short-term functional outcome in patients participating in either home-based progressive resistance training or standard physiotherapy following total hip replacement surgery.

5.1 Introduction

Total hip replacement (THR) is very successful in relieving pain and improving quality of life, (Ethgen, Bruyere et al. 2004; Hawker, Badley et al. 2009; Cushnaghan, Coggon et al. 2007; Nilsdotter, Petersson et al. 2003b). However, controversy exists regarding the impact of preoperative psychological distress on surgical outcomes such as pain, function, satisfaction, or quality of life after lower limb surgery, with some studies reporting poor outcomes (Lingard, Riddle 2007) and others showing no significant effect on functional gain (Hossain, Parfitt et al. 2011). A recent systematic review of psychological factors affecting the outcome of total hip or knee replacement suggests that in long term follow up, i.e. 1 year after total knee replacement surgery, evidence supported that lower preoperative mental health (assessed using the SF-12 or SF-36) was associated with poorer function and greater pain (Vissers, Bussmann et al. 2011). The evidence for total hip arthroplasty, however, is limited and conflicting (Vissers, Bussmann et al. 2011).

An inherent problem in reviewing the evidence base regarding the impact of psychological factors in THR outcome is the heterogeneity of measures used in the published studies (Vissers, Bussmann et al. 2011). Measures range from the mental health component of the SF-36 and the Hospital Anxiety and Depression Scale (HADS), to separate measures for anxiety (EuroQol-5D, Spielberger Anxiety Inventory Trait form (STAI-T)) and mood (Profile of Mood States, POMS) (Hossain, Parfitt et al. 2011; Riediger, Doering et al. 2010; Anakwe, Jenkins et al. 2011; Badura-Brzoza, Zajac et al. 2009; Montin, Leino-Kilpi et al. 2007; Rolfson, Dahlberg et al. 2009; Ayers, Franklin et al. 2004). Thus, studies have measured and defined psychological distress in different ways and this may be the critical factor in the lack of coherent evidence.

The Distress and Risk Assessment method (DRAM), which was originally developed for patients with low-back pain, provides a means of assessing preoperative psychological status (Main, Wood et al.

1992; Hobby, Lutchman et al. 2001). The components of the DRAM, the modified somatic perception questionnaire (MSP) and the modified Zung depression index (MZDI) are more highly associated with a patient's level of disability than with their personality traits (Main, Wood et al. 1992). The DRAM has been found to be effective as a simple first stage screening procedure for psychological distress and the need for subsequent counselling and intervention (15) On the DRAM scale, patients are classified as either 'normal' (MSP <12, MZDI <17), 'at risk' (MSP ≤ 12, MZDI 17 to 33), 'distressed somatic' (MSP >13, MZDI 17 to 33, or 'distressed depressive' (MZDI >33) (Main, Wood et al. 1992). The DRAM quantifies the level of patient distress (i.e. not clinical levels of depression) and has been shown to be a predictor of poor outcome in patients with low back pain who are treated conservatively (Main, Wood et al. 1992). The DRAM has also been shown to be predictive of outcome after lumbar surgery, with the combination of pain duration and DRAM stratification predicting 36% of the improvement in daily functional activities (Trief, Grant et al. 2000). The DRAM has, however, not been formally evaluated as a predictor of post-operative functional outcome for patients undergoing THR. This study aims to assess this, as well as evaluate the impact of the DRAM on the main primary objective measure used in Chapter 2, MVCOLQ.

5.2 Methods

This prospective single centre study was part of a randomised clinical trial performed at the Department of Orthopaedics, Ysbyty Gwynedd, Betsi Cadwaladr University Health Board, Wales, UK, from April 2010 to March 2012. Ethical committee approval, eligibility criteria, as well as details of the randomisation method are specified in section 2.2. The CONSORT flowchart (Figure 1) shows that 26 patients completed 9 to 12 month follow up and these patients form the cohort assessed using the DRAM.

The DRAM components were administered preoperatively to enable stratification of psychological distress as already described. These components, the MSP and MZDI are described in further detail below:

- **MSP:** This 13-item scale was designed to measure heightened somatic awareness or 'somatic anxiety' in patients with chronic pain (Main 1983). The MSP has demonstrated adequate validity and reliability but has not been shown to relate to patient related functional outcomes

(Deyo, Walsh et al. 1989) . However, in combination with the MZDI (i.e. the DRAM) it has been found to classify risk of poor outcome with significant accuracy (Main, Wood et al. 1992).

- **MZDI:** This consists of 23 items that assess depressive features, and has well-established reliability and validity (Zung 1965). The modified version was created by Main and Waddell (Main, Waddell 1987) for use in patients with pain, and was been shown to be more highly associated with pain-related disability than personality traits or hypochondriacal fears (Shutty, DeGood et al. 1986).

Two commonly used subjective functional assessment questionnaires; the Oxford Hip Score (OHS) and an abbreviated version of the Western Ontario and McMasters University Osteoarthritis personal function scale (rWOMAC PF) were also administered to the recruited patients preoperatively and then again at 6 weeks, 6 months, and 9-12 months postoperatively. The OHS is a 12-item, joint-specific, self-administered questionnaire, which has been studied extensively since its development and is a reliable, valid, and responsive instrument for assessing hip pain and disability in patients undergoing total hip replacement (Murray, Fitzpatrick et al. 2007). The 12 questions in the OHS in this study were scored from 0-48, with a higher score reflecting better function. The full WOMAC consists of 24 questions in 3 categories (Pain - 5 questions; stiffness - 2 questions; physical function - 17 questions) all scored on Likert scales from 0 (extreme difficulty) to 4 (no difficulty). In the orthopaedic literature, the overall score is routinely normalized to a 0-100 scale, with higher values reflecting a better state. Redundancy exists within the full WOMAC function scale as demonstrated by Rasch analysis; which provides an estimate of individual item difficulty, and allows examination of the spacing of items along the scale and detection of redundancy among items (Ryser, Wright et al. 1999), and subsequently a reduced scale with 7 items has been developed (Whitehouse, Lingard et al. 2003). A correlation value of 0.97 exists between the reduced scale and the full WOMAC function scale (Whitehouse, Crawford et al. 2008) thus supporting use of the shorter version. In this study the abbreviated scale, rWOMAC PF was used to assess subjective function.

For the purposes of data analysis, patients were grouped into ‘normal’ or ‘at risk/distressed’ based on the DRAM classification. 2 by 4 (2 between subjects factors i.e. DRAM stratification of ‘normal’ or

'at risk/distressed', and 4 within subjects factors i.e. the 4 assessment time points) repeated measures analyses of co-variance controlling for the effects of the trial randomisation were performed with the OHS and rWOMAC PF (absolute total value) scores as dependent variables. An exploratory ANCOVA analysis using the DRAM was also performed on the primary outcome measure used for the overall study (Chapter 2, MVCOLQ). The assumptions of sphericity and normality of distribution were verified by Mauchly's test and the Kolmogorov-Smirnov test, respectively. Any significant effects were investigated using independent samples t-tests. SPSS version 18 (SPSS for Windows v18, Rel. 30.07.2009. Chicago: SPSS Inc) was used for all statistical analysis. $P \leq 0.05$ was considered significant.

5.3 Results

For the 26 patients analysed (12 males, 14 females, mean (SD) age 63.8 (±10.1) years), 11 patients were 'normal' and 15 patients were 'at risk'/'distressed' preoperatively (Table 15). The psychological distress status of the patients randomly assigned to either the exercise intervention or standard rehabilitation groups is described in Table 16.

TABLE 15. Stratification of patient risk using the Distress and Risk Assessment Method (DRAM) tool in patients undergoing total hip replacement (n=26)

	DRAM scale				
	Normal (MSP <12, MZDI <17)	At risk (MSP ≤ 12, MZDI 17 to 33)	Distressed somatic (MSP >13, MZDI 17 to 33)	Distressed depressive (MZDI >33)	Total
Males n=12	6	5	0	1	12
Females n=14	5	8	0	1	14
Total	11	13	0	2	26

KEY: MSP: Modified Somatic Perception score
MZDI: Modified Zung Depression score

TABLE 16. Randomisation grouping of patient cohort in relation to DRAM stratification

Group	DRAM stratification (number of patients)		Total
	Normal	At risk/Distressed	
Exercise intervention	8	5	13
Standard rehabilitation	3	10	13
Total	11	15	26

KEY: DRAM: Distress and Risk Assessment Method

After controlling for the randomisation to either the home-based PRT (n=13) or SR (control, n=13) groups, repeated measures analysis of co-variance (ANCOVA) showed a significant effect for DRAM stratification (OHS, F = 4.881 df = 1, p=0.038; rWOMAC PF, F = 10.406 df = 1, p=0.004) with significant improvements for both OHS (F =6.675 df 3, p=0.001) and rWOMAC PF (F=5.979 df 3, p=0.001) over time .There was no significant interaction between the DRAM stratification and change in these measures over time (OHS, F = 0.087, df 3, p=0.967; rWOMAC PF, F=0.744, df 3, p=0.529). Differences between both groups were assessed at each of the 4 time points (preoperatively, and at 6 weeks, 6 months, and 9-12 months postoperatively), and both the absolute values and change from baseline in OHS and rWOMAC PF for the 2 groups over time appear in Tables 17 and 18.

For the OHS, 'at risk /'distressed' patients had a significantly lower preoperative score than those in the 'normal' category and this difference was also present 6 months postoperatively. The difference was not significant at 6 weeks and 9-12 months although there were trends towards significance (p values of 0.066 and 0.110 respectively). Both groups of patients improved significantly in terms of the changes from the baseline functional scores.

For the rWOMAC PF, 'at risk /'distressed' patients also had a significantly lower score than those in the 'normal' category preoperatively and this difference persisted at 6 weeks, 6 months and 9-12 months of follow up (Table 19). Figures 6 and 7 illustrate the changes in function observed in both groups (based on absolute values of the OHS and rWOMAC PF). For both functional measures there was a progressive increase in absolute scores from baseline to final follow-up (9-12 months) with no statistically significant difference between the DRAM groups in this regard. Thus, a DRAM

stratification of being ‘at risk/distressed’ indicated that such patients have statistically lower subjective function and this remains the case for up to a year of follow up.

An exploratory ANCOVA using the DRAM showed no impact of being ‘at risk/distressed’ or ‘normal’ in terms of the MVCOLQ (primary outcome of main study, chapter 2) at 9-12 month follow up ($F = 0.077$, $df = 1$, $p = 0.784$). The presence of psychological distress in this population therefore had no impact on post-operative recovery of muscle strength, but was important in self-reported measurement of physical function.

Table 17. Absolute values and change in Oxford Hip Scores in patients undergoing total hip replacement assessed for psychological distress according to the DRAM method (n=26)

DRAM Stratification	Oxford Hip Score (mean(SD))						
	Time of assessment						
	Preoperative	6 weeks post Post-operatively		6 months Post-operatively		9-12 months Post-operatively	
	Absolute value	Absolute value	Change from baseline	Absolute value	Change from baseline	Absolute value	Change from baseline
Normal (n=11)	24.81 (4.95)	38.80 (5.88)	14.70 (8.00)	46.27 (1.95)	21.45 (5.46)	47.27 (1.49)	22.45 (5.22)
At risk /Distressed (n=15)	18.00 (6.21)	32.66 (9.94)	14.67 (11.88)	42.46 (5.54)	24.47 (6.51)	44.53 (5.30)	26.53 (7.67)
95% C.I. of difference	2.29 to 11.34	-0.43 to 12.69	-8.19 to 8.25	0.18 to 7.42	-7.87 to 1.85	-0.67 to 6.15	-9.30 to 1.14
T test p value	0.005*	0.066	0.993	0.040*	0.213	0.110	0.120

Legend

DRAM - Distress and risk assessment method

C.I. -Confidence interval

** - $p<0.05$*

Table 18. Absolute values and change in rWOMAC PF in patients undergoing total hip replacement assessed for psychological distress according to the DRAM method (n=26)

	rWOMAC PF (mean (SD))						
	Time of assessment						
	Preoperative	6 weeks post Post-operatively		6 months Post-operatively		9 -12 months Post-operatively	
DRAM Stratification	Absolute value	Absolute value	Change from baseline	Absolute value	Change from baseline	Absolute value	Change from baseline
Normal n=11	55.52 (17.38)	90.70 (6.56)	33.56 (17.99)	97.08 (4.17)	41.55 (16.46)	98.70 (2.88)	43.18 (15.93)
At risk /distressed n=15	39.52 (13.86)	71.67 (17.77)	32.14 (18.16)	88.80 (13.14)	49.28 (17.03)	90.00 (12.68)	50.47 (17.54)
95% C.I. of difference	2.69 to 29.29	6.83 to 31.26	-13.85 to 6.71	0.65 to 15.89	-21.49 to 6.03	1.36 to 16.04	-21.13 to 6.54
T test p value	0.023*	0.001*	0.941	0.031*	0.338	0.021*	0.209

Legend

DRAM - Distress and risk assessment method

rWOMAC PF -reduced version of Western Ontario and McMasters University Osteoarthritis personal function scale

C.I. -Confidence interval

** - $p<0.05$*

Figure 6. Effect of Distress and Risk Assessment Method (DRAM) stratification on Oxford Hip Score over 9-12 months following total hip replacement

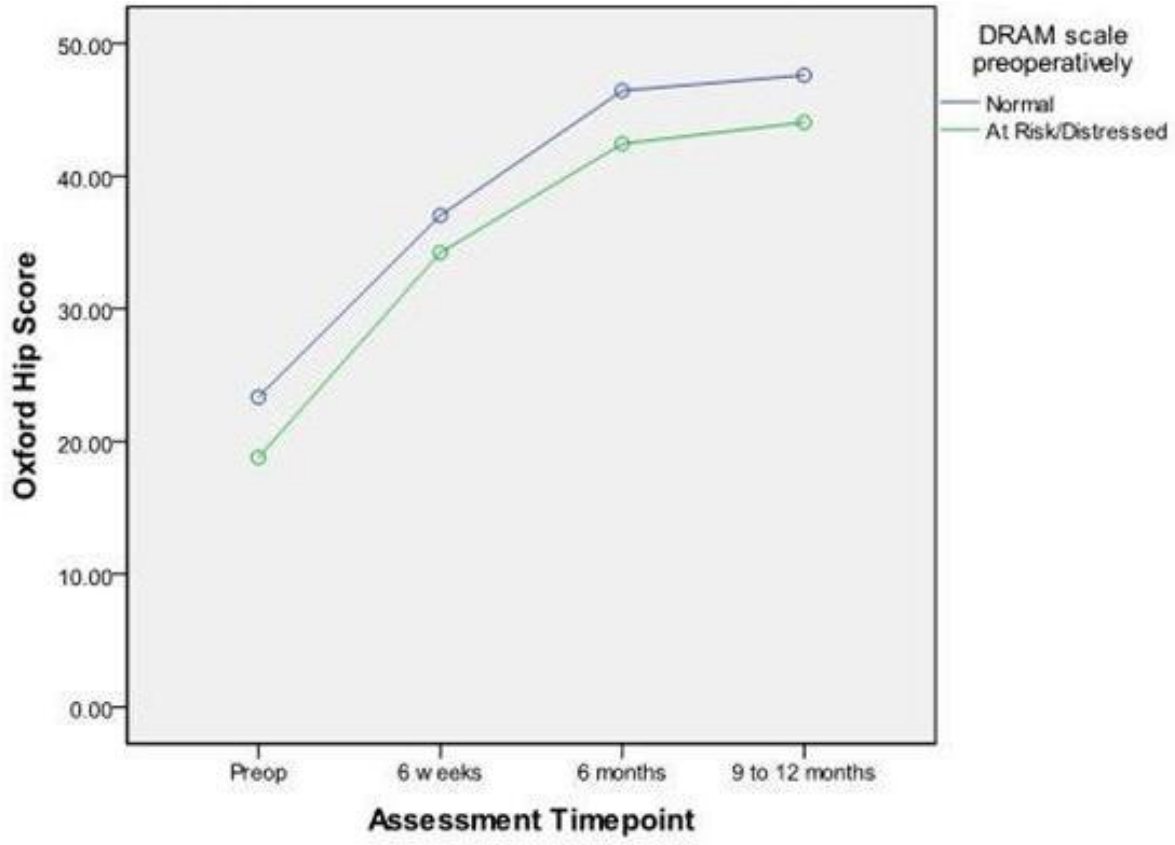
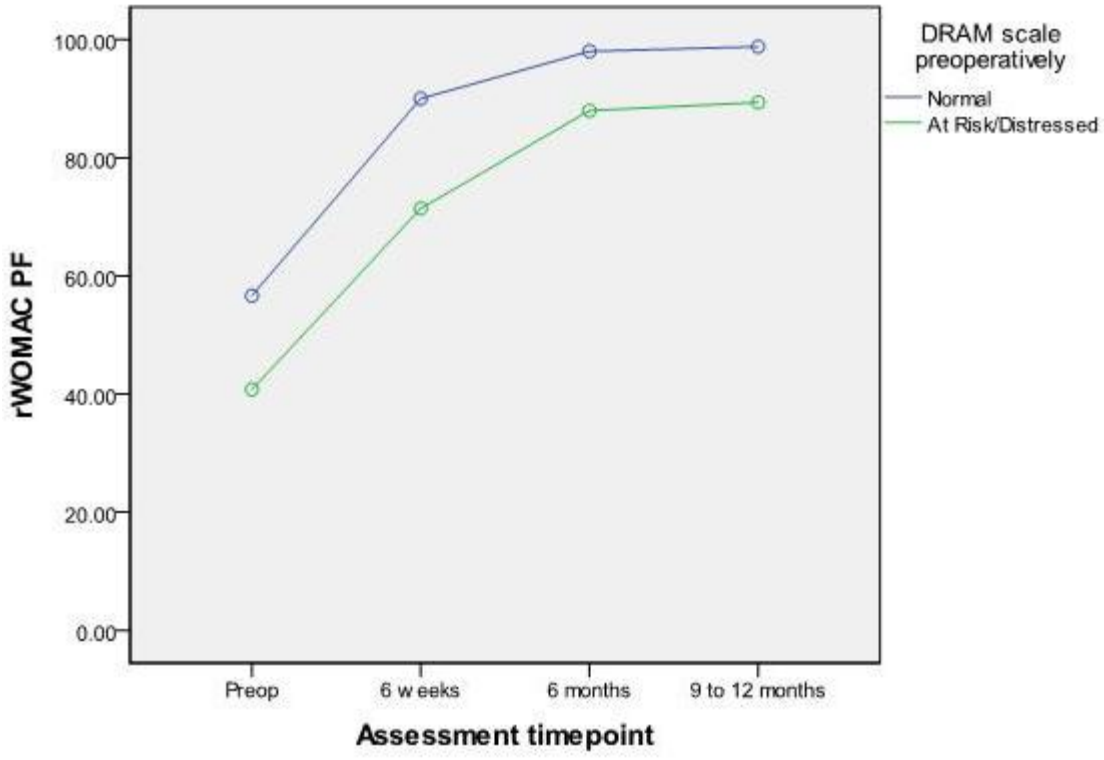


Figure 7. Effect of Distress and Risk Assessment Method (DRAM) stratification on reduced Western Ontario and McMasters University Osteoarthritis Personal Function (rWOMAC PF) scale over 9-12 months following total hip replacement



5.4 Discussion

This is the first study to demonstrate that the DRAM is predictive of subjective functional outcome in patients undergoing THR. The repeated measures ANCOVA performed demonstrated significant effects of the DRAM stratification, as well as significant improvement over time, on the absolute values for the subjective patient reported outcome measures assessed (OHS and rWOMAC PF). These findings were independent of randomisation into either the home-based PRT intervention or SR (control) groups. Subsequent analysis showed that the OHS was significantly different between the groups preoperatively but this difference was not observed at 6 weeks or 9-12 months. The differences between both groups in absolute terms are 6.81 points preoperatively, 5.83 points at 6 weeks, 3.81 points at 6 months and 2.74 points at 9-12 months. These differences show a trend to significance at 6 weeks and 9-12 months which, although not statistically significant, are likely to be

clinically relevant as the minimal clinically important change for the Oxford Hip Score is thought to be less than 3 points (Murray, Fitzpatrick et al. 2007).

