A lifestyle intervention to improve outcomes in men with castrate-resistant prostate cancer

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Collaborating organisations: Sheffield Teaching Hospitals NHS Trust and The University of Sheffield

Sheffield Hallam University

Statement of originality

I hereby declare that all the work contained in this thesis is original and was undertaken by the author unless otherwise stated below. Where reference is made to the work of others, citations are included with the authors name and year of publication.

The healthcare professional survey: The survey was designed and ethics approval was gained by the STAMINA team. A health services research consultancy service (Clinvivo) distributed the survey. The survey analysis was conducted by Rosa Greasley (RG) also referred to as the author.

Healthcare professional interviews: The ethics approval was gained as part of the STAMINA programme. The interview schedule was designed by RG guided by Liam Bourke (LB), Karen Collins (KC) and Derek Rosario (DR). All interviews were conducted by RG. The interviews were double coded by Rebecca Turner (RT). The framework analysis was guided and verified by KC and conducted by RG.

The feasibility randomised controlled trial (COMRADE): RG designed COMRADE guided by DR, LB and Janet Brown (JB). All trial documents were designed by RG and guided by LB and DR. The DEXA GP letter and set up of the DEXA scans for the trial was guided by Margaret Paggiosi (MP) and written and conducted by RG. Ethics application and approval conducted by RG and assisted by the R&D department at STH. Recruitment was conducted by RG (in the oncology department) and Claire Ward (CW) (in the urology department). All recruited participant screening was conducted by RG. Assessments were carried out by RG, blinded assessments were conducted by Sheffield Hallam University technical staff, Alan Ruddock (AR) and Brent Robbins (BR). DXA scans were conducted by MP, in The Clinical Research Facility at The Northern General Hospital. Seven exercise sessions were delivered by Richard Stevenson (RS) all other sessions were conducted by RG. CW and RS also assisted in venepuncture where participants were difficult to draw samples from, all other venepuncture was conducted by RG. Blood samples were sent to Sheffield Teaching Hospitals

central laboratories for analysis. Diet diary analysis conducted by undergraduate student Liam Oliver (LO) supervised by RG.

Participant focus groups: The focus group schedule was designed by RG guided by LB and DR. Focus group 1 was delivered by RT supported by RG, focus group 2 was conducted by RG supported by RT and focus group 3 was conducted by RG. Double coded by Helen Crank (HC) and verified by David Broom (DB). All analysis and interpretation was conducted by RG.