The differences observed in the absolute values of the rWOMAC PF scale between the time points are significant (Table 18), which implies that the DRAM tool is useful in predicting short-term functional outcome in this patient population. The differences between the absolute values for the normal and at risk/distressed groups' ranges from 16 points preoperatively to 19.03 points at 6 weeks, 8.28 points at 6 months and 8.70 points at 9-12 months. These differences were all both statistically and clinically significant, as the minimal clinically important change required for the WOMAC ranges from 3 to 6 points (Goldsmith, Boers et al. 1993). The differences observed within this small number of patients (n=26) implies that for patients undergoing THR for osteoarthritis, there is a clinical benefit in using the DRAM tool to classify patients according to their level of psychological distress. The DRAM therefore has the potential to identify patients requiring multidisciplinary assessment or management (Main, Wood et al. 1992).

Despite the DRAM stratification used in this study not showing a difference in terms of the MVCOLQ (primary outcome measure for main study in Chapter 2), the difference between the 'at risk/ distressed' and 'normal' groups was noted in the rWOMAC PF and OHS. Performance related measures such as muscle strength and objective measures of activities of daily living (ST, TUG, SCP, GS, 6MWT) may fail to reflect the true demands and exertions associated with activities of daily living (Wylde, Blom 2009). Hence, self reported PROMs such as the OHS and rWOMAC PF were devised based on perceptions of patients about the outcome of surgical intervention (Dawson, Fitzpatrick et al. 1996; Bellamy, Buchanan et al. 1988). Thus, it is appears that objective and subjective measures may be assessing different domains of a patients' function i.e. what is objectively assessed through performance related measures may not reflect what the patient perceives is an acceptable subjective functional state.

A limitation to this study is that we did not perform an assessment of the current state of psychological distress in the patients at each follow up assessment. It is possible that the distress caused by significant pain and functional impairment may be resolved somewhat following the

surgical intervention, however, as can be seen from Figures 8 and 9, patients who start off in the 'at risk/distressed' stratification have persistently lower levels of function postoperatively.

In a previous study of the incidence of psychological distress in patients awaiting THR, which used the Mental Health Score (MHS) component of the SF36, 24.1% of patients (108/448) were found to have an MHS≤ 56 which is indicative of psychological distress, whilst 75.9% (340/448) had an MHS ≥ 56 indicating that they were not distressed (Hossain, Parfitt et al. 2011). In the current study, 2 out of 26 patients were found to be 'distressed' (7.7%), with a greater proportion (13/25, 52%) classified as being 'at risk', whilst 42.3% (11/26) fell into the 'normal' category. This compares to DRAM classifications from a spinal population undergoing surgery for microdiscectomy, where, the 'normal' group accounted for 20.3%, the 'at risk' group accounted for 35%, and the 'distressed' group for 48% of the total number of patients (Hobby, Lutchman et al. 2001). There is no published literature on the DRAM classifications in patients awaiting THR and the values obtained in this study may be a poor estimate of the true incidence of distress in these patients due to the small sample size. Somatisation has previously been identified as a predictor of poor outcome in patients undergoing THR (using the full WOMAC scale) but the follow up period in this study was only 2 months (Riediger, Doering et al. 2010). The current study demonstrates the usefulness of the DRAM in assessing patients whilst also predicting their outcome at up to 12 months of follow-up.

Issues that remain to be resolved regarding the usefulness of the DRAM tool in this population relate to what type of psychological intervention would be appropriate and feasible for these patients. Due to the differences observed between the 'normal' and 'at risk/ distressed' groups at baseline, this study demonstrates that any intervention that is warranted is best started in the preoperative period. Future studies are needed to determine the optimal interventions that may help address these differences and to investigate which member of the healthcare team is most suited to initiate it.

5.5 Chapter summary

In summary the DRAM tool is predictive of subjectively assessed functional outcome in this sample of patients, and may be of use as a screening tool before THR. No impact on the primary outcome measure, MVCOLQ, was demonstrated. Chapter 6 focuses on the impact of behaviour cognitions (recovery locus of control and perceived behavioural control) on functional recovery. Behaviour

cognitions have been previously shown to influence functional recovery patients following stroke, as well as affect the degree of engagement with rehabilitation programs in patients with upper limb impairment (Johnston, Bonetti et al. 2007; Chen, Neufeld et al. 1999) and in this context such recovery will be assessed objectively (MVCOLQ, the primary outcome measure of the main study in Chapter 2), and subjectively (OHS and rWOMAC PF).

CHAPTER 6: An assessment of the impact of behavioural cognitions on function in patients participating in either home-based progressive resistance training or standard rehabilitation following total hip replacement surgery.

6.1 Introduction

Preoperative psychological factors such as poor preoperative mental health and pain catastrophizing have been shown to have an adverse effect on outcomes after joint replacement surgery (Vissers, Bussmann et al. 2011) . A good psychological state is an important index of health and factors that can influence such a state include life satisfaction, optimism, self esteem, and perception of social support (Mavros, Athanasiou et al. 2011). A less desirable psychological state includes anxiety, stress, depression and hostility and these can also affect one's health in various ways including the levels of adherence to post-operative exercise protocols (Davis 2009). Beliefs about 'control' influence strategies for coping with life stressors, including for example surgery, and hence exert influence upon coping outcomes (Leventhal, Nerenz et al. 1984) . 'Perceived control' has little consensus with regards to its definition (Jacelon 2007). Definitions are made in various theoretical contexts, including social learning theory (the extent to which an individual believes that they control key processes (Johnston, Morrison et al. 1999)) and social cognitive theory (an individual's beliefs about ability to effect desired outcomes and to avoid undesired outcomes (Bullers 2000)), and more behavioural specific theories such as the theory of planned behaviour (beliefs about the ease or difficulty of performing a specific behaviour (Conn 1998)). Stable perceived control has been shown to be predictive of better health outcomes whilst variable perceived control predicts poorer health outcomes, particularly functional ability (Chipperfield, Campbell et al. 2004).

If physical impairment is seen as the objective problem, then engagement in a physical exercise programme can be seen as being representative of coping efforts, some of which can be determined by mental representations (Johnston, Morrison et al. 1999). Mental representations (thoughts about ones illness and its treatment) have been shown to influence the impact of chronic disabling conditions either directly (Johnston, Bonetti et al. 2007) or indirectly via their influence on coping (Skelton, Croyle 1991). Perceived control has been shown to influence functional recovery in patients following

stroke (Johnston, Bonetti et al. 2007), and chronic polyneuropathy (Schroder, Johnston et al. 2007). Control cognitions have been directly related to positive engagement with rehabilitation regimes, with a significant predictive value in terms of compliance with a home exercise programme in for example, people with upper extremity impairment (Chen, Neufeld et al. 1999), or adherence to exercise programs in an older population (Ashworth, Chad et al. 2005).

Background personality and preoperative coping resources have been found to be significant predictors of clinical outcomes including postoperative analgesia requirements and length of hospital stay (Kopp, Bonatti et al. 2003). The number of previous operations undergone by these patients and their perceived control of their requirement for analgesia, adherence to advice given by healthcare staff, and personal 'will' to improve, were significant predictors of recovery (Kopp, Bonatti et al. 2003). In view of the gender differences that influence exercise behaviour adherence in the general population (see section 1.8), it was hypothesised that in a population of patients undergoing total hip replacement, gender may influence behavioural beliefs or exercise behaviour (coping), in addition to background factors such as actual social support and previous surgical experience. The purpose of this study was therefore to assess whether perceived control cognitions have an impact on an objective measure of physical function MVCOLQ (primary outcome measure for the main study intervention (Chapter 2), as well as subjective function in patients undergoing THR.

6.2 Methods

Patients participating in this study were recruited as part of a randomised trial comparing an early 6 week home based progressive resistance training (Home-based PRT) regime to standard rehabilitation (SR) after THR. Ethical committee approval, eligibility criteria, as well as details of the randomisation method are specified in section 2.2 with the CONSORT flowchart in Figure 1.

Demographic information was collected for each participant (age, sex, living situation, history of previous surgery) as well as body mass index (BMI), and two measures of behavioural cognition (the recovery locus of control scale (RLOC) and perceived behavioural control (PBC) items drawn from the theory of planned behaviour (TPB). The objective measure of physical function that acted as the primary outcome of the main study, MVCOLQ, was assessed preoperatively and at all review time points. A description of the methodology used for assessing MVCOLQ is previously described in

section 2.2.1. Subjective functional outcome was assessed using the Oxford Hip Score and a reduced version of the Western Ontario and McMasters University Osteoarthritis personal function scale (rWOMAC PF); see section 5.2 for full description. The questionnaire items were administered to the study participants preoperatively and at each follow up interval. RLOC and TPB PBC are described in further detail below:

6.2.1 Behavioural cognitions

1. *Recovery locus of control (RLOC):* The RLOC scale has 9 items rated on a Likert scale from 'strongly agree' to 'strongly disagree'. Five items are phrased in the direction of internal control (e.g. 'it's what I do to help myself that's really going to make all the difference') and four in the direction of external or chance (e.g. 'I have little or no control over my progress from now on'). The RLOC has been shown to have internal consistencies of 0.50 to 0.77 (Johnston, Morrison et al. 1999) and was adapted to suit assessment of the exercise programs in this study. All items were scored in the direction of internality with a maximum achievable score of 45. The absolute values for the RLOC were calculated for each study participant as well as the change values at each follow up interval.
2. *The Theory of Planned Behaviour (TPB) Perceived Behavioural Control (PBC) item:*

   As well as self regulation theory, the prediction of illness outcome can be aided by sociocognitive models of behaviour. The TPB attempts to conceptualise the cognitive processes that underpin attitudes that influence health behaviours (Bains, Powell et al. 2007). The theory assumes that an individual's intention to perform behaviour is the most accurate predictor of performance of that behaviour (Bains, Powell et al. 2007). Intention is therefore viewed as a function of 3 factors:

   a. Attitude towards behaviour: Based on the individual evaluation or expectation of the likely outcome of the relevant behaviour, and represents positive and negative aspects of engaging in the behaviour (Bains, Powell et al. 2007, Wade, Smith et al. 2010).
   b. Subjective norm: Individuals' belief about whether people who are important to them would approve of their performing that behaviour (AJZEN 1987). This represents the

social pressures which an individual feels to perform or not perform the behaviour, combined with their individual motivation to comply (Wade, Smith et al. 2010).

c. Perceived behavioural control (PBC): An individual's estimate of the extent to which he/she is able to exercise control over the behaviour (AJZEN 1987). This is based upon an individual's beliefs about inhibitory factors or perceived barriers, and therefore negative aspects of performing the behaviour (Bains, Powell et al. 2007). Perceived behavioural control can be influenced by both 'external and internal control factors' (Wade, Smith et al. 2010). Internal control factors are an individual's belief about their ability to perform behaviour for reasons such as self efficacy, knowledge and training, whereas external control factors are those environmental factors that may prevent or facilitate the behaviour (such as inadequate equipment, time constraints etc.) (Wade, Smith et al. 2010).

A single PBC item was used in this study which was scored on a Likert scale from 0 ('strongly disagree') to 7 ('strongly agree'). It addressed external factors i.e. the influence of regular review by a doctor or physiotherapist and was worded as below:

'Having a regular review with the doctor or physiotherapist would make it easier for me to do my exercises without missing a day'

The absolute and change values at each review time point for the TPB PBC were collated for the purpose of this study.

6.2.2 Statistical analysis

In order to investigate the impact of the RLOC and TPB PBC on objective (MVCOLQ) and subjective functional outcome (OHS and rWOMAC PF), factors such as sex, living situation, previous surgical experience were initially investigated to assess whether they were important mediators of these variables in this population. Independent samples t-tests were used to investigate each factor with $p<0.05$.

A correlation matrix was then run to assess which independent variables (age, BMI, TPB PBC, RLOC ;including change from baseline values at each review time point) had significant correlations with the

dependent variables (MVCOLQ, OHS and rWOMAC PF (absolute and change from baseline scores at 9-12 months)) controlling for any factors with significant effects as determined by the t-tests.

Three sets of regression analyses were then performed to determine the predictors for absolute subjective function and change scores from preoperative values for MVCOLQ, OHS and rWOMAC PF at 9-12 months. The first set of analyses was performed using the absolute values for the MVCOLQ, OHS and rWOMAC PF as DVs with the IVs determined from the correlation matrix for each review time point (i.e. Preoperative, 6 weeks, 6 months). The second set of analyses was performed using the final change from baseline values at 9-12 months for MVCOLQ,OHS and rWOMAC as the DVs with the IVs as previously determined from the correlation matrix for each review time point (i.e. preoperative, 6 weeks, 6 months). SPSS version 18 (SPSS for Windows v18, Rel. 30.07.2009. Chicago: SPSS Inc) was used for all analyses.

6.3 Results

The average age of the 35 patients entered into the analysis preoperatively was (mean (SD)) 65.80 (9.51) in males (n=15) and 64.55 (11.24) in females (n=20). The mean BMI for the cohort preoperatively was 28.79 (5.64) (overweight) with RLOC 30.06 (3.85) (moderate-high) and TPB PBC 6.25(1.19) (high external). Thirteen participants lived alone and 20 lived with a partner or relative (two non-responses). 8 participants had a previous experience of surgery whilst 18 did not. There was no significant difference in the absolute values or change from baseline values for neither behavioural cognitions (RLOC, TPB PBC) nor the objective (MVCOLQ) and subjective functional outcomes (OHS, rWOMAC PF) collated over the period of follow up between the home-based PRT and standard rehabilitation groups (Table 19). Thus, the groups are merged for subsequent analyses.

Independent samples t-test analysis revealed preoperatively that patients with no history of previous surgery had significantly higher BMI than those who had had a previous operation (25.01 (3.93) vs. 30.59 (6.08), p=0.028). Preoperatively men were found to have a significantly greater MVCOLQ than women (207.60 (88.63) N vs. 147.25 (58.85) N, p =0.032) with this difference also persisting at 6 weeks post-operatively (223.57 (58.29) N vs. 162 (47.85) N, p=0.03). There was no difference in the amount of gain in MVCOLQ between the sexes (males average gain 28.50(94.29) N vs. 83.77 (53.44), p=0.082). Patients with a history of previous surgery had statistically lower preoperative

muscle strength than those who hadn't (133.12 (58.96) N vs. 191.11 (74.96) N, p=0.049). Previous surgical experience also led to a more significant improvement in muscle strength at 1 year post-operatively (gain of 117.16 (56.28) N vs. 42.33 (58.48) N, p=0.025). Living alone as opposed to with a partner in this population leads to a lower absolute MVCOLQ pre-operatively (133.61 (43.74) N vs. 204.00 (85.54) N, p=0.010), and at 6 months postoperatively (169.27 (79.73) N vs. 266.94 (76.57) N, p=0.003). There was no effect of living situation on the improvement in MVCOLQ at 9-12 months post-operatively.

At 6 months postoperatively, women had a significantly higher TPB PBC than men (5.70 (1.96) vs. 4.00 (1.96), p=0.011). At 9-12 months, there was greater subjective functional gain in women as opposed to men (rWOMAC PF improvement of 53.57 (15.97) vs. 37.79 (14.88), p=0.014), patients who lived alone as opposed to with a partner (rWOMAC PF improvement 53.57 (13.48) vs. 39.73 (15.91), p=0.032), as well as those with no previous history of surgery (rWOMAC PF improvement 47.45 (16.89) vs. 30.95 (11.66), p=0.025). At 12 months living alone led to a more significant reduction in the change from baseline values of RLOC than living with a partner (-2.66 (1.21) vs. -1.00 (1.93), p=0.028).

Table 19. Absolute values (mean (SD)) for measures of behavioural cognition and functional outcome for home-based progressive resistance training (PRT) and standard rehabilitation, SR (control) groups preoperatively and at 9-12 month follow up.

	Preoperative [#]		**6 weeks postoperatively**[#]		**6 months postoperatively**[#]		**9-12 months postoperatively**[#]	
Behavioural cognitions	Home-based PRT n=20	SR (control) n=15	Home-based PRT n=17	SR (control) n=15	Home-based PRT n=16	SR (control) n=13	Home-based PRT n=13	SR (control) n=13
RLOC	30.36(4.38)	29.61(3.01)	31.78(4.90)	31.07(2.81)	31.17(4.07)	31.46(3.09)	29.13(2.99)	28.31(3.01)
TPB PBC	6.25(1.25)	6.26(1.16)	5.50(2.12)	4.92(2.23)	5.22(2.01)	4.58(1.67)	4.40(2.09)	5.00(1.63)
Functional measures								
MVCOLQ (N)	172.3 (85.1)	174.2 (70.3)	181.8 (49.5)	196.7 (73.4)	233.8 (87.8)	227.5 (101.4)	247.4 (85.1)	240.3 (87.4)
OHS	24.50(8.47)	20.79(7.16)	36.42(6.59)	32.53(11.12)	42.71(7.46)	43.92(3.82)	45.86(5.11)	45.50(3.34)
rWOMAC PF	54.13(23.99)	42.38(16.30)	81.34(10.14)	75.27(22.51)	88.23(17.75)	92.58(9.16)	94.38(12.34)	92.03(9.24)

KEY
[#] No statistically significant differences between groups
RLOC Recovery locus of control (scored internally)
OHS Oxford Hip Score
MVCOLQ Maximal voluntary contraction operated leg quadriceps in Newtons (N)
TPB PBC Theory of planned behaviour perceived behavioural control item
rWOMAC PF Reduced version of Western Ontario and McMasters University osteoarthritis personal function scale

Sex, living situation and previous surgical experience were therefore entered as control variables in a partial correlation matrix with all the independent and dependent variables included.

RLOC at 6 months correlated negatively with absolute MVCOLQ at 9-12 months (r=-0.562, p=0.045). As expected MVCOLQ preoperatively, at 6 weeks and 6 months was found to correlate with MVCOLQ at 9-12 months, with the strongest correlation at the 6 month time point (r = 0.855, p=0.0001).

MVCOLQ at 9-12 months also correlated significantly with the subjectively assessed measures at 6 weeks (rWOMAC PF- r=0.553, p=0.05), 6 months (OHS- r=0.823, p=0.001; rWOMAC PF- r=0.746, p=0.003) and 9-12 months (OHS- r=0.654, p=0.015).

Preoperative RLOC, 6 week RLOC and the RLOC change from 6 weeks to 6 months were found to correlate with the change in objectively assessed MVCOLQ at 9-12 months (r=0.590 , p=0.034; r=0.777, p=0.002; r = -0.732, p=0.004 respectively). The TPB PBC item score at 9-12 months also correlated significantly with the change in MVCOLQ at 9-12 months (r = 0.570, p=0.042).

None of the pre-operative behavioural cognitions affected subjective outcome. Preoperative rWOMAC PF was found to correlate with absolute rWOMAC PF at 9-12 months (r=0.636, p=0.019); with the rWOMAC score at 6 weeks also showing a significant relationship with the same measure (r=0.567, p=0.043). At 6 months, RLOC and OHS were found to correlate significantly with absolute OHS at 9-12 months (r = -0.647, p=0.017; and r=0.870, p=0.0001, respectively), with rWOMAC PF at 6 months also correlating significantly with absolute rWOMAC PF at 12 months (r=0.838, p=0.0001). There was also a trend to significance for the RLOC change score (difference between 6 months and 6 weeks) in terms of correlation to absolute OHS (r = -0.535, p=0.059) and absolute rWOMAC PF at 9-12 months (r = -0.535, p=0.060).

In terms of the change from preoperative values for OHS and rWOMAC PF at 12 months, there was a significant relationship with the preoperative values of the same scores (preoperative OHS r=0.556, p=0.049; preoperative rWOMAC PF r= -0.560, p=0.047) with no other relationships evident at 6 weeks or 6 months. The rWOMAC PF correlated significantly with OHS demonstrating construct validity, comparable to the published literature (Garbuz, Xu et al. 2006). The correlation matrix is illustrated in Table 20.