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Abbreviations

3RM Three repetition maximum testing

5α-R 5 alpha-reductase

95% CI 95% confidence interval

ADT Androgen deprivation therapy

AE Adverse event

APPR Acute phase protein response

AR Androgen receptor

ACSM American College of Sports Medicine

BAUN British Association of Urological Nurses

BAUS British Association of Urological Surgeons

BPH Benign prostatic hyperplasia

BMD Bone mineral density

BMI Body mass index

BRCA Breast cancer

BUG British Uro-Oncology Group

CAB/MAB Complete/Maximal androgen blockade

CCG Clinical commissioning groups

CNS Clinical nurse specialist

CONSORT Consolidated Standards of Reporting Trials

COREQ Consolidated criteria for reporting qualitative research

CRPC Castrate resistant prostate cancer

CRUK Cancer Research UK

CSTS Chair sit to stand test

CT Computed tomography

CV Cardiovascular

CVD Cardiovascular disease

DHT 5α-Dihydrotestosterone

DLT Dose limiting toxicity

DRE Digital rectal examination

DXA Dual-energy X-ray absorptiometry

E1 Ubiquitin-activating enzyme

E2 Ubiquitin-conjugated enzyme

E3 Ubiquitin protein ligase

EAU European Association of Urology

ECOG Eastern Cooperative Oncology Group

EDMS Electronic document management system

ER Oestrogen receptor

FACT-P The Functional Assessment of Cancer Therapy - Prostate

FACT-F Functional Assessment of Cancer Therapy - fatigue

FDA Food and Drug Administration

FM Fat mass

FMD Flow-mediated dilatation

FSS Fatigue Severity Scale

GnRH Gonadotrophin releasing hormone

GP General practitioner

HCP Healthcare professional

HGPIN High grade prostatic intraepithelial neoplasia

HR Hazard ratio

IFN Interferon

IL Interleukin

iSKM Skeletal muscle mass index

KPS Karnofsky performance status

LBM Lean body mass

LDH Lactate dehydrogenase

LH Luteinizing hormone

LMF Lipid mobilising factor

LUTS Lower urinary tract symptoms

MAFbx Muscle atrophy F-box protein

MDT Multidisciplinary team

MRC The Medical Research Council

MRI Magnetic Resonance Imaging

MSK Musculoskeletal

MuRF-1 Muscle specific ring-finger

NCSI National Cancer Survivorship Initiative

NHS National Health Service

NICE The National Institute for Health and Care Excellence

OR Odds ratio

OS Overall survival

PCUS Primary Care Urology Society

PIF Proteolysis inducing factor

PIS Patient information sheet

PS Performance score

PSA Prostate Specific Antigen

PTHrP Parathyroid hormone related peptide

QoL Quality of Life

RCT Randomised control trial

RPE Rate of perceived exertion

RR Relative risk

RTx Radiotherapy

SAE Serious adverse event

SD Standard deviation

SE Standard error

SHBG Sex hormone binding globulin

SHU Sheffield Hallam University

SLR Systematic literature review

SMD Standardised mean differences

SMWT Six minute walk test

STE Severe toxicity events

STH Sheffield Teaching Hospitals

TNF-α Tumour necrosis factor-α

UK United Kingdom

UPP Ubiquitin proteasome pathway

US United States

WCRF-CUP World Cancer Research Fund - Continuous Update Project

Wk Week

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Abstract

Background

There is increasing evidence demonstrating that lifestyle interventions of exercise and diet may represent a useful supportive therapy for men with prostate cancer, improving physiological and psychosocial outcomes. There has been limited investigation of the effects of such interventions in men with castrate resistant prostate cancer (CRPC), the terminal phase of the disease.

It is not clear how exercise has been implemented in the prostate cancer care pathway and what a successfully implemented exercise programme might look like. Furthermore, the specific treatment and disease related barriers men with CRPC might face engaging in exercise is not documented, particularly when considering their advanced stage of disease.

This work described in this thesis covers an exploration of the feasibility and acceptability of an exercise and dietary intervention to improve outcomes in men with CRPC.

Methods

A healthcare professional survey was conducted to assess the extent to which NHS trusts are meeting the NICE guidelines (CG175, 1.4.19) for exercise training for men with prostate cancer on androgen deprivation therapy (ADT).

Semi-structured interviews of UK healthcare professionals, specialising in prostate cancer care and based in UK National Health service (NHS) trusts were conducted. These explored underlying reasons behind the variability in NHS trusts in delivering exercise training programmes and probed the views of the HCPs regarding exercise training, including the acceptability of concurrent use of an anabolic agent for men with CRPC.

A feasibility randomised controlled trial (RCT) of an exercise and dietary intervention in CRPC patients was conducted (COMRADE). Men with CRPC recruited to the RCT were randomised on a 1:1 ratio to either the intervention or usual care for 16 weeks. Men allocated the intervention received up to

three sessions of supervised resistance exercise a week; supplemented with whey protein and creatine monohydrate; and given dietary advice. They were also asked to partake in at least one independent moderate intensity aerobic activity lasting at least 30 minutes a week.

Following the RCT, post study participant focus groups addressed patients' views on aspects of the study, particularly with regards to acceptability of trial procedures, barriers and facilitators to exercise training and the impact of living with CRPC.

Results

The healthcare professional survey demonstrated significant variability between NHS trusts in the UK in delivering the NICE guidelines and that a supervised exercise training programme is not currently embedded within "usual care" for prostate cancer.

The healthcare professional interviews (n=12) demonstrated support for an individualised and adaptable exercise programme for men with CRPC which could improve fitness and mitigate some of the long term effects of their cancer/cancer therapy. Their opinions reflected that comorbidities and disease/treatment specific barriers to exercise must be taken into account to support better adherence.

In the feasibility RCT, n=31 men were recruited from a total of n=3607 screened (recruitment rate=13.6%). There were eighteen in the intervention and thirteen randomised to the control group. The attrition rate was 16%, with n=4 dropping out of the intervention and n=1 death in the control. Adherence to the supervised and independent exercise sessions was 69% and 78% respectively. The adherence to the whey protein was 68% and creatine was 71%. There were 4 AEs associated with trial procedures, none of which were serious.

Three primary themes were identified from the participant focus groups (n=3); these included 1) living with CRPC, 2) experience and opinions of the trial, 3) attitudes and experiences of exercise training and physical activity. The findings demonstrated that the study procedures were well received by

the participants, including the trial assessments and format of the intervention. Valuable insights were gained for implementing future exercise intervention studies - providing participant perspectives for the success of a lifestyle behaviour study such as COMRADE.

Conclusions

The findings suggest that it is feasible to randomise and retain men with CRPC to an exercise and diet intervention, however there was a high rate of attrition in the study, due to the complex nature of the disease in these men. Further work is required to address the barriers related to implementation of exercise in the prostate cancer pathway for men with CRPC.

Chapter 1 Introduction

1. Prostate cancer

1.1 A brief history of prostate cancer: The evolution of our understanding and treatment

Since Huggins and Hodges demonstrated that hormone manipulation was effective in alleviating symptoms of metastatic prostate cancer more than 70 years ago, androgen deprivation therapy (ADT) has been the cornerstone for the treatment for advanced prostate cancer (Huggins, Stevens et al. 1941). However, men with metastatic prostate cancer eventually relapse:, if he lives long enough, despite castrate blood serum levels of androgens a man with prostate cancer will develop disease progression, referred to as castrate-resistant prostate cancer (CRPC). Up until 2010, docetaxel, a taxane-based antimitotic agent was the only agent that had demonstrated an overall survival (OS) benefit in CRPC (Petrylak, Tangen et al. 2004, Berthold, Pond et al. 2008). Since then, there has been an introduction into clinical practice of five other therapeutic options which have shown a survival benefit in phase III trials: carbazitaxel, sipuleucel-T, radium-223, abiraterone and enzalutamide. This has led to a dramatic change in how CRPC is treated (Kantoff, Higano et al. 2010, de Bono, Logothetis et al. 2011, Oudard 2011, Scher, Fizazi et al. 2012, Parker, Nilsson et al. 2013). The landscape continues to evolve rapidly with ever-changing indications and introduction of new therapies directed at castrate-resistant prostate cancer (Nuhn, De Bono et al. 2018).

Regardless of this expanding armamentarium for CRPC, therapies are not curative and therefore essentially palliative for these men. CRPC is still the terminal phase of the disease and those with metastatic disease (mCRPC) are expected to live <19 months (Heidenreich, Pfister et al. 2013). These men are faced not only with the burden of advanced disease but also of many years of cancer treatment, with attendant adverse events. For this reason, when a clinician is faced with a treatment decision, considerations of preservation of quality of life (QoL) become paramount as men enter this phase of the disease. Treating clinicians often face a difficult trade-off between treating with the intention to improve overall survival (OS) and the associated treatment adverse events (AEs) impacting on QoL. In comparison

to men at earlier stages of disease, many men with CRPC are elderly and have competing comorbidities (Scosyrev, Messing et al. 2012). In this case, there is further complication as to whether the primary risk to survival is indeed the disease, and therefore treatment may be unnecessary. To date, there is no comprehensive management strategy demonstrated to improve or sustain good QoL among these men (Rosario, Greasley et al. 2016).