Standard regression analyses were then performed on the absolute and change scores (at 9-12 months from preoperative values) for the MVCOLQ, OHS, and rWOMAC PF based on the results of the aforementioned partial correlations.

The significant predictors in the regression models are reported in Table 21. For the absolute MVCOLQ at 9-12 months post-operatively, the most significant predictor was the MVCOLQ at 6 months (61.5% of the variance in 9-12 month absolute MVCOLQ explained), with a unit change in MVCOLQ at 6 months meaning an increase in the final follow up MVCOLQ of 0.723N.

The RLOC change from 6 weeks to 6 months post-operatively proved to be the most significant predictor of the amount of improvement in MVCOLQ at 9-12 months (predictive of 23.5% of variance), with a unit improvement in this value causing a reduction in MVCOLQ improvement from preoperative values by 10.27 N.

From Table 21, it can be seen that the most important predictor of absolute scores for rWOMAC PF at 12 months are the absolute values of the same measure at 6 weeks and 6 months respectively. A unit increase in the rWOMAC PF at 6 weeks causes an increase in the final rWOMAC PF at 12 months of 0.264 whilst at 6 months this figure increases to 0.817. 17.8% of the variance in the final rWOMAC PF absolute score is explained for by the score at 6 weeks whilst 67.3% of the variance is explained for by the score at 6 months.

Table 20. Correlation[#] coefficients (R value (p value)) for variables assessed as predictors of objective and subjective functional outcome in patients undergoing a trial of home based progressive resistance training versus standard rehabilitation after total hip replacement surgery

Variables	MVCOLQ (N) at 9-12 months	MVCOLQ (N) change from pre-operative value (at 9-12 months)	OHS at 9-12 months	OHS change from pre-operative value (at 9-12 months)	rWOMAC PF score at 9-12 months	rWOMAC PF change from preoperative value (at 9-12 months)
Age	0.001 (0.998)	0.384 (0.195)	0.227(0.455)	-0.018(0.954)	0.117(0.703)	-0.054(0.860)
Preoperative						
TPB PBC	-0.021 (0.946)	0.523 (0.067)	0.256(0.398)	0.112(0.716)	0.253(0.404)	0.073(0.813)
RLOC	-0.126 (0.683)	0.590 (0.034)*	0.053(0.864)	-0.173(0.572)	0.121(0.694)	0.194(0.526)
MVCOLQ	0.678 (0.008)**	-0.357 (0.210)	0.322 (0.262)	0.252 (0.385)	0.147 (0.616)	0.110 (0.709)
OHS	0.276 (0.361)	0.363 (0.223)	0.441(0.132)	-0.556(0.049)*	0.560(0.046)*	-0.430(0.142)
rWOMAC PF	0.168 (0.582)	0.202 (0.508)	0.456(0.117)	-0.378(0.203)	0.636(0.019)*	-0.560(0.047)*
6 weeks						
TPB PBC	0.237 (0.435)	0.453 (0.120)	0.367(0.217)	0.043(0.888)	0.232(0.446)	0.069(0.823)
RLOC	0.119 (0.698)	0.777 (0.002) **	0.135(0.659)	-0.132(0.668)	0.230(0.451)	0.151(0.622)
OHS	0.210 (0.491)	0.160 (0.601)	0.333(0.266)	-0.106(0.730)	0.440(0.132)	-0.284(0.347)
MVCOLQ	0.594 (0.025) *	-0.228 (0.433)				
rWOMAC PF	0.553 (0.05)*	0.315 (0.295)	0.533(0.061)	-0.076(0.805)	0.567(0.043)*	-0.149(0.627)
6 months						
TPB PBC	-0.157 (0.609)	0.183 (0.549)	0.290(0.336)	0.357(0.232)	0.244(0.421)	0.297(0.324)
RLOC	-0.562 (0.045) *	0.107 (0.729)	-0.647(0.017)*	-0.413(0.160)	-0.488(0.091)	-0.302(0.315)
MVCOLQ	0.855(0.0001) ***	0.160 (0.585)				
OHS	0.823 (0.001)**	0.579 (0.038)*	0.870(0.0001)***	0.354(0.235)	0.813(0.001)**	0.346(0.246)
rWOMAC PF	0.746 (0.003)**	0.514 (0.072)	0.856(0.0001)***	0.344(0.249)	0.838(0.0001)***	0.243(0.424)
9-12 months						
TPB PBC	-0.141 (0.646)	0.570 (0.042) *	0.240(0.429)	-0.083(0.787)	0.293(0.332)	-0.092(0.765)
RLOC	-0.146 (0.634)	0.296 (0.326)	-0.128(0.678)	-0.336(0.262)	-0.061(0.843)	-0.064(0.835)
MVCOLQ	1	0.445 (0.111)	0.625 (0.017)*	0.377 (0.184)	0.477 (0.085)	0.383 (0.176)
OHS	0.654 (0.015)*	0.450 (0.123)	1	0.501(0.081)	0.936(0.0001)***	0.438(0.135)
rWOMAC PF	0.523 (0.067)	0.506 (0.077)	0.936(0.0001)***	0.327(0.276)	1	0.283(0.348)
6 weeks to preoperative change						
TPB PBC	0.364 (0.222)	0.265 (0.382)	0.342(0.253)	-0.022(0.944)	0.146(0.633)	0.045(0.883)
RLOC	0.343 (0.252)	0.312 (0.299)	0.122(0.691)	0.047(0.880)	0.165(0.591)	-0.047(0.878)

6 month to 6 week change						
TPB PBC	-0.417 (0.156)	-0.421 (0.152)	-0.230(0.449)	0.223(0.463)	-0.098(0.750)	0.146(0.635)
RLOC	-0.467 (0.108)	-0.732 (0.004) **	-0.535(0.059)	-0.118(0.701)	-0.535(0.060)	-0.340(0.255)
9-12 month to 6 month change						
TPB PBC	0.263 (0.385)	0.341 (0.254)	-0.044(0.886)	-0.388(0.190)	0.043(0.890)	-0.344(0.250)
RLOC	0.325 (0.279)	0.176 (0.565)	0.410(0.165)	0.036(0.906)	0.340(0.256)	0.187(0.540)

KEY	#	Controlling for gender, living situation and previous surgery as appropriate	BMI	Body mass index	
	TPB PBC	Theory of planned behaviour perceived behavioural control item	RLOC	Recovery locus of control	
	rWOMAC PF	Reduced version of Western Ontario and McMasters	OHS	Oxford Hip Score	
		University osteoarthritis personal function scale	*p<0.05	**p<0.01	***p<0.001
	MVCOLQ (N)	Maximal voluntary contraction of operated leg quadriceps in newtons (N)			

This indicated that functional recovery appears to be optimal between the 6 week and 6 month intervals. For the OHS, the value at 9-12 months in the regression analysis is mainly dependent on the OHS value at 6 months, with a predictive value of 67.5%. A unit increase in the OHS at 6 months would cause an increase in the final OHS of 0.770.

Table 21. Results of regression analyses for absolute and change scores (at 9-12 months from preoperative values) for the MVCOLQ, OHS and rWOMAC PF.

Dependent Variable	**Independent Variable(s)**	**Beta-coefficient**	**P value**	**R^2**
MVCOLQ (absolute value at 9-12 months)	**MVCOLQ (6 months post-op)**	**0.723**	**0.0001***	**0.615**
rWOMAC PF (absolute value at 9-12 months)	rWOMAC PF (6 weeks post-op)	0.264	0.032*	0.178
	rWOMAC PF (6 months post-op)	0.817	0.0001*	0.673
OHS (absolute value at 9-12 months)	OHS (6 months post-op)	0.770	0.0001*	0.675
MVCOLQ (change from preoperative values at 9-12 months)	RLOC (Change from 6 months to 6 weeks post-op)	-10.274	0.016*	0.235
rWOMAC PF (change from preoperative values at 9-12 months)	rWOMAC PF (Preoperative)	-0.810	0.0001*	0.638
OHS (change from preoperative values at 9-12 months)	OHS (Preoperative)	-0.842	0.0001*	0.637

KEY:	OHS	Oxford Hip Score
	rWOMAC PF	Reduced version of the Western Ontario and McMasters University Osteoarthritis personal function scale
	RLOC	Recovery locus of control score
	*	$p<0.05$
	MVCOLQ	Maximal voluntary contraction of the operated leg quadriceps in newtons (N)

For the change from baseline values of the rWOMAC PF and OHS at 12 months, the most significant predictors were the preoperative values. In the case of rWOMAC PF, a unit change in the preoperative value leads to a reduction in the amount of change or functional gain at 12 months by

0.810, whilst for the OHS, this value is 0.842 in relation to a unit change in its preoperative value. The amount of variance explained for by the regression analyses for both measures is wholly similar (63.8% and 63.7% for change from baseline values at 12 months for rWOMAC PF and OHS respectively).

6.4 Discussion

This study hypothesised that behavioural cognitions, specifically perceived control (derived from social learning theory and the theory of planned behaviour) would influence functional outcome in patients undertaking a home-based PRT regime as opposed to standard rehabilitation after THR. Contrary to this hypothesis the perceived control items used (RLOC, TPB PBC) were not found to be predictive of absolute objective or subjective functional recovery in this group of patients after controlling for the effects of gender, previous surgical experience and the presence of social support, although a bivariate association between 6 month RLOC and OHS was found. The change in RLOC from 6 weeks to 6 months was found to negatively predict the improvement in MVCOLQ at 9-12 months, with a unit improvement causing a reduction in MVCOLQ improvement from preoperative values by 10.27N. This suggests that this time period may not be optimal for improvement in objective function via modulating behavioural cognitions. These results are exploratory, however, due to the small population size assessed.

There was a significant correlation found between the objective (MVCOLQ) and subjective measures (OHS and rWOMAC PF) of function assessed in this analysis but these relationships proved not to be predictive in the regression models. This contrasts with recent literature which suggests that greater preoperative knee extensor strength of the operated site is associated with better physical function, measured by using the Western Ontario and McMaster Universities Osteoarthritis Index, subscale physical function (WOMAC PF) at 12 weeks postoperatively (Holstege, Lindeboom et al 2011). The review time point for this current study is later and the impact of greater extensor strength may be relevant only in the early post-operative period. Previous studies have demonstrated a significant role for perceived behavioural control, as assessed by the SF36, in explaining variance in the performance of a walking task (9%), and self reported physical activity (24%) in patients with chronic idiopathic axonal polyneuropathy (Schroder, Johnston et al. 2007). Similar effects have also been demonstrated

in patients with stroke, with perceived control predicting recovery from disability (Johnston, Pollard et al. 2004). Stroke survivors and their caregivers have been shown not to have adequate time to deal with the shock and crisis of the acute onset stroke event, let alone the crisis of discharge from the hospital setting (Lutz, Young et al. 2011), and thus it may be that perceived control beliefs take on added importance in such situations (Johnston, Morrison et al. 1999). Patients undergoing THR on the other hand report that their preoperative expectations for the outcome of their surgery had been fulfilled after review at 4 years post-operatively, with specific expectations ranging from being able to cut their toenails (63% fulfilled), or participate in sports and recreational activities (92% fulfilled) (Mancuso, Jout et al. 2009).

This study demonstrated that the most important predictors of the rWOMAC PF at 9-12 months were the pre-existing scores, with the amount of variance explained increasing through the period of follow up i.e. as the independent variables get closer to the dependent variables in terms of assessment time point (8.8% preoperatively to 67.3% at 6 months postoperatively). At 9-12 months, the degree of functional gain as assessed by the change in the rWOMAC PF from preoperative values is also significantly affected by the preoperative value (63.8% of the variance explained in the regression model). These findings are consistent with the existing literature, with a combination of the preoperative WOMAC function score, gender and the presence of co morbidities predicting 25.3% of variance in the WOMAC function score at 9-12 month follow up (Wang, Morrison et al. 2010). Age was not entered in the regression model in our study as it was not shown to correlate with either the absolute or change scores from preoperative values for rWOMAC PF. The presence of co-morbidities was also not assessed, as the primary investigation was to determine the role of behavioural cognitions. Patient expectations, however, have previously been shown to be predictive of the amount of improvement assessed by the WOMAC at 12 months post-THR with the achievement of each individual patient expectation (ranging from wanting to be able to cut toenails and improved psychological well being, to the being able to participate in recreational or social activities) associated with a 34% increase in the probability of improvement (especially in the stiffness and function domains) (Judge, Arden et al. 2011). Patients' fulfilment of pre-surgical expectations is highly correlated with the amount of satisfaction from THR (Mancuso, Salvati et al. 1997). However,

satisfaction is a global concept that is influenced by multiple factors, including personality and perceived quality of care (Mancuso, Jout et al. 2009). These factors may have more of a role to play in this population than behavioural cognitions such as perceived control assessed using the RLOC and TPB PBC.

The regression analysis for the absolute OHS at 9-12 months shows that the 6 month value predicts 62.3% of the variance, with no further significant effect for the perceived control item (RLOC, p=0.754) at the same follow up interval. The change from preoperative values for the OHS at 9-12 months was influenced mainly by the preoperative values of the same score (63.7% of the variance explained) with no other independent variables showing an effect. To the author's knowledge, no previous regression analyses have been published demonstrating this relationship. Studies have tended to focus on the predictive value of the OHS in terms of patient satisfaction (no relationship demonstrated between preoperative OHS and patient satisfaction at 6 months postoperatively (Judge, Arden et al. 2011), the risk of revision surgery (a point decrease in OHS at 6 months predicts a revision risk of 9.7% at 2 years (Rothwell, Hooper et al. 2010), and quality of life using the EQ-5D instrument (Pinedo-Villanueva, Turner et al. 2012).

6.5 Chapter summary

In summary, behavioural cognitions had no impact on absolute objective or subjective functional outcome in this population when multivariate analyses using previous levels of function were performed. However, some bivariate associations (significant and with a trend towards significance ($p < 0.1 > 0.05$) suggest that similar questions should be asked amongst larger samples. Exploratory analysis revealed that change in RLOC from 6 weeks to 6 months predicts the improvement in MVCOLQ at 9-12 months post-operatively, withsubjective function (OHS and rWOMAC PF) at 9-12 months post-operatively, as well as the level of functional gain, influenced mainly by the pre-existing functional status of the patient Having an idea of the cost implications of improving a patients' functional status in the early post-operative period with the home-based PRT regime performed in Chapter 2 is important in the current climate of financial prudence that exists in the NHS. With this is mind, an exploratory cost consequences analysis exercise is described in Chapter 7.

CHAPTER 7: Home based progressive resistance training in the early postoperative period in patients after total hip replacement: a cost consequences analysis.

7.1 Introduction

Considering the volume of elective NHS care, and the sizable budget of orthopaedic surgery in the UK (patterns reflected internationally), there are very few cost-effectiveness studies of orthopaedic interventions. The cost-effectiveness of some joint replacement procedures have been estimated (Sigurdsson, Siggeirsdottir et al. 2008), and there have been some studies of the economics of waiting list management (Edwards, Boland et al. 2003, Edwards 1996, Edwards 1999). Measurement of outcome in orthopaedics for economic evaluation can be through the measurement of physical functioning e.g. changes in joint flexibility and muscle strength, or by how the patient is generally feeling in terms of self-reported health related quality of life (Ahmad, Xypnitos et al. 2011). The National Institute of Health and Clinical Excellence (NICE) in the UK recommend the Euroqol (5 dimensions) quality of life questionnaire (EQ-5D) is used for this kind of analysis (National Institute for Health and Clinical Excellence (NICE) June 2008).

At 24 months following total joint arthroplasty, patients with low pre-operative function are five times more likely to require assistance from another person for their activities of daily living compared to those with high preoperative function (relative risk 5.2, 95% CI 1.9-14.6; (Fortin, Penrod et al. 2002)). The average yearly cost for an older or disabled person in the UK who pays for ten hours of home care a week is now £7,015 a year, a 6% increase over the last two years (Walker 2011).

Early discharge and home intervention after total hip replacement has been shown to lead to a 28% cost reduction when compared to 'conventional' rehabilitation augmented by a stay at a rehabilitation centre if needed (average total cost for early discharge and home intervention group $8,550 vs. $11,952 for 'conventional' rehabilitation) (Sigurdsson, Siggeirsdottir et al. 2008). Targeted home-based early rehabilitation after THR has also been shown to save on costs, when the reduction in length of hospital stay is included in the analysis (Iyengar, Nadkarni et al. 2007). Home-based rehabilitation programs that include resistance exercises have also been shown to be effective in improving function post-THR, although the follow up period in the two available randomised studies

in the literature did not extend beyond the time frame of the prescribed exercise interventions (8 and 12 weeks, respectively- Jan, Hung et al. 2004;Trudelle-Jackson, Smith 2004). In response to this lack of published evidence, an assessment of the cost of the home-based, progressive resistance training (PRT) exercise intervention regime, delivered with minimal one to one supervision by local physiotherapists during the early post-operative phase following THR, relative to home-based standard physiotherapy rehabilitation (SR; control).

The aims of this study were (1) to explore the cost consequences of implementing home-based PRT as opposed to SR after THR, and (2) to perform a sensitivity analysis based on the use of other healthcare professionals other than physiotherapists for administering home-based PRT.

7.2 Methods

7.2.1 Study setting and population:

This economic evaluation took place alongside a randomised controlled trial comparing a 6 week home-based PRT regime to SR (control) after THR. The trial was conducted in 35 THR patients' homes in North Wales. Ethical committee approval, eligibility criteria, as well as details of the randomisation method are specified in section 2.2, with the CONSORT flowchart depicted in Figure 1.

7.2.2 Measurement of costs of the home-based PRT regime:

Recurrent costs of the home-based PRT regime data was collected by means of cost diaries from participating physiotherapists during the 6 week PRT intervention. Four participating physiotherapists each completed a weekly cost diary. The cost diaries included an assessment of travel (mileage, duration), duration of home visits (hours), and phone consultation time with patients (hours). The non-recurrent costs were composed of the total mileage used by the trainer (primary investigator, TO) in commuting to the local centres, as well as the trainer's travel duration and phone consultation time (both in hours) for providing training and consultation to the participating physiotherapists in the study.

We took an annuitization approach in the calculation of the non-recurrent costs (training costs) as training was taken as a one-off investment. An attempt was made not to overestimate the assessed years' costs and also to avoid underestimating the cost of future years. Annuitization therefore, for

the non-recurrent costs over a 5 year period with a discount rate of 3.5% (NICE, 2008), was calculated as shown in Box 1 below:

Box 1. Annuitization calculation

$$C = \left[P - S * \frac{1}{(1+r)^t}\right] * (AF)^{-1}$$

where AF= $\left[1 - \frac{1}{(1+r)^t}\right] r^{-1}$

C = calculated equivalent annual cost of the unit
P = cost of purchasing the unit
S = scrap value of the unit after t years of service = 0
r = discount rate = 3.5%
AF= annuity factor
t = time factor = 5 years

7.2.3 Measurement of costs for trial participants:

For the purposes of consistency in the cost consequences analysis, all data obtained for the outcome measures assessed at 9-12 months were taken to be at 1 year follow up. A self-administered Client Service Receipt Inventory (CSRI; Beecham & Knapp, 1992) was administered to study participants at the final follow up to determine the type and frequency of participants' contacts with healthcare services within the preceding 12 months. A total of 20 patients completed the CSRI questionnaires (n=11 home-based PRT group, n=9 SR (control) group), giving a response rate of 76.9% (20/26). National costs from published sources (Curtis L 2011, NHS National Schedule of Reference Costs Year: 2010-11, 2011) were applied to costing the healthcare resource use reported by study participants. All costs are in pounds sterling (£), were measured from an NHS perspective, and were not discounted if they fell within a one year time horizon.