1.2 Androgens, the androgen receptor and the prostate

In men, androgens are involved in male sexual differentiation and reproductive organ growth in embryogenesis (Murashima, Kishigami et al. 2015). The prostate gland also forms during embryogenesis, and develops from multiple buds that grow out of the proximal urethra into the surrounding connective tissue where 5α reductase (5αR) is expressed in epithelial cells (Wilson 2011). These organs mature during early post-natal puberty where there is a peak in circulating androgens known as a "mini puberty" (Pasterski, Acerini et al. 2015). In "mini puberty", testosterone levels peak between one to three months. The early periods of androgen production are necessary for the formation and development of the urogenital tract and external genitalia (Pasterski, Acerini et al. 2015). Post "mini puberty", androgen levels remain relatively constant up until adrenarche, puberty and adulthood. The usual age of adrenarch is 6 to 8 years which precedes and can occur independently of puberty. Adrenarch, results from increased androgen secretion from the adrenal glands, independent of gonadal androgen secretion. Adrenal androgen levels will continue to increase until the third decade of life, thereafter a continuous and variable decrease is present (Hiort 2002). During normal male puberty gonadotrophin stimulates the gonads increasing levels of testosterone. Changes start with the enlargement of the testes and penis in addition to increases in muscle and bone mass, enlargement of the larynx (resulting in deepening of the voice), secondary hair changes including increased trunk hair growth, skin thickens, a growth spurt occurs and erythrocyte cell mass increases (Hiort 2002). Furthermore, testosterone may alter behaviour, these effects include stimulation of sexual libido and aggressiveness (Hiort 2002).

Whereas androgens are clearly involved in the development of the prostate and other male reproductive glands (Wilson 2011), the exact interplay between androgenic activity and the aetiology and evolution of prostate cancer remains uncertain. In men, androgens are synthesised primarily in the testes under the regulation of luteinizing hormone (LH) released from the anterior pituitary gland. LH release is regulated by gonadotrophin releasing hormone (GnRH; also known as luteinizing hormone-releasing hormone) from the hypothalamus. Androgens control normal prostate cell growth by regulating the ratio of cells proliferating to those undergoing apoptosis (Minutoli, Rinaldi et al. 2016). Testosterone is the main circulating androgen in males and is normally produced by Leydig cells in the testes (Feldman and Feldman 2001). Testosterone circulates in the blood where it is predominantly in a protein-bound state to either albumin or sex-hormone binging globulin (SHBG), with only a small proportion circulating free in the blood (Feldman and Feldman 2001). Also synthesised in the testes is 5α-reductase (5α-R), an enzyme responsible for the conversion of testosterone to 5α-dihydrotestosterone (DHT), a more active metabolite of testosterone with a five-fold higher affinity for the androgen receptors (AR) (Heinlein and Chang 2004, Wilson 2011). Testosterone and DHT exhibit their effects on the prostate by binding to the AR in prostate cells resulting in transcriptional activity. This includes prostate cell differentiation, proliferation and apoptosis, necessary to complete prostate formation and maturation (Heinlein and Chang 2004, Attar, Takimoto et al. 2009). AR activity is mediated by androgens and regulates the biological activity of the prostate, with the exception of dysfunctional AR activity which can occur independent of androgens as can be the case in prostate cancer. As apoptosis in prostate cells can be hormone regulated, the removal of gonadal androgens can cause normal prostate and prostate cancer cells to undergo apoptosis, demonstrated in early preclinical studies (Kyprianou and Isaacs 1988, English, Kyprianou et al. 1989, Kyprianou, English et al. 1990, Colombel, Olsson et al. 1992).