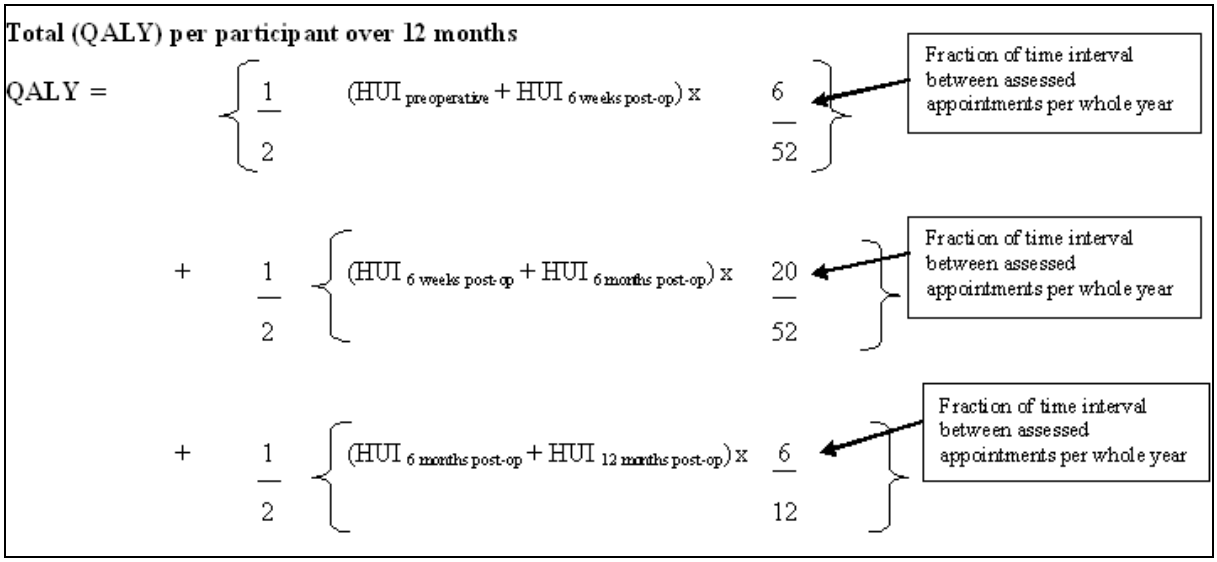
7.2.4 Measurement of Outcome:

The assessment of gain in muscle function (maximal voluntary contraction of the operated leg quadriceps muscle (MVCOLQ) measured in Newtons (N)) was used as the primary outcome measure

for this study (see section 2.2.1 for full description). The MVCOLQ was assessed preoperatively and at intervals up to 12 months postoperatively (6 weeks, 6 months, and 9-12 months).

Quality-adjusted life year (QALY) was the secondary outcome measure for the economic analysis. NICE (National Institute for Health and Clinical Excellence (NICE) June 2008) recommends and supports the use of QALY as the measure of health effects for economic analysis, and it is regularly used to quantify the net health benefits from health care interventions, and to allow cost comparisons of different interventions (Drummond, Sculpher et al. 2005, Morris, Devlin et al. 2007). QALY is calculated by weighting a person's length of life by a valuation of their self-reported health-related quality of life (HRQoL) over that period (Glick, Doshi et al. 2007). Participants' HRQoL was assessed using the EQ-5D questionnaire, a validated generic preference-based measure that measures health gain (EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. 1990). The EQ-5D questionnaire comprises the following 5 dimensions: mobility, self care, usual activities, pain or discomfort, and anxiety or depression. Each of the 5 dimensions is divided into three levels of severity: 'no problems', 'moderate problems', and 'severe problems'. In all, the EQ-5D captures a total of 243 different health states (Kind, Hardman et al. 1999; Dolan 1997)). The reported HRQoL states were converted into single health utility index (HUI) scores using the most common tariff, the UK time trade-off values (Kind, Hardman et al. 1999), with scores ranging from -0.594 ('state worse than death') and 1 ('best possible health state') (Kind, Hardman et al. 1999; Dolan 1997; Ahmad, Xypnitos et al. 2011). A value of zero indicates a state 'equivalent to death' and values less than zero are classified as states 'worse than death' (Dolan 1997). For this study, the EQ-5D data were collected from patients at four time points over the 12 month study period i.e. preoperatively (baseline), and postoperatively at 6 weeks, 6 months and 12 months. Box 3 illustrates the calculation of the total QALYs per participant over the 12 month study period.

Box 2. The calculation of total Quality Adjusted Life Years (QALYs) using the EQ-5D health utility index (HUI) per participant for the four time points (preoperative, 6 week post op, 6 month post-op and 12 month post-op) over the 12 month study period.



7.2.5 Sensitivity analysis

This was performed in order to test whether changes in the key variables will change the results obtained from the base case analysis (James, Stokes et al. 2005). In the base case analysis, the physiotherapists were responsible for administering the home-based PRT intervention. The sensitivity analysis was performed based on the assumption that other healthcare professionals could be trained to administer the home-based PRT intervention. The unit costs were therefore collated for the GP practice nurse, district nurse, health visitor and members of the re-ablement services from published UK sources (Curtis L 2011) in order to re-calculate the recurrent costs, and thus the intervention cost. Re-ablement services are provided by adult social care services in the UK as part of their range of home-care provision, and are typically short-term interventions that aim to maximise independent living skills (Curtis L 2011). It was assumed that these professionals could be trained and be able to deliver the home-based PRT regime in the same way as the physiotherapists for the base case analysis who completed and returned their cost diaries.

7.2.6 Analysis strategy

Uncertainty around the cost estimates for primary and secondary care as well as the grand total costs was tackled with 1000 replication bootstrapping to provide a bootstrapped 95% confidence interval

(Fenwick, Marshall et al. 2006). The costs and outcomes data was collated and analysed using SPSS version 18(SPSS for Windows v18, Rel. 30.07.2009. Chicago, SPSS Inc). Computation of the 1000 replication bootstrap was carried out using Microsoft Office EXCEL 2007.

7.3 Results

7.3.1 Demographic characteristics, MVCOLQ and EQ-5D HUI values of the study participants

The sample for the economic analysis is smaller than for the clinical trial as there was incomplete data on costs and effects for two participants in the intervention group and four in the control group at 12 month follow up. Full economic data was available for, and analysed from, 11 patients in the home-based PRT group and 9 in the SR (control) group. Table 22 describes the demographic characteristics of the study participants, with preoperative MVCOLQ (Newtons (N)) and EQ-5D HUI values. Independent samples t-tests found no significant differences between the home-based PRT and SR (control) groups in terms of age, MVCOLQ and EQ-5D HUI values at baseline.

Table 22. Pre-operative (baseline) demographic characteristics, MVCOLQ and EQ-5D Health Utility Index (HUI) values of total hip replacement (THR) patients randomized to 6 weeks of either home-based progressive resistance training (PRT) or standard rehabilitation (control).

Characteristic	**Home-based PRT group** (n=11)	**Standard rehabilitation SR (control) group** (n=9)
Age in years ; mean (SD); range*	64.27 (8.59); 45-77	62.55 (11.95); 37-78
Gender Females Males	 n=5 n=6	 n=5 n=4
MVCOLQ in Newtons (N), mean (SD) range #*	193.1 (103.3); 42-372	184.3 (62.9); 86-254
EQ-5D HUI *#	0.531(0.241); -0.016 - 0.727	0.386 (0.301); -0.016 - 0.691

KEY:

*	No statistically significant differences between intervention and control groups.
#	Data normally distributed: Shapiro-Wilk test p >0.05.
PRT	Progressive resistance training
MVCOLQ	Maximal voluntary contraction of operated leg quadriceps

Outcome measures

The clinical effectiveness findings were based on the sample used for economic analysis (n=20). In the main study (Chapter 2), with all trial participants who completed 9-12 month follow up included;

there was no statistically significant effect of treatment (home-based PRT or SR (control) on MVCOLQ (Table 23).

The mean QALY for the SR group at 12 months was 0.7901(SD 0.1285) and 0.8643 (SD 0.1172) for the home-based PRT group. This represented a QALY gain of 0.0742 for participants in the home-based PRT group (bootstrapped 95% CI: -0.0343, 0.1778; Table 23).

Table 23. The findings of outcome measures for economic analysis of patients undergoing a trial of home-based progressive resistance training (PRT) or standard rehabilitation after total hip replacement over a 12 month period.

	Home-based PRT group n=11	Standard rehabilitation SR (control) group (n=9)	Intervention minus Control (Bootstrapped 95% CI)
Mean MVCOLQ change from baseline; Mean (SD)	59.82 (102.04)	46.11 (68.80)	13.71 (-54.64,83.83)
Mean QALY gained; Mean (SD)	0.8643 (0.1172)	0.7901 (0.1285)	0.0742 (-0.0343, 0.1778)

KEY:

MVCOLQ	Maximal voluntary contraction of the operated leg quadriceps in Newtons (N)
QALY	Quality-adjusted life year
PRT	Progressive resistance training
SR	Standard rehabilitation

7.3.2 Home-based PRT programme costs

Table 24 summarises the reported annuitized non-recurrent (implementing) and recurrent (running) costs based on the weekly cost diaries completed and returned by four physiotherapists. The annuitized non-recurrent costs include travel and consultation costs of the trainer; whereas the recurrent costs consist of the running costs reported by the four physiotherapists. The mileage costs assume a figure of 45 pence per mile and an average driving speed in the North Wales area of up to 60 miles per hour (this is as some returned diaries only included travel time not distances covered). The non-recurrent costs by the trainer (TO) do not take account of the number of hours spent exploring the literature or preparing the training sessions. From the diaries returned by the four physiotherapists, the total recurrent cost was £1224.80. Thus, the mean recurrent cost per physiotherapist per patient for a 6 week duration was £306.20 (i.e. a total cost of £3980.60 for 13 patients). Adding the total cost of

£3680.60 to the annuitized non-recurrent costs, the total cost for administering the home-based PRT programme for 13 patients was £4081.31. This meant that the 6 week home-based PRT programme cost £313.95 per patient for having a one-to-one supervision at his/her home by a trained NHS physiotherapist over a 6 week duration following their THR surgery.

Annuitization for the non-recurrent costs, C, was calculated as below:

$$C = \left[P - S * \frac{1}{(1+r)^t}\right] * (AF)^{-1}$$

where AF= $\left[1 - \frac{1}{(1+r)^t}\right] r^{-1}$

C= calculated equivalent annual cost of the unit
P= cost of purchasing the unit = £ 454.75
S= scrap value of the unit after t years of service = 0
r= discount rate = 3.5 %
AF= annuity factor
t= time factor = 5 years

$$C = \left(454.75 - 0 \times \frac{1}{(1+3.5)^5}\right) \times \left(1 - \frac{1}{(1+3.5)^5} \times (3.5)^{-1}\right)^{-1}$$

C = £100.72.

Table 24. Total costs and cost per patient for implementation of the home-based progressive resistance training (PRT) programme (6 week duration)

Items	Unit Costs(£)	Number of units	Total Cost (£)
Non-recurrent costs (Training costs)			
Mileage (miles)	0.45	240.00	108.00
Travel time for trainer (hours)	73.00	4.00	292.00
Phone consultation time with trainer (hours)	73.00	0.75	54.75
Non-recurrent costs (Training costs)			454.75
SUBTOTAL Non-recurrent costs annuitized over a 5-year period			**100.72 (a)**
Recurrent costs(Physiotherapists' costs)			
Mileage (miles)	0.45	678	305.10
Travel time for physiotherapists to patients' home (hours)	34.00	11.30	384.20
Phone consultation time with patients (hours)	34.00	1.50	51.00
Physiotherapists' (n=4) home visit duration (hours)	34.00	14.25	484.50
SUBTOTAL Recurrent Costs (Physiotherapists' costs)			**1224.80(b)**
Cost of administering home-based PRT for 4 patients over 6 weeks excluding non-recurrent costs			1224.80
Cost per patient = (b)/4			306.20
Total physiotherapists' costs for 13 patients			**3980.60 (c)**
Total cost of establishing and running home-based PRT for 6 week period for 13 patients = **(a)** + **(c)**			**4081.31**
Mean cost per patient for home-based PRT			**313.95**

7.3.3 Health service use by trial participants

Table 25 summarises the results of the service use of contacts with primary and secondary care services by the study participants over the 12 month period. There was a trend to statistical significance for increased contact with the nurse at the GP surgery for the SR (control) group as opposed to the home-based PRT group (1.55 (0,5) vs. 0.27 (0,3); p=0.095). No statistically significant difference was found in the frequency of contacts with other healthcare services between the groups. Table 26 shows the mean costs for contacts with healthcare services over the 12 months following THR. Before taking the intervention costs into account, the home-based PRT group saves £274 in the total primary care and secondary care costs compared to the SR (control) group. When the

intervention costs were taken into account, the home-based PRT group costs £33 more than the SR (control) group.

Table 25. Frequency of contacts with healthcare services by post-operative total hip replacement patients over a 12 month period

Healthcare service	**Home-based progressive resistance training (PRT) group (n=11)** Mean, median (min, max)	**Standard rehabilitation SR (control) group (n=9)** Mean, median (min, max)	**Mann-Whitney Test** (P value)
Primary care			
GP surgery	0.73, 0.00 (0,5)	2.44, 0.00 (0,14)	0.412
GP home visit	0.00, 0.00 (0,0)	0.00, 0.00 (0,0)	1.000
GP out of hours	0.00, 0.00 (0,0)	0.11, 0.00 (0,1)	0.710
Nurse surgery	0.27, 0.00 (0,3)	1.55, 1.00 (0,5)	0.095
Nurse home	0.90, 0.00 (0,3)	0.55, 0.00 (0,2)	0.824
Health visitor	0.18, 0.00 (0,2)	0.11, 0.00 (0,1)	1.000
Occupational therapy	0.09, 0.00 (0,1)	0.00, 0.00 (0,0)	0.766
Physiotherapist	4.90, 6.00 (0,8)	8.33, 2.00 (0,48)	0.261
Secondary care			
Outpatient visit	1.36, 2.00 (0,2)	1.88, 2.00 (0,5)	0.552
Outpatient visit via Ambulance	0.00, 0.00 (0,0)	0.00, 0.00 (0,0)	1.000
Inpatient admission	0.00, 0.00 (0,0)	0.00, 0.00 (0,0)	1.000
A&E visit	0.07, 0.00 (0,0)	0.00, 0.00 (0,0)	0.781
A&E visit via Ambulance	0.00, 0.00 (0,0)	0.00, 0.00 (0,0)	1.000
Other	0.00, 0.00 (0,0)	0.00, 0.00 (0,0)	1.000

Table 26. Mean costs of contacts with healthcare services by post-operative total hip replacement patients (£) over a 12 month period

Type of cost	Home-based progressive resistance training (PRT) group (n=11); mean (SD)	Standard rehabilitation SR (control) group (n=9); mean (SD)	Mean difference, Home-based PRT minus Control (95% CI bootstrapped)
Primary care			
Exercise kit	16 (10)	0 (0)	16
GP surgery	26 (56)	76 (165)	-50
GP home visit	0 (0)	0 (0)	0
GP out of hours	0 (0)	13 (40)	-10
GP total cost	26 (56)	89 (205)	-63
Nurse surgery	16 (54)	93 (124)	-38
Nurse home	66 (95)	41 (53)	25
Nurse total cost	83 (132)	134 (136)	-51
Health visitor	13 (44)	8 (24)	5
Occupational therapist	8 (25)	0 (0)	8
Physiotherapist	167 (85)	283 (539)	-116
Primary care cost	**305 (186)**	**515 (489)**	**-210 (-562,96)**
Secondary care			
Outpatient visit	166 (99)	230 (177)	-64
Outpatient visit via Ambulance	0 (0)	0 (0)	0
Inpatient admission	0 (0)	0 (0)	0
A&E visit	0 (0)	0 (0)	0
A&E visit ambulance	0 (0)	0 (0)	0
Other	0 (0)	0 (0)	0
Secondary care cost	**166(99)**	**230(177)**	**-64 (-192,51)**
Total Primary and Secondary Care costs (m)	**471(255)**	**745(506)**	**-274 (-619,58)**
Home-based PRT cost (n)	**307(0)**	**0(0)**	**307**
Grand total costs (m) + (n)	**778 (254)**	**745 (506)**	**33 (-318, 366)**

7.3.4 Sensitivity analysis results

The base case analysis revealed a mean cost of £313.95 per patient for the 6 week home-based PRT programme, administered by a qualified physiotherapist. Table 27 shows the results of the analysis assessing the cost per patient from an NHS perspective, if other healthcare professionals are trained to administer the same regime. This was performed based on the assumption that the other health professionals identified would be utilised in the same way for calculation of their recurrent costs. There is an increased cost if the GP practice nurse, district nurse, or health visitor are trained and subsequently used to implement the home-based PRT programme. If the re-ablement services are utilised instead, there is a reduction in costs of £81.16 compared to using a qualified physiotherapist.

Table 27. Sensitivity analysis for alternative healthcare professionals administering the 6 week home-based progressive resistance training (PRT) programme in patients after total hip replacement surgery

Health care professional	**Cost per unit (£)**	**Annuitized non-recurrent costs (a), £**	***Recurrent costs for 13 patients (b) , £**	**Total cost (a)+(b), £**	**Mean cost per patient for 6 week home-based PRT, £**	**Cost difference (Alternative minus base case), £**
Physiotherapist (base case analysis)	34	100.72	3980.60	4081.32	**313.95**	-
Alternatives						
GP Practice nurse	60	100.72	6266.33	6367.05	489.77	175.82
District nurse	73	100.72	7409.19	7509.91	577.69	263.74
Health visitor	73	100.72	7409.19	7509.91	577.69	263.74
Re-ablement services	22	100.72	2925.65	3026.37	232.79	-81.16

KEY:

* Assumption made that Healthcare professionals are utilised in same way in calculation of intervention costs as base case analysis; see Table 24.

7.4 Discussion

The total cost per patient for physiotherapists to implement the 6 week home-based PRT programme was £313.95. From an NHS perspective, sensitivity analysis revealed that the use of re-ablement services would lead to a mean cost-reduction of £81.16, meaning that it would be a lower cost in comparison to other healthcare professionals potentially capable of performing the same task. Thus policy makers should consider such services as a viable alternative to administration of home-based exercise regimes in the context of functional improvement post-THR, assuming a similar effect is obtained.

Though there was no statistically significant difference in frequency of contacts with healthcare services between groups, patients in the home-based PRT group had, on average, lower frequency of healthcare service contacts than patients in the SR (control) group. It is interesting to speculate that perhaps the increased initial contact may have led to less utilisation of healthcare services as many initial queries regarding the recovery process may have been addressed by having weekly physiotherapy contact. A single participant in the SR (control) group may have skewed these results; however, as she documented on the CSRI that she had had thrice weekly contact with a physiotherapist for 16 weeks from the date of her operation. There was also a trend to significance ($p=0.095$) for increased contact with the nurse at the GP surgery for the SR (control) group. Increased contact with nursing staff is frequent in weeks 1 and 2 postoperatively (McMurray, Grant et al. 2002), most probably indicating patients' need for further information or assistance regarding for example, surgical wound management, or swollen limbs. Patients in the home-based PRT group would have had access to weekly physiotherapy input and would have therefore been able to have these issues addressed expeditiously.

The results of the full randomised trial showed no statistically significant difference between the early home-based PRT regime and SR (control) groups at 9-12 months but patients in the home-based PRT group gained 13.71 more Newtons in MVCOLQ (bootstrapped 95% CI: -55.64, 83.83) and cost £33 more per patient (bootstrapped 95% CI : -£318, £366). This implies that the home-based PRT regime was equally effective but not cost-saving when compared to standard rehabilitation in the 12

months following THR. The PRT regime, however, fails to provide marginal functional gain for the patients recruited and the inference is that centre-based regimes utilised in the early period after surgery may be the only way to provide functional gain over and above that seen in this trial.

The home-based PRT group showed the same level of functional gain as the SR group, indicating that there was no detriment to its implementation. A comparator group that does not receive any standard rehabilitation at all would have been ideal for the purpose of analysis but due to the variability that exists in care in the UK, and also locally, some patients would have had no contact with physiotherapy whilst others would have had increased contact. This is a very pragmatic study representing halfway between the ranges of rehabilitation packages offered.

The mean EQ-5D HUI for all 20 patients recruited to this study was 0.458 which is significantly less than that for a cohort of age and sex matched individuals in the UK (~0.79; Kind, Hardman et al. 1999). At 12 months, there was an improvement in EQ-5D HUI up to an average of ~0.87 which is 10% better than age and sex matched individuals in the UK. The improvements obtained in EQ-5D HUI compare favourably with previously published data from the Swedish Arthoplasty Registry in which mean preoperative EQ-5D HUI was 0.49 and mean 12 month EQ-5D HUI was 0.80 (Jansson, Granath 2011). However, it needs to be recognised that the present study cohort was self selected, in that eligible participants were willing to participate in the randomised trial.

Health economic analyses of rehabilitation interventions after THR have previously reported that accelerated centre-based rehabilitation has a cost-saving effect over standard rehabilitation. Significant QALY (EQ-5D) gain (p=0.006) and reduced costs of ~£2580 over a year of follow up have also been noted in a Danish study (Larsen, Hansen et al. 2009). Functional gain (measured with the McMaster Toronto Arthritis (MACTAR) patient preference disability questionnaire) significantly improved at 1 year follow up with reduced total costs of ~£575 in a study from Holland (Bulthuis, Mohammad et al. 2008). There is a paucity of studies, however, focusing on the cost consequences of home-based resistance training regimes in comparison to standard rehabilitation. To the authors' knowledge, this is the first study that attempts to quantify the costs associated with provision and utilisation of healthcare resources after such a regime.

Although when home-based standard rehabilitation regimes were compared with centre based regimes in a study performed in Canada, the former were found to cost ~£2650 less ($p<0.001$) (Mahomed, Davis et al. 2008). Mahomed et al. (2008) also noted that there is a need to ensure that appropriate home-care rehabilitation strategies are in place to maintain quality of care whilst containing costs (Mahomed, Davis et al. 2008).

7.5 Chapter summary

In conclusion, home based PRT does not provide additional significant functional gain (MVCOLQ or QALY) nor is it cost-saving (£33 more expensive per patient (bootstrapped CI -£318, £366)) when compared to standard rehabilitation after THR. From an NHS perspective, alternative healthcare professionals working in re-ablement services are a cost-saving alternative to physiotherapists in implementing the home based PRT regime, only if they achieve a comparable level of effectiveness.

CHAPTER 8: Summary and conclusions

8.1 Thesis findings

At the time the studies that underpin this thesis were conceived, there was no existing literature on the effects of early home based PRT on muscle strength and objective function post-THR (see section 1.7). Therefore, the pilot randomised trial performed (Chapter 2) aimed to address this gap. In comparing a 6 week home-based PRT program (with weekly physiotherapy supervision) in the early postoperative period after THR against standard rehabilitation (control), it was hypothesised that there would be improvements in the primary outcome measure, MVCOLQ. Exploratory analyses were also performed on objective measures of physical function that reflect the ability to perform ADLs: ST, GS, TUG, 6MWT and SCP, as well as an increase in lean mass of the operated leg. However, in this study, there was no observed benefit of the home-based PRT relative to SR (control) in terms of the primary outcome measure assessed, i.e. MVCOLQ. Contrary to expectations, from the exploratory analyses, significant improvements in three of the secondary outcomes assessed; GS (estimated effect 0.185m/s; p0.009), SCP (estimated effect -5.665s, p=0.038), and 6MWT (estimated effect 86.393m, p=0.004) were observed for the SR group at 9-12 month follow up relative to the PRT group. Except for the lean mass of the operated leg, , there were significant improvements in the primary outcome and secondary outcomes for both groups up to 9-12 months post- THR. Overall, the early home-based PRT was found to be deliverable, safe, and well tolerated (high compliance rate in patients who returned training diaries, see Table 6) but not successful in providing functional gain beyond that achievable by standard rehabilitation in patients undergoing THR. The results are to be interpreted with caution however as there was a loss to follow up of 30% for patients enrolled at the start of the study. The findings of the study however, were comparable to the findings of a very recently published trial (published after this study had commenced) of an early home based resistance training regime after THR in which the exercise intervention programme lasted 12 weeks and no differences were noted between the intervention and control groups at the end of the follow up period (Mikkelsen, Mikkelsen et al. 2012).

Standard rehabilitation post-THR is noted to be variable in the existing literature, being typically home-based on discharge and depending on local custom, healthcare system, and preferences of the patient (Bulthuis, Mohammad et al. 2008). These inherent variations in standard rehabilitation practice led to the investigations performed in Chapter 3, where, for the first time, an attempt was made to quantify standard rehabilitation practice in the UK post-THR. Questionnaire item development about standard rehabilitation practice was guided by an initial focus group interview with 4 practising physiotherapists from a variety of backgrounds (all >5 years experience; 2 community based, 1 hospital based, and 1 outpatient based). The resultant online questionnaire was then sent via email to physiotherapists working in the UK. 106 responses were obtained from a total of 130 physiotherapists' contacted (81.5% response rate). From these responses it was found that the most important muscles to target in all phases of rehabilitation were considered to be the hip abductors (62.2%), followed by the quadriceps (16.9%), and other muscles (21%). There was no consensus with regard to exercise type prescribed, with weight bearing (42%), functional (45%) and bed-based/bridging/postural exercises (13%) favoured; and whilst 83.7% of the respondents were able to define the basis of progressive resistance training (PRT), only 33% prescribed it. Thus the study concluded that standard rehabilitation in the UK after THR is variable, and usually does not feature PRT. The omission of this training method, delivered at an appropriate intensity, could be a contributing factor to the prolonged poor function generally seen in post-THR patients.

Significant muscle wasting exists in the muscles about the hip in patients with hip OA, and this muscle loss typically persists for at least 2 years following surgery (Rasch, Bystrom et al. 2009). As there was no additional benefit on a macroscopic level in favour of participating in the home-based PRT programme (no difference in MVCOLQ, Chapter 2), an attempt was made to assess the cellular metabolic changes that occur in the quadriceps muscle of the operated leg. The impact of joint replacement and rehabilitation on end-stage hip OA patients at a molecular level was investigated by, assessing mRNA expression using the reverse-transcriptase polymerase chain reaction (RT-PCR) from *vastus lateralis* (VL) muscle biopsy samples obtained intraoperatively and at intervals up to 9-12 months post-THR. The gene panel for RT-PCR was chosen on the basis of anticipated muscle hypertrophy, atrophy, lipid metabolism and inflammation responses. It was hypothesised that there

would be no effect of biopsy site (proximal versus distal) on gene expression of the VL muscle in patients at the time of THR surgery, and that patients undergoing early home-based PRT would demonstrate increases in genetic markers of hypertrophy and lipid metabolism, and attenuation of genetic markers of inflammation and atrophy relative to standard rehabilitation (control) patients. The results of the former analyses performed showed that hip joint inflammation appeared to have no statistically significant effect on gene expression in the VL intraoperatively (section 4.3.1), suggesting that for these sorts of analyses, single site muscle sampling is appropriate subsequent analyses of training effects. In terms of the latter hypothesis, muscle inflammation in the VL of the operated leg at the 6 week time point was reduced. Despite increases in markers of hypertrophy, these did not reach significance. Significant reductions in markers of lipid metabolism were found and this perhaps warrants further investigation, with regards to metabolic efficiency in this group of patients. Participation in the home-based PRT regime did not demonstrate an objective difference in mRNA expression of the genetic panel chosen, confirming at a cellular level, the lack of a significant difference in the objective outcome measures assessed in Chapter 2 (see section 4.3.2).

Many factors can impact on a patients' ability to participate wholly in an exercise program (section 1.8) including their age, gender, psychological well being and coping behaviour. Chapters 5 and 6 describe studies performed in order to investigate the effects of psychological distress and behavioural cognitions (issues that can affect patient motivation to engage in an exercise programme) on subjective functional outcome of patients undergoing THR. Chapter 5 used the DRAM (distress and risk assessment method) to assess the impact of psychological distress on the primary outcome measure for the main study (MVCOLQ) as well as two commonly utilised subjective measures of physical function: the Oxford Hip Score (OHS) and a reduced version of the Western Ontario and McMasters University Osteoarthritis personal function scale (rWOMAC PF) at 9-12 month follow up The DRAM measure was shown not to have any effect on MVCOLQ even after controlling again for randomisation into the home-based PRT or SR (control) groups. The DRAM stratification ('normal' or 'at risk/distressed') was however, found to be predictive of subjective functional outcome. Patients who were 'at risk/distressed' had persistently lower OHS and rWOMAC PF scores (statistically significant differences) than the 'normal' patients preoperatively and at all postoperative review time

points (section 5.3). This investigation was the first in the literature to use the DRAM tool in patients undergoing THR (it is typically administered to patients undergoing spinal surgery) and its use should perhaps be advocated routinely in the screening of patients for psychological distress. The issues that remain to be resolved, however, are what intervention preoperatively is most appropriate for patients identified as 'at risk/distressed'? And what member of the healthcare team would be most appropriate to deliver them?

Chapter 6 reports that behavioural cognitions (Recovery Locus of Control, RLOC; Theory of Planned Behaviour Perceived Behavioural Control (TPB PBC)) did not show any impact on MVCOLQ, OHS nor rWOMAC PF in this population (again with comparison of the home-based PRT and SR (control) groups). The regression analysis preformed revealed a negative predictive relationship between improvement in a measure of behaviour cognition (RLOC) between 6 weeks and 6 months and improvement in the MVCOLQ at 9-12 months from preoperative values. It also showed that subjectively assessed function at 9-12 months (OHS, rWOMAC PF), as well as the levels of functional gain over time, were best explained by the patients' baseline functional status (section 6.3). Consistent with all our other results, there was no apparent benefit in taking part in home-based PRT in terms of RLOC or TPB PBC, and perhaps in this population the operation (THR) as well as patient expectations play a greater role in the recovery process (see Section 6.4).

Finally, in Chapter 7 the home-based PRT program was compared to standard rehabilitation (control) in terms of a health economics (cost consequences) analysis. Although there was a reduced sample for analysis at 9-12 month follow up (home-based PRT n=11, SR (control) n=9), the average cost per patient for physiotherapists to implement the home-based PRT programme was £313.95. This meant that the home-based PRT was £33 more expensive (bootstrapped 95% confidence interval (CI) -£318, £366) than SR (control), although the PRT intervention conferred an incremental benefit of 13.71N for the primary outcome measure, MVCOLQ; albeit neither of these effects achieved statistically significance. Additionally, there were no differences between the groups in terms of healthcare service contacts over 1 year following THR.

From an NHS perspective, re-ablement services proved to be a lower cost alternative than physiotherapists (£81.16 cheaper per patient; assuming the same utilisation as implied by

physiotherapists' cost diaries; section 7.3.4), when the cost implications of training other healthcare professionals to implement the PRT intervention was estimated,). A significant benefit was gained for the THR operation (EQ-5D HUI improved from 0.46 to 0.87 for the whole study cohort). The EQ-5D HUI at final follow up was also 10% better than that obtained from a normal population of age and sex matched individuals in the UK (see section 7.4).

8.2 Implications and future directions

In summary, in the pilot study undertaken, early home-based PRT was not shown to be clinically superior to standard rehabilitation post-THR. These results need to be interpreted with caution however, due to the loss to follow up that occurred during study recruitment and implementation. Psychological distress plays an important role in recovery post-THR, and the DRAM tool for assessing this is easily administered and predictive of poor functional outcome. Molecular processes that signify protein catabolism appear to persist in the recovery phase post-THR, independent again of participation in the home-based PRT programme, indicating that higher intensity regimes (previously shown to be deliverable in a centre-based setting) are required to encourage protein anabolism and consequently improve muscle mass, strength and function in patients following THR.

- Potential areas of future research from this thesis are the following:Screening for psychological distress using the DRAM in patients awaiting THR and investigating the feasibility of, and delivery methods for, therapeutic interventions
- Assessment of behavioural cognitions in a larger cohort of patients undergoing THR
- Characterisation of the *vastus lateralis* of the contra lateral leg in patients undergoing THR using the molecular techniques described and relating these to physical function measures
- Cost effectiveness analysis of early centre-based PRT exercise interventions post-THR

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APPENDICES

APPENDIX 1: Ethical approval

FILE COPY

NHS

Pwyllgor Moeseg Ymchwil Gogledd Orllewin Cymru
North West Wales Research Ethics Committee

PRIVATE & CONFIDENTIAL

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14 January 2010

Dear Mr Okoro,

Study Title: **Optimising patient function following elective total hip replacement (THR) surgery**
REC reference number: **09/WNo01/52**
Protocol number: **2**

Thank you for your letter of 11 January 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The favourable opinion applies to the following research sites:

Research Site	Principal Investigator / Local Collaborator
Betsi Cadwaladr University Health Board	Mr Tosan Okoro
Bangor University	Mr Tosan Okoro

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Sponsors are not required to notify the Committee of approvals from host organisations. It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site, as applicable.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		30 November 2009
REC application	39636/60301/1/284	30 November 2009
Response to Request for Further Information		11 January 2010
~~Protocol~~ superseded	~~1~~	~~17 November 2009~~
Protocol	2	11 January 2010
~~Participant Information Sheet~~ superseded	~~1~~	~~17 November 2009~~
Participant Information Sheet	2	11 January 2010
~~Participant Information Sheet: Muscle biopsy~~ superseded	~~1~~	~~17 November 2009~~
Participant Information Sheet: Muscle biopsy	2	11 January 2010
~~Participant Consent Form~~ superseded	~~1~~	~~17 November 2009~~
Participant Consent Form	2	11 January 2010
~~Participant Consent Form: Muscle biopsy~~ superseded	~~1~~	~~17 November 2009~~
Participant Consent Form: Intra-operative Muscle biopsy	1	11 January 2010
Participant Consent Form: Post-operative Muscle biopsy	2	11 January 2010
~~Participant Consent Form: DEXA scan~~ superseded	~~1~~	~~17 November 2009~~
Participant Consent Form : DEXA scan	2	11 January 2010
GP/Consultant Information Sheets	1	17 November 2009
Questionnaire: Oxford Hip Score		
Questionnaire: EUROQOL5D		
Questionnaire: SQUASH		
Questionnaire: WOMAC		
Questionnaire: Modified Somatic Perceptions		
Questionnaire: Theory of planned behaviour		
Investigator CV (Mr T Okoro)		
Supervisor CV (Dr A Lemmey)		
Co-investigator CV (Prof P Maddison)		
Co-investigator CV (Mr J G Andrew)		
Evidence of Insurance or Indemnity	UMAL	01 August 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *'After ethical review – guidance for researchers'* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/WNo01/52	**Please quote this number on all correspondence**

Yours sincerely

Mr David Owen
Chairman

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Sponsor: Professor Michael Rees, School of Medical Sciences, Bangor University*
R&D office for Betsi Cadwaladr University Health Board

APPENDIX 2: RESEARCH PROTOCOL

RESEARCH PROTOCOL Version 7, 22nd August 2011

1. TITLE:

Optimising patient function following elective total hip replacement (THR) surgery

2. ABSTRACT

Symptomatic hip osteoarthritis occurs in 3% of the elderly and is associated with poor general health status. Surgical intervention (joint replacement) is the most effective treatment for end stage disease but whilst this generally resolves pain, function usually remains substantially sub-optimal. This protracted disability has detrimental economic, social and health consequences. Exercise rehabilitation following THR that is supervised and performed in a gym produces good results in terms of muscle strength and function. However, this makes program delivery expensive due to the high costs associated with supervision, provision of facility, and transport. Evidence is lacking regarding whether home based regimes with weekly supervision that incorporate the early postoperative period are efficacious in restoring function in THR patients.

3. AIMS OF STUDY

i) Research objectives:

1. To assess whether an inexpensive home-based progressive resistance training program with weekly supervision in the early post-operative phase after total hip replacement surgery has a benefit in improving muscle strength and patient function relative to routine physiotherapy rehabilitation.
2. To assess the relationship between previous activity, and the degree of muscle impairment and function at the time of hip replacement surgery.
3. To assess changes in muscle histology and architecture with outcome following THR secondary to home-based progressive resistance training.

ii) Deliverables

1. If the trial is successful, an exercise intervention regime that may be applicable to the wider NHS without significant increase in cost or labour, which also improves outcome in terms of muscle strength and function after total hip arthoplasty surgery.
2. Results will be disseminated via workplace presentations, academic conferences and scientific publications.

4. BACKGROUND TO INVESTIGATION

i) Relevant Literature and Background

Symptomatic hip osteoarthritis occurs in 3% of the elderly (Felson 2004) and is associated with poor general health status (Dawson et al, 2004).Treatment strategies for hip pain have traditionally involved conservative measures (analgesia, exercise, education, weight reduction) with surgical intervention (joint replacement) the most effective treatment for end stage disease (Di Domenica et al 2005; Birrel et al, 2000). According to the National joint registry, the number of primary total hip replacements performed in England and Wales in 2008/2009 totalled 77608 which is a steady rise from that performed in 2007/2008 (73632) and 2006/2007 (51981) (National Joint Registry England and Wales, 2009).

The most common preoperative complaints by patients who elect to have THR are pain and loss of mobility i.e. function (Trudelle-Jackson et al, 2004). It therefore follows that the most commonly reported outcomes of THR in the literature relate to pain relief and restoration of physical function (Trudelle-Jackson et al, 2004). Whilst THR is generally successful in alleviating pain (Wang et al, 2002), restoration of function is typically incomplete (Trudelle-Jackson et al, 2002). Functional

limitations that persist after THR include reduced walking speed, ability to climb stairs, and overall lower ratings on various assessment tools used to measure function after THR (Trudelle-Jackson et al, 2002; Wilcock 1978; Brander et al 1997). Function and pain in patients with lower preoperative physical function has been shown not to be improved postoperatively to the level achieved by those with higher preoperative function (Fortin et al, 1999). At 24 months following total joint arthroplasty, patients with low pre-operative function are five times more likely to require assistance from another person for their activities of daily living compared to those with high preoperative function (relative risk 5.2, 95% CI 1.9-14.6; Fortin et al, 2002).

Outcome studies performed at least 1 year after THR reveal these physical impairments e.g. decreased muscle strength and postural stability on the side of the replaced hip, also persist in the absence of pain. (Trudelle-Jackson et al, 2002; Shih et al, 1994; Long et al, 1993).

Immobilisation due to major surgery and hospitalisation can cause a severe decline in muscle mass, and consequently losses in muscle strength and function (Bloomfield 1997; Hill et al, 1993; Covinsky et al, 2003). Frail elderly persons with sarcopenia often undergo musculoskeletal-related surgery, and the hospitalisation-associated immobilisation further compromises the skeletal system, with potentially grave consequences (Suetta et al, 2004).

The current evidence suggests that significant improvements are possible with home based largely unsupervised training in patients at average times of 4 months (8 week intervention), 6 to 48 months (6 week intervention) and 1.5 years (12 week intervention) post-THR (Trudelle-Jackson et al, 2004; Jan et al, 2004; Sashika et al, 1996). However, an efficacious home based exercise intervention regime that is unsupervised in the early post-operative phase has not yet been described. We aim to perform a feasibility study to test the efficacy of such a program. This would enable us to acquire the data necessary to calculate the sample size required for a larger multi-centre low-cost intervention study.

It is important to note that muscle strength declines 4% per day during the first week of immobilisation, making it very important that physical training is commenced as soon as possible after surgery (Wigerstad-Lossing et al 1988). Recent studies have shown that this is feasible following THR in a supervised facility and that it is efficacious in increasing maximal muscle strength, and improving muscle fibre size and pennation angle in elderly postoperative THR patients (Suetta et al, 2008).

The most commonly used rehabilitation regimes for elderly individuals are based on functional types of exercises without external loading although this type of intervention does not prevent further muscle atrophy (Reardon et al, 2001). Resistance training is an effective method to induce muscle hypertrophy and increase muscle strength and functional performance in the elderly (Harridge et al, 1998). Supervised progressive resistance training has been shown to restore muscle function in this group of patients (Hauer et al, 2002; Suetta et al, 2008). A disadvantage of these programs is the need for patients to exercise under the supervision of professional staff at a hospital or rehabilitation centre (Galea et al, 2003). This makes program delivery expensive due to the high costs associated with supervision, provision of facilities and transport (Galea et al 2003). In addition, some THR patients are excluded because difficulties with mobility and transport to a centre exclude participation (Marotolli et al 1992).

ii) Work specifically done by the applicant(s) related to the topic of research

- Palan J, **Andrew JG** et al. 'The trainer, the trainee and the surgeons' assistant: clinical outcomes following total hip replacement' J Bone Joint Surg Br.2009 Jul; 91(7):928-34.
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5. PLAN OF INVESTIGATION

i) Methodology

This would be a prospective single blinded randomised controlled trial. Patients who are undergoing elective hip surgery for osteoarthritis will be recruited. Previous studies have demonstrated that significant changes in functional outcome measures are achievable after supervised exercise programs in THR patients with control and intervention groups totalling between 11 and 18 patients each (Trudelle-Jackson et al, 2004, Suetta et al 2004, 2008; Jan et al, 2004). We therefore intend to recruit 20-25 patients per group.

Primary outcomes: Objective measures of physical function (related to activities of daily living): timed up and go test, 6 minute walk test, gait speed, stair climbing performance, and sit to stand score, maximal voluntary contraction of quadriceps muscle and hip abductors.

Secondary outcomes: Subjective measures of physical function (Oxford Hip Score (OHS) and Western Ontario and McMasters University Osteoarthitis Personal Function (WOMAC PF) subscale, short questionnaire to assess health-enhancing physical activity (SQUASH)), EuroQoL Quality of life index, objective assessment of physical activity (pedometers for 3 days to assess activity pre-operatively and during the intervention) as well as clinical assessment. Recovery locus of control questionnaire, theory of planned behaviour questionnaire, Modified Zung Depression index and modified somatic perception questionnaire will be used to assess motivation to exercise, mood, and perceptions in the recruited population. Mood and perceptions will be assessed in comparison to a panel of patients without hip pathology who will not be participating in the randomisation process.

Magnetic resonance imaging (MRI) will be performed to assess the quality of the quadriceps muscle groups of both patient populations as well as quantitatively estimate the levels of intramuscular fat. A dual energy x-ray absorptiometry (DEXA) scan will be used to assess lean muscle mass changes in the lower limbs as a result of the exercise intervention. The MRI scan will involve a single axial slice taken from a fixed distance from a bony landmark pre-operatively and at 6 weeks and 1 year post-operatively. The DEXA assessment will be performed at similar time intervals as the MRI and involves no extra cost to the study.

Biochemical analysis of muscle biopsies taken from patients intraoperatively and at 6 weeks and 1 year post-operatively will also be performed. This will be done to assess fibre type composition, as well as the metabolic capacities of the fibre types. Fibre type assessment will be done by the use of SDS-PAGE, silver staining and quantification. Metabolic capacities of the fibre types will be measured by assessing protein expression levels of GADPH, CS, ACC and PGC1 by Western Blotting and ECL detection. Additionally, protein degradation and turnover in the muscle biopsies will be assessed by ubiquitinylation.

The inclusion criteria for the study are: patients undergoing primary total hip arthroplasty via a posterior approach which can either be cemented or uncemented. The joint affected should be the only severely arthritic joint, with no evidence of inflammatory arthropathy. Patient agreement to inclusion is also necessary.

The exclusion criteria are dementia, or neurological impairment, presence of cancer or muscle wasting illness, severe musculoskeletal impairment, unstable chronic or terminal illness, major depression, and co-morbid disease that contraindicates resistance training.

Patients will be identified from the waiting list for elective total hip replacement surgery at Ysbyty Gwynedd. An invitation letter with the information sheet (version 2 dated 11/01/10) and

confirmation of interest form (version 1 dated 08/06/10) will be sent out before their pre-assessment clinic appointment. Patients who agree to be contacted will then be invited by a member of the research team to attend the University for informed consent and the initial assessment. Patients will be randomised to either be in the control group (standard rehabilitation regime) or the intervention group. All patients in either group will have assessments pre-operatively and post-operatively at 6 weeks, 6 months and 1 year.

A separate panel of patients (n=50) who will be age and sex matched with the study population and without hip pathology will also be recruited for the sole purpose of comparing mood (Modified Zung Depression Index and Modified Somatic Perception Scores). This group will be approached by post (invitation letter mood v2 8.2.11 attached) and identified from the waiting list for other orthopaedic surgical procedures at Ysbyty Gwynedd. . They will also be sent an abridged questionnaire including these measures (Postal Questionnaire v1 17.1.11 attached). This separate population will not participate in the randomisation process and their responses will be treated anonymously.

The intervention group will be shown the training exercises in the pre-assessment clinic and given information sheets. On post-operative day 2 (allowing for complications), these exercises will again be shown to them by an experienced physiotherapist. On discharge home, they will be seen by a qualified physiotherapist and the program will be adapted to their home environment. They will then be reviewed on a weekly basis for 6 weeks where the exercises shall be reviewed and resistance increased. They will also receive weekly telephone calls from the Research team and be encouraged to keep an exercise diary. The exercises to be performed are: sit to stand, stepping up unto and off a block, stair climbing, walking, knee extension against resistance, and weight transfer. The exercise intervention shall be costed by estimating the service utilisation by the participants (Client Service Receipt Inventory (CSRI) version 1 22/08/2011) and the cost of the physiotherapy input (Cost Diary Physiotherapists' (CDP) version 1 22/08/2011). The CSRI will be sent to patients by post at the 6month and 1 year intervals whilst the CDP will be given to the physiotherapists who administer the exercise intervention in the community to complete before the end of the follow up period.

ANCOVA (analysis of covariance) will be used to assess the improvement in objective measures of physical function at the different time points (6 weeks, 6 months and 1 year) as this would take account of the variation in the pre-operative scores. This would help us define the question of which time point could be critical in improving post-operative function and therefore estimating the sample size required for a definitive study based on subjective outcome measures. We also intend to assess the presence of any correlation between previous activity and improvements in function with levels of intramuscular fatty infiltration, and muscle fibre type, proportion and size.

ii) Research timetable

Oct/Nov 2009	-Apply for ethical approval
March 2010	-Commence study
July 2010	-Quality control meeting with stakeholders
September 2010	-Assess results re: relationships between pre-operative activity and muscle structure/architecture/intramuscular fat content
November 2010	-Quality control meeting with stakeholders
December 2010	-Assess 6 week results of total 40 patients
March 2011	-Quality control
June 2011	-Quality control + 6 month results
October 2011	-Quality control
March 2012	-Quality control + 1 year results

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APPENDIX 3. CONSORT CHECKLIST

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Chapter 2, p49
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Not applicable
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Section 2.1,p49
	2b	Specific objectives or hypotheses	Section 2.1,p49
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Section 2.2,p51
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	Section 2.2,p51
	4b	Settings and locations where the data were collected	Section 2.2,p51
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Section 2.2.2, p56
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Section 2.2.1, p52
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Section 2.2.4, p57
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Section 2.2,p51
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Section 2.2,p51
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Section 2.2,p51
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Section 2.2,p51
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Section 2.2,p51

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Section 2.2.4,p57
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Section 2.2.4,p57
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1,p54
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1,p54
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Section 2.2.1,p52
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 4,p58
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1,p54
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 7,p64; Table 8,p65
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Tables 7 p64; Table 8 p65; Section 2.3.3.p62; Section 2.3.4.p62
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Section 2.4.1,p68
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Section 2.4, p66
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Section 2.4, p66
Other information			
Registration	23	Registration number and name of trial registry	Section 2.2, p51
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

APPENDIX 4: Home-based progressive resistance training (PRT) regime

EXERCISE DIARY

The Exercises below will be shown to you by your physiotherapist. The aim is for you to start performing them at least 5 times a week from 4 days after your operation. Depending on how you perform them, your physiotherapist will increase the intensity of each of the exercises during the course of your participation in this study. Please mark in the diary how many repetitions you perform of each exercise for each of the days you do the exercise. If there are any problems please contact the physiotherapist in charge of your care or Mr Tosan Okoro, Clinical researcher and Orthopaedic Registrar, at Bangor University on 01248 388776.

Please note that these exercises are for both your operated and non-operated legs. Please record the repetitions you perform for each side in the diary.

EXERCISES

1. **Sit to stand:** Get up from a sitting position taking the precaution of using the chair that has been identified as being the optimum height by the occupational therapist. Progress will be by reducing hand support, and increasing repetitions.

2. **Block step:** Stepping up onto and down off a block holding onto a table or the kitchen sink for support. Progress by reducing the amount of hand support, increasing height of block, and increasing repetitions. Repeat using the other leg.

3. **Knee extension:** Straightening your knee from a bent position with weight strapped to the ankle. After full extension, contract the thigh muscles maximally for 5 seconds before bending your knee again. This is to be performed in a sitting position using the chair identified as being the optimum height by your occupational therapist. . Progress by increasing repetitions, and weight strapped to the ankle. Initial weights strapped to the ankles may be different as the operated leg will be weaker initially. Repeat using the other leg.

4. **Weight transfer:** This involves progressively trying to improve your side-to-side balance by initially leaning to one side. Progress will be by increasing the repetitions performed, and being able to lift the heel off the ground (as shown in (b)), progressing to the whole leg (as shown in (c)). Repeat, leaning to the other side and standing as straight as you can.

(a) (b) (c)

5. **Walk:** In conjunction with your physiotherapist, you will agree a route around your house to walk. Progress will be by increasing distance covered (i.e. increasing the number of laps performed), and increasing number of walks performed per day.

6. **Stair Climb (If you have stairs in the house):** Progress will be by reducing hand support, and increasing the number of times the flight of stairs is climbed
Exercise Repetitions. Grouping of intensity levels: 0-3, 4-6, 7-10. Physiotherapist will decide when it is appropriate to increase difficulty of each exercise.
Physiotherapists:

Anglesey	- CODE A
Blaenau Ffestiniog	- CODE B
Caernarfon	- CODE C

APPENDIX 5: Exercise training diary given to patients randomized to home-based progressive resistance training (PRT) group

Week 1. Week commencing……..

Exercise (Physiotherapist to tick as appropriate)	Repetition Level (0-3, 4-6, 7-10)	Number of Repetitions Performed													
		Monday		Tuesday		Wednesday		Thursday		Friday		Saturday		Sunday	
		R	L	R	L	R	L	R	L	R	L	R	L	R	L
Sit to stand 2 arm support ☐ 1 arm support ☐ No arm support ☐															
Block step 2 inch ☐ 4 inch ☐ 6 inch ☐															
Knee extension No weight ☐ ..kg wt *Left* ☐ ..kg wt *Right* ☐ ..kg wt *Left* ☐ ..kg wt *Right* ☐															
Weight transfer Lateral sway ☐ Heel off ground ☐ Leg off ground ☐															
Stair Climb Half flight ☐ Full Flight ☐															
Walk Frame used ☐ 2 walking sticks ☐ 1 walking stick ☐ No Mobility aid ☐															

Physiotherapist Code: …….

R- Right **L - Left**

APPENDIX 6:

Rationale and methodology for RT-PCR

1. **Real time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)**

The rationale for real-time PCR is illustrated in Box A. Real time RT-PCR is the technique of collecting data throughout the PCR process as the genes of interest are amplified, thus combining amplification and detection into a single step (Wong, Medrano 2005). PCR can be broken into four major phases: the linear ground phase, early exponential phase, log-linear (exponential) phase and plateau phase: Figure i (Tichopad, Dilger et al. 2003). During the linear ground phase (usually the first 10-15 cycles), PCR is just beginning, and fluorescence emission at each cycle has not yet risen above background. Baseline fluorescence is calculated at this time. At the early exponential phase, the amount of fluorescence has reached a threshold where it is significantly higher (usually 10 times the standard deviation of the baseline) than background levels. The cycle at which this occurs is referred to as the cycle threshold (C_T). This value is representative of the starting copy number in the original template and is used to calculate experimental results (Heid, Stevens et al. 1996). During the log-linear phase, PCR reaches its optimal amplification period with the PCR product doubling after every cycle in ideal reaction conditions. Finally, the plateau stage is reached when reaction components become limited and the fluorescence intensity is no longer useful for data calculation (Bustin 2000).

Box A. The real time reverse transcriptase Polymerase Chain Reaction (RT-PCR)
(Valasek, Repa 2005)

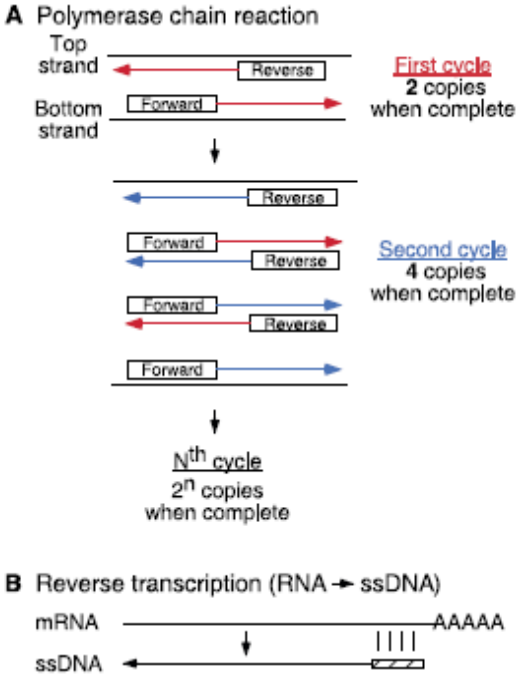
Theory

- Exploits DNA polymerases e.g. *Taq* DNA polymerase (from *Thermus aquaticus*), or *Pfu* DNA polymerase (from *Pyrococcus furiosus*), to amplify specific pieces of DNA using short, sequence- specific oligonucleotides added to the reaction to act as primers.
- Capabilities of DNA polymerases that make them useful for PCR:

1) They can generate new strands of DNA using a DNA template and primers

2) They are heat resistant.

- The latter attribute is necessary because after each round of DNA copying, the resulting double-stranded DNA (dsDNA) must be "melted" into single strands by high temperatures within the reaction tube (95°C). The reaction is then cooled to allow the oligonucleotide primers to anneal to the now single-stranded template DNA and direct the DNA polymerase enzyme to initiate elongation by adding single complementary nucleotides to create a new complete strand of DNA. Thus double stranded (ds) DNA is created.
- This new dsDNA must then be melted apart before the next cycle of copying can occur. Therefore, if the reaction works with perfect efficiency, there will be twice as much specific dsDNA after each cycle of PCR.



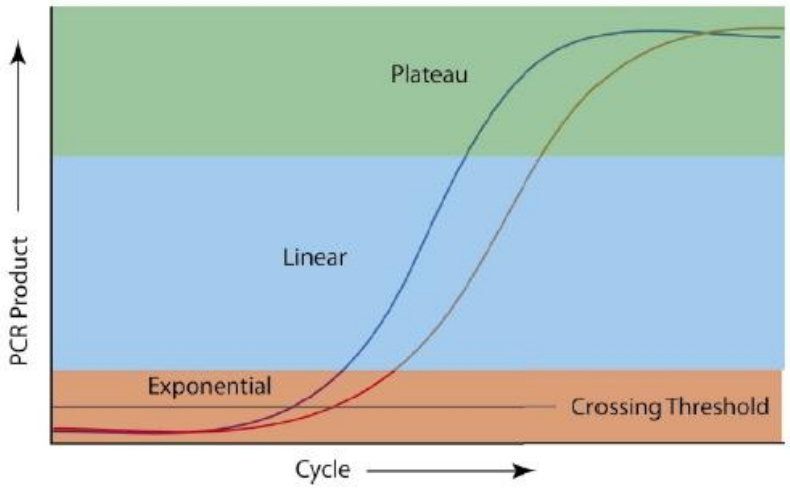
A: High temperatures are used to 'melt' double stranded DNA into its top and bottom strands. This mixture is cooled in the presence of sequence specific primers (forward and reverse) that anneal to their targets, and an optimal temperature is then applied to allow elongation of complementary DNA by the action of DNA polymerase to complete the cycle. This is repeated numerous times, and 2^n copies of the desired DNA fragment can be obtained

B: Because DNA polymerase does not utilise RNA as a template, the conversion of RNA to DNA can be achieved using the enzyme reverse transcriptase.

Reverse transcriptase is used to convert RNA to complementary DNA (cDNA) that can then be used for PCR. The relative amount of a given cDNA generated by reverse transcription is proportional to the relative amount of its RNA template. Therefore it is possible to quantify RNA expression using real time reverse transcriptase PCR (real-time RT-PCR).

Figure i. Phases of the Polymerase Chain Reaction (Van Guilder, Vrana et al. 2008)

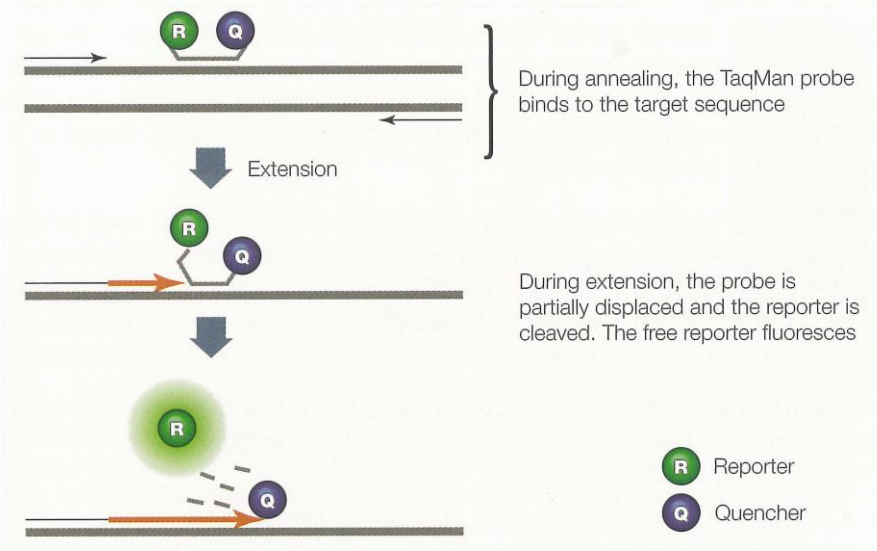
Initially, when the amount of product is small and enzyme and reagents are not limiting, product generation is exponential and the reaction is closest to 100% efficiency (exponential growth is hard to detect initially through real time fluorescence as the amount of product is small). In the linear phase products continue to accumulate, but the reaction efficiency begins to fall and reagents become limiting. In the plateau phase, accumulation of product ceases as the reaction is exhausted.



The fluorescence based technologies that are used in real time RT-PCR include (i) probe sequences that fluoresce upon hydrolysis (Taqman; Applied Biosystems, Austin, TX, USA) or hybridisation (Lightcycler; Roche, Indianapolis, IN, USA); (ii) fluorescent hairpins; or (iii) intercalating dyes (SYBR Green) (Van Guilder, Vrana et al. 2008). Taqman (used in this study, Figure ii) uses the 5'-3' exonuclease activity of Taq DNA polymerase, which degrades a non-extendable fluorescent DNA probe following hybridisation and extension in the PCR (Heid, Stevens et al. 1996). Sequence specific Taqman probes are labelled with both a fluorescent reporter and a quencher, which are maintained in close proximity until hybridisation to the target occurs. Following annealing of the forward and reverse primers to the target sequence, the Taqman probe is designed to anneal between these primer sites and is hydrolyzed by the 5'-3' exonuclease activity of the Taq polymerase (VanGuilder, Vrana et al. 2008). If no product is present, the probe does not bind and is not degraded, hence the reporter remains quenched. Probe hydrolysis results in de-suppression of the reporter and a subsequent cumulative increase in fluorescence proportional to the amount of transcript present (VanGuilder, Vrana et al. 2008).

Figure ii. Real time reverse transcriptase polymerase chain reaction (RT-PCR) detection using the Taqman (Applied Biosystems, Austin, TX, USA) hydrolysis probe (Valasek, Repa 2005) (BIORAD 2005)

The Taqman probe contains a fluorescent reporter at the 5' end and a quencher at the 3' end. When intact, the fluorescence of the reporter is quenched due to its proximity to the quencher. During the combined annealing/extension step of the amplification reaction, the probe hybridizes to the target and the double stranded (ds)-DNA-specific 5'→3' exonuclease activity of Taq cleaves off the reporter. As a result, the reporter is separated from the quencher, and the resulting fluorescence signal is proportional to the amount of amplified product in the sample.



2. RNA isolation and real time RT-PCR protocol

In order to be able to perform RT-PCR on the bioptic material, the RNA had first to be extracted. This was achieved as described below:

1. Homogenisation

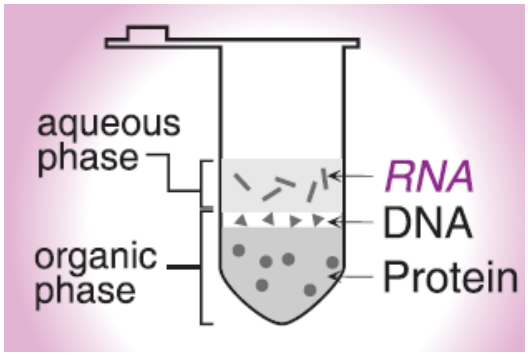
   Each muscle biopsy sample was pulverised in 1ml TRIzol® Reagent (Ambion, USA) at a speed of 2000 – 6000 revolutions per minute (rpm), using a T10 Basic Ultra-Turrax handheld homogeniser (IKA, Germany) to disrupt the cell and nuclear membranes. Samples were

incubated for 5 minutes at room temperature to permit complete dissociation of the nucleoprotein complex before being stored at -20°C.

2. Phase partition

   To separate homogenate phases, 2ml chloroform was added (Sigma-Aldrich Company Ltd. Dorset, UK) per 1ml TRIzol® Reagent used for homogenisation, followed by 15 seconds vigorous hand shaking. Samples were centrifuged at 12,000 × g for 15 minutes at 4°C. The mixture separates into a lower red phenol-chloroform phase, an interphase, and a colourless upper aqueous phase (Figure iii). RNA remains exclusively in the upper aqueous phase, which comprises ~50% of the total volume (0.5ml). The aqueous phase was transferred into new tubes for further processing and analyses.

Figure iii. Phase partition in RNA isolation.
http://www.komabiotech.com/product/product_detail.php?item=K33210



3. RNA precipitation

   An equal volume of isopropanol (Sigma-Aldrich Company Ltd. Dorset, UK) was added to the RNA supernatant for each of the samples and incubated at room temperature for 5 minutes. The samples were then further centrifuged at 12000xg for 10 minutes at 4°C. A gel-like pellet of RNA was precipitated following centrifugation (Figure iv).

4. RNA washing

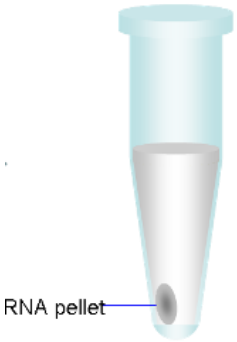
   The supernatant was removed from the sample and 800µl 75% Ethanol (volume per volume (v/v)) was added to the RNA pellet. The sample was centrifuged at 8000xg for 15 minutes at

4°C. The supernatant was removed and the pellet was allowed to dry at room temperature for ~10 minutes until it became colourless in appearance.

5. RNA resuspension

   The RNA pellet was dissolved in 45µl pyrogen-free H_20 (this inhibits Reverse Transcriptase) and the samples were stored at -20°C.

Figure iv. RNA Pellet obtained after centrifugation and washing with isopropanol
(http://molecularhub.blogspot.com/2011/01/rna-isolation-principle-and-procedure.html)



6. DNA decontamination

   All RNA samples were vortexed to ensure RNA was completely re-suspended in pyrogen-free H_2O.

   A master mix of the DNA digestion reagents (DNA-free™, Applied Biosystems, Austin, Texas, USA) was prepared for 49 RNA samples as follows:

DNase 1 buffer (Ambion , Austin, Texas, USA)	0.5µl × 55	=	27.5µl
DNase (Ambion , Austin, Texas, USA)	1µl × 55	=	55µl
Pyrogen-free H_2O (Ambion, Austin, Texas USA)	5µl × 55	=	275µl

   0.1% of the total volume of the RNA solution (0.5µl) of DNase buffer and 1µl of DNase were added to the RNA samples (6.5µl of the master mix; 45µl of the RNA solution made up to 50µl with the addition of the 5µl of the pyrogen-free H_2O) and mixed gently.

   The samples were incubated at 37°C for 30 minutes prior to addition of 0.5µl (0.1% of total volume) DNAse inactivation agent (Ambion, Austin, Texas, USA). After incubation for 2 minutes at room temperature, the samples were centrifuged at 13000xg for 1.5 minutes. The

supernatant was removed and RNA from all samples was transferred to 0.5ml microfuge tubes (Ambion, Austin, Texas USA). All samples were stored at -20°C.

Care was taken to avoid introducing the DNase Inactivation Reagent (white milky pellet at the side of the tube) into the stored sample; solutions that may be used for downstream enzymatic reactions, because it can inhibit the RT-PCR reaction.

7. RNA Quantification
Each RNA sample underwent the following processes to determine its concentration:

    1. Dilution to a 1:50 solution; 2μl stock RNA and 98μl pyrogen-free RNAse free water with sterile pipette tips.
    2. 1μl RNAse free water was used to blank the nanodrop spectrophotometer (ND-1000 v 3.3.0 set at path length 10mm with nucleic acid RNA-40 setting)
    3. Depending on the concentration of sample obtained, the concentration of stock RNA sample was determined in order that a volume containing 50ng RNA stock was added to each well on the microarray PCR plate

    For example:

    Sample 1- concentration 14.2ng/μl with a dilution factor of 1 in the spectrophotometer but 1:50 as detailed above.

    14.2ng/μl in the 1:50 dilution = 710ng/μl in stock 1:1 solution

    We needed 50ng for each polymerase chain reaction (PCR), and with 10% extra plates catered for, i.e. 36 wells rather than 32, the total concentration of RNA was 50×36 =1800ng total RNA.

    To obtain 1800ng of RNA, 2.53 μl (1800/710) of the RNA stock solution was required.

8. Design of the PCR microarrays

    96-well PCR microarray plates were used in the configuration shown in Figure v. Each plate contained a total of 3 samples (32 wells (genes) per sample). The rationale for each gene included in the plates is described in Table 14.

9. Constituting the PCR Wells

TaqMan® RNA-to-CT ™ 1-Step Kit (Applied Biosystems, Austin, TX, USA) was used to make a master mix for each sample (36 wells instead of 32) with a total volume of 20µl per well

Enzyme volume	0.5µl × 36	= 18µl
Taqman master mix	10µl × 36	= 360µl
RNA volume	9.5µl × 36	= 342µl

For sample 1, if 1420ng in 100µl (1:50 dilution), 1800ng would be in x µl,

Where x = 1800/1420 × 100 = 126.7µl (of 1:50 dilution)

∴ To make up 342µl of RNA volume containing 50ng per well, 126.7µl of the 1:50 dilution was added to 215µl of pyrogen-free RNAse water. 9.5µl of this solution is added to the master mix volume in each of the wells indicated for sample 1 in the first 4 columns of the 96 well plate as in Figure v. The same process was repeated for Samples 2 and 3 before the plates were analysed in the 7900HT Real-Time PCR System (Applied Biosystems, Austin, TX, USA)

The values of the dilutions and stock concentrations of RNA used are indicated for all 49 samples in Table i.

Analyses of 6 samples (8, 11, 18, 19, 20 and 30) were repeated due to insufficient volumes of master mix for the initial runs performed (i.e. >3 wells unfilled). The values for the repeated RNA quantifications and well volumes are given in Table i. The repeat values were used in the microarray gene expression analyses.

Figure v. 96-well plate configuration used for real time polymerase chain reaction (RT-PCR) microarray analysis of muscle biopsy samples.

	1	2	3	4	5	6	7	8	9	10	11	12
A	18S	CAPN1	CAPN2	CAST	18S	CAPN1	CAPN2	CAST	18S	CAPN1	CAPN2	CAST
B	FOS	JUNB	RCAN1	MAPK14	FOS	JUNB	RCAN1	MAPK14	FOS	JUNB	RCAN1	MAPK14
C	IGFBP5	IGFBP2	ADRB2	CAPN3	IGFBP5	IGFBP2	ADRB2	CAPN3	IGFBP5	IGFBP2	ADRB2	CAPN3
D	FBXO32	GSK3A	CTSL1	CTSL2	FBXO32	GSK3A	CTSL1	CTSL2	FBXO32	GSK3A	CTSL1	CTSL2
E	TRIM63	MSTN	PSMA7	FABP3	TRIM63	MSTN	PSMA7	FABP3	TRIM63	MSTN	PSMA7	FABP3
F	PPARA	PPARG	LPL	MT-CO1	PPARA	PPARG	LPL	MT-CO1	PPARA	PPARG	LPL	MT-CO1
G	IGF2 INS-IGF2	IL6	MYOD1	TNF	IGF2 INS-IGF2	IL6	MYOD1	TNF	IGF2 INS-IGF2	IL6	MYOD1	TNF
H	TNFRSF1B	SIRT1	SIRT2	ELF1	TNFRSF1B	SIRT1	SIRT2	ELF1	TNFRSF1B	SIRT1	SIRT2	ELF1

Key (http://www.genecards.org)

ADRB2	Adrenergic, beta-2-, receptor	*JUNB*	Jun B proto-oncogene
CAPN1	Calpain1	*LPL*	Lipoprotein Lipase
CAPN2	Calpain2	*MAPK14*	Mitogen activated Protein kinase 14
CAPN3	Calpain3	*MSTN*	Myostatin
CAST	Calpastatin	*MT-CO1*	Mitochondrially encoded Cytochrome C Oxidase I
ELF1	E26 Transformation Specific Domain Transcription factor1	*MYOD1*	Myogenic Differentiation 1
CTSL1	Cathepsin L1	*PPARA*	Peroxisome Proliferator-Activated Receptor Alpha
CTSL2	Cathepsin L2	*PPARG*	Peroxisome Proliferator-Activated Receptor Gamma
FABP3	Fatty Acid Binding Protein 3	*PSMA7*	Proteasome Subunit, Alpha type, 7
FBX032	F-Box protein 32	*RCAN1*	Regulator of calcineurin transcript variant 3
FOS	FBJ Murine Osteosarcoma viral oncogene homolog	*SIRT1*	Sirtuin 1
GSK3A	Glycogen Synthase Kinase 3 alpha	*SIRT2*	Sirtuin 2
IGFBP5	Insulin-like Growth Factor Binding Protein 5	*TNF*	Tumour Necrosis Factor
IGFBP2	Insulin-like Growth Factor Binding Protein 2	*TNFRSF1B*	Tumor Necrosis Factor receptor Superfamily, member 1B
IL6	Interleukin-6	*TRIM63*	Tripartite Motif containing 63
INS-IGF2	Insulin-like Growth Factor 2 read-through	*18S*	RNA, **18S** ribosomal 1; Manufacturer's housekeeping gene

Table i. ***Concentrations of RNA stock solutions constituting Polymerase Chain Reaction microarray wells***

			Concentration of 1:50 dilution (ng/ml)			RNA stock concn. ng/µl	Vol. of Dilution to use in Master mix (µl)	Volume Pyrogen free H_20 to make up 342µl master mix volume (µl)
Sample	Study Group	ID	1st dilution	2nd dilution	Average			
1	Standard	1104 proximal VL preop	14.3	14.1	14.2	710	126.7	215
2	Intervention	1115 proximal VL preop	14.8	14.4	14.6	730	123.3	218
3	Intervention	1121 proximal VL preop	13	12.4	12.7	635	141.7	201
4	Intervention	1122 proximal VL preop	6.4	7.9	7.15	357.5	252	90
5	Standard	1124 proximal VL preop	12.6	11.6	12.1	605	148.7	193
6	Intervention	1201 proximal VL preop	12.7	11.3	12	600	150	192
7	Intervention	1201 distal VL preop	6.2	5.9	6.05	302.5	297	55
8	Intervention	1202 proximal VL preop	10.7	11.5	11.1	555	162	180
9	Intervention	1203 proximal VL preop	12.5	11.9	12.2	610	148	194
10	Standard	1206 proximal VL preop	10.2	10.7	10.45	522.5	172	170
11	Intervention	1209 proximal VL preop	5.2	6.6	5.9	295	305	37
12	Standard	1210 proximal VL preop	12.1	13.3	12.7	635	142	200
13	Standard	1301 proximal VL preop	7.6	7.5	7.55	377.5	239	103
14	Intervention	1302 proximal VL preop	8.4	7.3	7.85	392.5	229	113
15	Standard	1305 proximal VL preop	9.2	10.5	9.85	492.5	183	159
16	Standard	1308 proximal VL preop	19.7	17.8	18.75	937.5	96	246
17	Standard	1401 proximal VL preop	11.4	11.7	11.55	577.5	155	187
18	Standard	1402 proximal VL preop	7.7	5.2	6.45	322.5	279	63
19	Standard	1104 distal VL preop	1.1, 1.0	1.7	1.26	63	28.5µl stock	314
20	Intervention	1115 distal VL preop	4.3, 4.5	3.1	3.96	198	18.4µl stock	324
21	Intervention	1118 distal VL preop	11.1	10.6	10.85	542.5	166	176
22	Intervention	1121 distal VL preop	5.2	6.9	6.05	302.5	297	45
23	Intervention	1203 distal VL preop	4.6	6.9	5.75	287.5	313	30
24	Intervention	1209 distal VL preop	1.4	2.9	2.15	107.5	16.74µl stock	325
25	Standard	1210 distal VL preop	9.3	9.5	9.4	470	191	151
26	Standard	1305 distal VL preop	7.2	5.3	6.25	312.5	288	54
27	Standard	1308 distal VL preop	9.8	8.9	9.35	467.5	193	50
28	Intervention	1202 distal VL preop	5.8	5.6	5.7	285	315	27
29	Intervention	1118 distal VL preop	4.5	4	4.25	212.5	8.47µl stock	333
30	Intervention	1122 distal VL preop	10.1	9.3	9.7	485	185	57
31	Standard	1124 distal VL preop	1.9	3.2	2.55	127.5	14.11µl stock	327
32	Standard	1402 distal VL preop	5.3	5.2	5.25	262.5	342	0
33	Intervention	1202 distal VL 6/52 postop	7.2	8.4	7.8	390	230	112
34	Intervention	1115 distal VL 6/52 postop	15.6	14.2	14.9	745	120	222
35	Intervention	1121 distal VL 6/52 postop	7.7	7.8	7.75	387.5	232	110
36	Intervention	1122 distal VL 6/52 postop	5.4	5.6	5.5	275	327	15
37	Standard	1124 distal VL 6/52 postop	7.6	5.7	6.65	332.5	270	162
38	Intervention	1201 distal VL 6/52 postop	4.9	6.3	5.6	280	321	22
39	Standard	1210 distal VL 6/52 postop	4.3	3.6	3.95	197.5	9.11µl stock	333
40	Intervention	1302 distal VL 6/52 postop	6.9	6.1	6.5	325	276	66
41	Standard	1305 distal VL 6/52 postop	5.2	6.2	5.7	285	316	26
42	Standard	1308 distal VL 6/52 postop	9	9.7	9.35	467.5	192	150
43	Intervention	1115 distal VL 6/12 postop	1.4	2.7	2.05	102.5	17.5µl stock	325
44	Intervention	1121 distal VL 6/12 postop	5.6	4.6	5.1	255	7.06µl stock	335
45	Standard	1305 distal VL 6/12 postop	4.9	5	4.95	247.5	7.27µl stock	335
46	Intervention	1201 distal VL 1 year postop	5.7	5.4	5.55	277.5	324	18
47	Intervention	1202 distal VL 1 year postop	6.2	4.6	5.4	270	333	10
48	Intervention	1302 distal VL 1 year postop	4.6	4.2	4.4	220	8.2µl stock	334
49	Standard	1308 distal VL 1 year postop	12.7	13.6	13.15	657.5	136	206
Key	Intervention	Home based exercise intervention						
	Standard	Standard physiotherapy						

10. Analysis of the pre-labelled Taqman Array 96 well RT-PCR plates using the 7900HT Real-Time PCR System (Applied Biosystems, Austin, TX, USA).

    Each 96 well plate was sealed and centrifuged briefly (12000g for 1min). Analyses were performed on the machine specified above using the SDS software version 2.4. The PCR was performed under the following parameters for the thermal cycling conditions (Table ii). The Taqman protocol contains a denaturation step at 60°C as illustrated, instead of the traditional three-step PCR cycle of denaturation, annealing and extension (Box A). This is in order to ensure that the Taqman probe remains bound to its target during primer extension (BIORAD 2005).

Table ii. Thermal cycling conditions used for PCR analysis
(7900HT Teal-Time PCR system; Applied Biosystems, Austin, TX)

Step	Temp °C	Duration	Cycles
Reverse Transcriptase (RT) step	48	15 min	Hold
Enzyme activation	95	10 min	Hold
Denature	95	15 sec	40
Anneal/Extend	60	1 min	40

11. Quantification of RNA expression ($\Delta\Delta C_T$) using Data Assist Software (v3.0, Applied Biosystems, Austin, TX, USA)

    The results obtained for all 49 samples were analysed to determine which gene was suitable to be used as an endogenous control. CTSL1 was found to have uniform C_T expression across all the samples, which meant it was the most stably expressed mRNA within the samples studied. All the ΔC_T values for the genes were made in comparison to CTSL1. The fold changes were assessed (comparator/control) using unpaired t-tests with the Benjamini-Hochberg false discovery rate (FDR) correction which controls the expected proportion of incorrectly rejected null hypotheses (type I errors) (Benjamini, Drai et al. 2001); the default analysis for the Data Assist Software (v3.0, Applied Biosystems, Austin, TX, USA).

APPENDIX 7: Absolute values for fold change (relative quantity (RQ) and %)) for comparison of distal vastus lateralis gene expression at 6 months (G2 n=3) versus the pooled intra-operative proximal and distal vastus lateralis biopsies (G1 n=32)

At 6 months, there were significant changes in markers of hypertrophy (FOS (+400% (p=0.0009) and RCAN 1 (-91.81% (p=0.015)). A trend to significance was observed for markers of atrophy and lipid metabolism (SIRT1 (+72.89%, p=0.0725), CTSL2 (-81.31%, p=0.0751), LPL (-60.21%, p=0.0751) and PPARA (-80.74%, p=0.0587). There was also a significant reduction in a marker for inflammation (IL-6; -92.48% (p=0.0113)).

Metabolic response	Gene	Anticipated Change	Actual Fold change	p value	RQ
Hypertrophy	ADRB2-Hs00240532_s1	↑	-74.58%	0.1088	0.2542
	CAPN1-Hs00559804_m1	↑	26.79%	0.5709	1.2679
	CAPN2-Hs00965092_m1	↑	99.60%	0.1814	1.996
	CAST-Hs00156280_m1	↑	27.32%	0.5741	1.2732
	FOS-Hs99999140_m1	↑	**399.82%**	**0.0009**	4.9982
	IGF2;INS-IGF2-Hs01005963_m1	↑	-35.46%	0.1088	0.6454
	IGFBP2-Hs00167151_m1	↑	-45.51%	0.6454	0.5449
	JUNB-Hs00357891_s1	↑	-30.21%	0.368	0.6979
	RCAN1-Hs01120953_m1	↑	**-91.81%**	**0.015**	0.0819
Atrophy	CAPN3-Hs00181057_m1	↓	32.24%	0.3482	1.3224
	CTSL2-Hs00426731_m1	↓	-81.31%	0.0751	0.1869
	FBXO32-Hs00369714_m1	↓	-50.50%	0.1228	0.495
	GSK3A-Hs00219856_m1	↓	-82.40%	0.368	0.176
	MAPK14-Hs00176248_m1	↓	-17.92%	0.549	0.8208
	MSTN-Hs00976237_m1	↓	-49.25%	0.2196	0.5075
	PSMA7-Hs00895424_m1	↓	-58.76%	0.1088	0.4124
	TRIM63-Hs00822397_m1	↓	42.86%	0.368	1.4286
	IGFBP5-Hs01052296_m1	↑	-37.90%	0.2586	0.621
	MYOD1-Hs00159528_m1	↑	-44.86%	0.2985	0.5514
Lipid metabolism	FABP3-Hs00269758_m1	↑	-57.28%	0.2099	0.4272
	LPL-Hs00173425_m1	↑	-60.21%	0.0751	0.3979
	MT-CO1-Hs02596864_g1	↑	-42.47%	0.2586	0.5753
	PPARA-Hs00947538_m1	↑	-80.74%	0.0587	0.1926
	PPARG-Hs00234592_m1	↑	-58.70%	0.1956	0.413
	SIRT1-Hs01009006_m1	↑	72.89%	0.0725	1.7289
	SIRT2-Hs00247261_m1	↓	-61.07%	0.1088	0.3893
Inflammation	IL6-Hs00985639_m1	↓	**-92.48%**	**0.0113**	0.0752
	TNF-Hs00174128_m1	↓	-0.20%	0.4558	0.8043
	TNFRSF1B-Hs00961748_m1	↓	-57.04%	0.1088	0.4296
None	ELF1-Hs00152844_m1	↔	-71.97%	0.0091	0.2803
	18S-Hs99999901_s1	↔	10.17%	0.9107	1.1017

APPENDIX 8: Absolute values for fold change (relative quantity (RQ) for comparison of distal vastus lateralis gene expression at 1 year (G2 n=4) versus the pooled intra-operative proximal and distal vastus lateralis biopsies (G1 n=32)

At 1 year, there was a significant reduction in the expression of PPARA (-79.23% (p=0.0003)) with CAPN3 (+90.57%, p=0.0655) and TRIM63 (+170.40%, p=0.0715) showing a trend to significance. FOS was overtly expressed (+439.43%) but as for all the other genes in this analysis, no significance was attained.

Metabolic response	Gene	Anticipated Change	Actual Fold change	p value	RQ
Hypertrophy	ADRB2-Hs00240532_s1	↑	-68.23%	0.173	0.3177
	CAPN1-Hs00559804_m1	↑	113.50%	0.181	2.135
	CAPN2-Hs00965092_m1	↑	123.33%	0.181	2.2333
	CAST-Hs00156280_m1	↑	58.31%	0.448	1.5831
	FOS-Hs99999140_m1	↑	439.43%	0.448	5.3943
	IGF2;INS-IGF2-Hs01005963_m1	↑	-31.58%	0.3064	0.6842
	IGFBP2-Hs00167151_m1	↑	-22.33%	0.5649	0.7767
	JUNB-Hs00357891_s1	↑	-48.65%	0.181	0.5135
	RCAN1-Hs01120953_m1	↑	-73.02%	0.4871	0.2698
Atrophy	CAPN3-Hs00181057_m1	↓	90.57%	0.0655	1.9057
	CTSL2-Hs00426731_m1	↓	-59.83%	0.448	0.4017
	FBXO32-Hs00369714_m1	↓	0.42%	0.9987	1.0042
	GSK3A-Hs00219856_m1	↓	158.69%	0.212	2.5869
	MAPK14-Hs00176248_m1	↓	17.18%	0.6734	1.1718
	MSTN-Hs00976237_m1	↓	-52.75%	0.1949	0.4725
	PSMA7-Hs00895424_m1	↓	-32.13%	0.1676	0.6787
	TRIM63-Hs00822397_m1	↓	170.40%	0.0715	2.704
	IGFBP5-Hs01052296_m1	↑	-0.05%	0.9995	0.9995
	MYOD1-Hs00159528_m1	↑	-8.57%	0.9143	0.9143
Lipid metabolism	FABP3-Hs00269758_m1	↑	-22.70%	0.448	0.773
	LPL-Hs00173425_m1	↑	-42.99%	0.3775	0.5701
	MT-CO1-Hs02596864_g1	↑	23.58%	0.448	1.2358
	PPARA-Hs00947538_m1	↑	**-79.23%**	**0.0003**	0.2077
	PPARG-Hs00234592_m1	↑	-39.48%	0.3775	0.6052
	SIRT1-Hs01009006_m1	↑	91.45%	0.1632	1.9145
	SIRT2-Hs00247261_m1	↓	-40.78%	0.3064	0.5922
Inflammation	IL6-Hs00985639_m1	↓	-49.36%	0.802	0.5064
	TNF-Hs00174128_m1	↓	-30.26%	0.1949	0.6974
	TNFRSF1B-Hs00961748_m1	↓	-16.95%	0.5649	0.8305
None	ELF1-Hs00152844_m1	↔	-65.18%	0.0715	0.3482
	18S-Hs99999901_s1	↔	103.36%	0.5243	2.0336

APPENDIX 9: Absolute values for fold change (relative quantity (RQ) and %)) for Comparison of distal (G2 n=15) versus proximal (G1 n=17) vastus lateralis gene expression intra-operatively in patients undergoing total hip replacement

Metabolic response	Gene	Anticipated Change	Actual Fold change	p value	RQ
Hypertrophy	ADRB2-Hs00240532_s1	↑	-4.30%	0.9738	0.957
	CAPN1-Hs00559804_m1	↑	63.24%	0.7154	1.6324
	CAPN2-Hs00965092_m1	↑	110.09%	0.6489	2.1009
	CAST-Hs00156280_m1	↑	130.14%	0.6399	2.3014
	FOS-Hs99999140_m1	↑	-36.49%	0.7154	0.6351
	IGF2;INS-IGF2-Hs01005963_m1	↑	-3.12%	0.9738	0.9688
	IGFBP2-Hs00167151_m1	↑	-13.78%	0.862	0.8622
	JUNB-Hs00357891_s1	↑	-27.43%	0.7945	0.7257
	RCAN1-Hs01120953_m1	↑	172.75%	0.6257	2.7275
Atrophy	CAPN3-Hs00181057_m1	↓	-16.38%	0.7154	0.8362
	CTSL2-Hs00426731_m1	↓	0.18%	0.9965	1.0018
	FBXO32-Hs00369714_m1	↓	13.96%	0.9738	1.1396
	GSK3A-Hs00219856_m1	↓	-0.69%	0.9965	0.9931
	MAPK14-Hs00176248_m1	↓	2502.00%	0.7945	1.2502
	MSTN-Hs00976237_m1	↓	-26.99%	0.5499	0.7301
	PSMA7-Hs00895424_m1	↓	-18.44%	0.6489	0.8156
	TRIM63-Hs00822397_m1	↓	50.19%	0.7154	1.5019
	IGFBP5-Hs01052296_m1	↑	10.31%	0.9738	1.1031
	MYOD1-Hs00159528_m1	↑	-15.97%	0.7154	0.8403
Lipid metabolism	FABP3-Hs00269758_m1	↑	-23.93%	0.7078	0.7607
	LPL-Hs00173425_m1	↑	6.77%	0.9359	1.0677
	MT-CO1-Hs02596864_g1	↑	-27.59%	0.5499	0.7241
	PPARA-Hs00947538_m1	↑	-26.27%	0.7154	0.7373
	PPARG-Hs00234592_m1	↑	15.25%	0.7154	1.1525
	SIRT1-Hs01009006_m1	↑	-2.03%	0.9873	0.9797
	SIRT2-Hs00247261_m1	↓	-27.97%	0.6257	0.7203
Inflammation	IL6-Hs00985639_m1	↓	15.76%	0.9738	1.1576
	TNF-Hs00174128_m1	↓	16.94%	0.7154	1.1694
	TNFRSF1B-Hs00961748_m1	↓	-27.01%	0.5499	0.7299
None	ELF1-Hs00152844_m1	↔	44.92%	0.7154	1.4492
	18S-Hs99999901_s1	↔	302.46%	0.7078	4.0246

APPENDIX 10: Absolute values for fold change (relative quantity (RQ and %)) for comparison of distal vastus lateralis gene expression at 6 weeks (G2 n=10) postoperatively versus pooled intra-operative proximal and distal vastus lateralis muscle biopsies (G1 n=32)

Metabolic response	Gene	Anticipated Change	Actual Fold change	p value	RQ
Hypertrophy	ADRB2-Hs00240532_s1	↑	**-60.68%**	**0.0003**	0.3932
	CAPN1-Hs00559804_m1	↑	66.11%	0.2951	1.6611
	CAPN2-Hs00965092_m1	↑	129.24%	0.0867	2.2924
	CAST-Hs00156280_m1	↑	52.17%	0.4559	1.5217
	FOS-Hs99999140_m1	↑	**1463.68%**	**0.0158**	15.6368
	IGF2;INS-IGF2-Hs01005963_m1	↑	-36.52%	0.1402	0.6348
	IGFBP2-Hs00167151_m1	↑	-10.51%	0.711	0.8949
	JUNB-Hs00357891_s1	↑	-35.34%	0.5681	0.6466
	RCAN1-Hs01120953_m1	↑	-43.08%	0.6758	0.5692
Atrophy	CAPN3-Hs00181057_m1	↓	**103.21%**	**0.0039**	2.0321
	CTSL2-Hs00426731_m1	↓	-42.54%	0.5005	0.5746
	FBXO32-Hs00369714_m1	↓	-27.06%	0.528	0.7294
	GSK3A-Hs00219856_m1	↓	108.02%	0.156	2.0802
	MAPK14-Hs00176248_m1	↓	22.83%	0.5438	1.2283
	MSTN-Hs00976237_m1	↓	-25.89%	0.4278	0.7411
	PSMA7-Hs00895424_m1	↓	**-44.76%**	**0.0158**	0.5524
	TRIM63-Hs00822397_m1	↓	113.01%	0.1402	2.1301
	IGFBP5-Hs01052296_m1	↑	14.87%	0.711	1.1487
	MYOD1-Hs00159528_m1	↑	-22.78%	0.1402	0.7722
Lipid metabolism	FABP3-Hs00269758_m1	↑	-43.47%	0.0755	0.5653
	LPL-Hs00173425_m1	↑	**-42.45%**	**0.0158**	0.5755
	MT-CO1-Hs02596864_g1	↑	4.70%	0.7869	1.047
	PPARA-Hs00947538_m1	↑	-78.68%	0	0.2132
	PPARG-Hs00234592_m1	↑	-26.30%	0.4278	0.737
	SIRT1-Hs01009006_m1	↑	**108.21%**	**0.0039**	2.0821
	SIRT2-Hs00247261_m1	↓	**-33.45%**	**0.0376**	0.6655
Inflammation	IL6-Hs00985639_m1	↓	-82.72%	0.2951	0.1728
	TNF-Hs00174128_m1	↓	**-29.64%**	**0.0228**	0.7036
	TNFRSF1B-Hs00961748_m1	↓	**-35.71%**	**0.0039**	0.6429
None	ELF1-Hs00152844_m1	↔	**-63.74%**	**0.0158**	0.3626
	18S-Hs99999901_s1	↔	108.68%	0.5005	2.0868

APPENDIX 11: Absolute values for fold change (relative quantity (RQ and %)) for comparison of distal vastus lateralis gene expression at 6 weeks postoperatively for the home-based progressive resistance training (PRT) group (G2 n=6) versus the standard rehabilitation (SR) group (G1 n=4)

Metabolic response	Gene	Anticipated Change	Actual Fold change	p value	RQ
Hypertrophy	ADRB2-Hs00240532_s1	↑	-20.67%	0.7545	0.7933
	CAPN1-Hs00559804_m1	↑	-3.51%	0.9208	0.9649
	CAPN2-Hs00965092_m1	↑	-35.71%	0.7545	0.6429
	CAST-Hs00156280_m1	↑	-29.38%	0.7545	0.7062
	FOS-Hs99999140_m1	↑	-51.07%	0.7545	0.4893
	IGF2;INS-IGF2-Hs01005963_m1	↑	-37.45%	0.7545	0.6255
	IGFBP2-Hs00167151_m1	↑	48.73%	0.7545	1.4873
	JUNB-Hs00357891_s1	↑	258.71%	0.7545	3.5871
	RCAN1-Hs01120953_m1	↑	5616.90%	0.7545	57.169
Atrophy	CAPN3-Hs00181057_m1	↓	-71.06%	0.7545	0.2894
	CTSL2-Hs00426731_m1	↓	857.22%	0.7545	9.5722
	FBXO32-Hs00369714_m1	↓	-62.65%	0.7545	0.3735
	GSK3A-Hs00219856_m1	↓	195.60%	0.7545	2.956
	MAPK14-Hs00176248_m1	↓	-18.52%	0.7545	0.8148
	MSTN-Hs00976237_m1	↓	-4.84%	0.9208	0.9516
	PSMA7-Hs00895424_m1	↓	-39.41%	0.7545	0.6059
	TRIM63-Hs00822397_m1	↓	-67.20%	0.7545	0.328
	IGFBP5-Hs01052296_m1	↑	-45.51%	0.7545	0.5449
	MYOD1-Hs00159528_m1	↑	-10.81%	0.7545	0.8919
Lipid metabolism	FABP3-Hs00269758_m1	↑	-58.37%	0.7545	0.4163
	LPL-Hs00173425_m1	↑	-21.03%	0.7545	0.7897
	MT-CO1-Hs02596864_g1	↑	-89.63%	0.7545	0.1037
	PPARA-Hs00947538_m1	↑	-19.24%	0.7545	0.8076
	PPARG-Hs00234592_m1	↑	87.71%	0.7545	1.8771
	SIRT1-Hs01009006_m1	↑	-19.19%	0.7545	0.8031
	SIRT2-Hs00247261_m1	↓	-18.86%	0.7545	0.8114
Inflammation	IL6-Hs00985639_m1	↓	1791.41%	0.7545	18.9141
	TNF-Hs00174128_m1	↓	182.88%	0.7545	2.8288
	TNFRSF1B-Hs00961748_m1	↓	55.14%	0.7545	1.5514
None	ELF1-Hs00152844_m1	↔	-32.27%	0.7545	0.6773
	18S-Hs99999901_s1	↔	-93.09%	0.7545	0.0691

APPENDIX 12: Absolute values for fold change (relative quantity (RQ and %)) for comparison of distal vastus lateralis gene expression at 6 weeks postoperatively for the home-based progressive resistance training (PRT) group (G2 n=6) versus pooled proximal and distal vastus lateralis samples obtained intra-operatively from the same population (G1 n=17)

Metabolic response	Gene	Anticipated Change	Actual Fold change	p value	RQ
Hypertrophy	ADRB2-Hs00240532_s1	↑	**-62.96%**	**0.0131**	0.3704
	CAPN1-Hs00559804_m1	↑	81.67%	0.3916	1.8167
	CAPN2-Hs00965092_m1	↑	122.64%	0.2622	2.2264
	CAST-Hs00156280_m1	↑	54.87%	0.6296	1.5487
	FOS-Hs99999140_m1	↑	2507.88%	0.1187	26.0788
	IGF2;INS-IGF2-Hs0100596	↑	-33.57%	0.5536	0.6643
	IGFBP2-Hs00167151_m1	↑	0.26%	0.9959	1.0026
	JUNB-Hs00357891_s1	↑	6.27%	0.9959	1.0627
	RCAN1-Hs01120953_m1	↑	359.83%	0.1187	4.5983
Atrophy	CAPN3-Hs00181057_m1	↓	**107.14%**	**0.0457**	2.0714
	CTSL2-Hs00426731_m1	↓	-3.80%	0.9959	0.962
	FBXO32-Hs00369714_m1	↓	-19.37%	0.8771	0.8063
	GSK3A-Hs00219856_m1	↓	136.65%	0.1187	2.3665
	MAPK14-Hs00176248_m1	↓	52.47%	0.5101	1.5247
	MSTN-Hs00976237_m1	↓	-28.50%	0.5101	0.715
	PSMA7-Hs00895424_m1	↓	-43.69%	0.2431	0.5631
	TRIM63-Hs00822397_m1	↓	165.37%	0.2725	2.6537
	IGFBP5-Hs01052296_m1	↑	56.26%	0.5536	1.5626
	MYOD1-Hs00159528_m1	↑	-19.93%	0.3916	0.8007
Lipid metabolism	FABP3-Hs00269758_m1	↑	-38.72%	0.2504	0.6128
	LPL-Hs00173425_m1	↑	-32.70%	0.388	0.673
	MT-CO1-Hs02596864_g1	↑	2.59%	0.9959	1.0259
	PPARA-Hs00947538_m1	↑	-80.25%	0.0702	0.1975
	PPARG-Hs00234592_m1	↑	-9.54%	0.9449	0.9046
	SIRT1-Hs01009006_m1	↑	**138.96%**	**0.0026**	2.3896
	SIRT2-Hs00247261_m1	↓	-31.44%	0.2745	0.6856
Inflammation	IL6-Hs00985639_m1	↓	-41.97%	0.9449	0.5803
	TNF-Hs00174128_m1	↓	-29.62%	0.2725	0.7038
	TNFRSF1B-Hs00961748_	↓	-36.60%	0.1187	0.634
None	ELF1-Hs00152844_m1	↔	-57.85%	0.2725	0.4215
	18S-Hs99999901_s1	↔	134.98%	0.5536	2.3498

APPENDIX 13: Absolute values for fold change (relative quantity (RQ and %)) for comparison of distal vastus lateralis gene expression at 6 weeks postoperatively for the standard rehabilitation group (G2 n=4) versus pooled proximal and distal vastus lateralis samples obtained intra-operatively from the same population (G1 n=15)

Metabolic response	Gene	Anticipated Change	Actual Fold change	p value	RQ
Hypertrophy	ADRB2-Hs00240532_s1	↓	-53.24%	0.1778	0.4676
	CAPN1-Hs00559804_m1	↓	-13.98%	0.6596	0.8602
	CAPN2-Hs00965092_m1	↓	27.91%	0.3915	1.2791
	CAST-Hs00156280_m1	↓	-21.44%	0.2489	0.7856
	FOS-Hs99999140_m1	↓	556.44%	0.371	6.5644
	IGF2;INS-IGF2-Hs01005963_m1	↓	-32.97%	0.3403	0.6703
	IGFBP2-Hs00167151_m1	↓	-20.25%	0.3915	0.7975
	JUNB-Hs00357891_s1	↓	-72.77%	0.2144	0.2723
	RCAN1-Hs01120953_m1	↓	**-91.60%**	**0.0303**	0.084
Atrophy	CAPN3-Hs00181057_m1	↑	94.93%	0.2489	1.9493
	CTSL2-Hs00426731_m1	↑	-59.88%	0.3893	0.4012
	FBXO32-Hs00369714_m1	↑	-39.17%	0.4511	0.6083
	GSK3A-Hs00219856_m1	↑	43.50%	0.7075	1.435
	MAPK14-Hs00176248_m1	↑	-6.47%	0.7932	0.9353
	MSTN-Hs00976237_m1	↑	-22.04%	0.7075	0.7796
	PSMA7-Hs00895424_m1	↑	-44.01%	0.2489	0.5599
	TRIM63-Hs00822397_m1	↑	42.33%	0.6077	1.4233
	IGFBP5-Hs01052296_m1	↓	-22.52%	0.6077	0.7748
	MYOD1-Hs00159528_m1	↓	-23.21%	0.3915	0.7679
Lipid metabolism	FABP3-Hs00269758_m1	↓	-44.88%	0.3915	0.5512
	LPL-Hs00173425_m1	↓	**-46.88%**	**0.0435**	0.5312
	MT-CO1-Hs02596864_g1	↓	8.77%	0.7932	1.0877
	PPARA-Hs00947538_m1	↓	**-74.55%**	**0.0303**	0.2545
	PPARG-Hs00234592_m1	↓	-40.40%	0.3959	0.596
	SIRT1-Hs01009006_m1	↓	79.15%	0.2489	1.7915
	SIRT2-Hs00247261_m1	↑	-33.68%	0.2489	0.6632
Inflammation	IL6-Hs00985639_m1	↑	**-93.99%**	**0.0506**	0.0601
	TNF-Hs00174128_m1	↑	-27.13%	0.2116	0.7287
	TNFRSF1B-Hs00961748_m1	↑	-28.70%	0.2116	0.713
None	ELF1-Hs00152844_m1	↔	**-69.54%**	**0.0303**	0.3046
	18S-Hs99999901_s1	↔	-51.58%	0.2489	0.4842