Benign prostatic hyperplasia (BPH) is the most common benign proliferative disease among men (Wei, Calhoun et al. 2005). The histological prevalence

of BPH has been estimated at 8%, 50%, and 80% in the 4th, 6th, and 9th decades of life, respectively (Lim 2017). Men with BPH commonly experience lower urinary tract symptoms (LUTS), resulting in the need for medical or surgical treatment (Izumi, Mizokami et al. 2013). A common treatment for BPH is the use of 5αR inhibitors, which suppress testosterones conversion to DHT and suggest the androgen and androgen receptor signalling play a key role in the development of BPH (Izumi, Mizokami et al. 2013).

1.2 Epidemiology of prostate cancer

1.2.1 Incidence and mortality

There are significant geographical variations in the incidence of prostate cancer with over 70% of diagnoses made in the most developed regions of the world. Amongst the highest rates are Australia/New Zealand and the United States (US) with 111.6 and 97.2 cases per 100,000, respectively (GLOBOCAN 2012). Incidence in Asian countries is much lower and in some parts of China, it's a relatively rare disease.

In the United Kingdom (UK), prostate cancer is the most common cancer in men with 47,151 new cases reported in 2015 (Office of National Statistics 2015), putting the UK incidence rate 17th highest in Europe. It accounts for around 26% of cancer diagnoses in men and around 84% of men diagnosed with prostate cancer can expect to live 10 or more years (Office of National Statistics 2015). In Europe, around 417,000 new cases of prostate cancer were estimated to have been diagnosed in 2012.

Prostate cancer is the 5th leading cause of cancer death in men worldwide. (GLOBOCAN 2012). An estimated 1.1 million men diagnosed with prostate cancer in 2012 (GLOBOCAN 2012). There is significant difference in the distribution of mortality and incidence rates of prostate cancer worldwide :less than 10% of those in the US die of their disease comparative to over a third in the Caribbean nations (GLOBOCAN 2012). What is evident is that although the incidence of prostate cancer varies more than 25-fold across the globe, there is only a 10-fold difference in mortality. Furthermore, relatively speaking, the prognosis of prostate cancer remains worst in the

less-developed areas, whereas incidence has risen in more developed. Much of this variation is likely to be related to the prevalence of opportunistic prostate specific antigen (PSA) screening in the more developed countries. In addition, the disparity between mortality between developing countries compared to more developed regions such as Europe and North America can possibly be attributed to the higher total expenditures on health/gross product (GDP), with more favourable outcomes associated with greater spend on cancer care (Chen, Wang et al. 2017).

1.2.2 Risk factors for prostate cancer

As there is some difficulty in establishing the raw incidence of prostate cancer due to the disparities in PSA testing in different regions, there is some uncertainty regarding the incidence of significant prostate cancer impacting survival and of prostate cancer mortality. As a result there is limited consistent risk factor data for prostate cancer with the exception of three non-modifiable factors: age, race and family history.

Prostate cancer incidence increases with age, the incidence rate of prostate cancer is 9.2/100,000 for men aged 40–44 years, this increases to 984.8/100,000 in men aged 70–74 years, after which it slightly decreases (Leitzmann and Rohrmann 2012).

Prostate cancer is most common in black males, followed by white males and least common in Asian men in the UK (Lloyd, Hounsome et al. 2015). Black men are 2-3 times more likely to be diagnosed with prostate cancer compared to white men of the same age in the UK, furthermore black men are more likely to be diagnosed earlier than white men (Ben-Shlomo, Evans et al. 2008).

There are risk factors associated with having a family history of prostate cancer (Albright, Stephenson et al. 2015). If one first-degree relative has prostate cancer, such as father or brother, the risk is at least doubled. The risk increases further, to 5–11 times when two or more first-line relatives are affected (Albright, Stephenson et al. 2015). The risk also increases based on earlier age at diagnoses, where risk increases by 6 times for one or more first-degree relatives diagnosed before age 50 years. Less than 10% of men

with prostate cancer have hereditary disease associated with a mutation, which is associated with an earlier onset (around 6-7 years). Carriers of the breast cancer 1, early onset (BRCA1) and breast cancer 2, early onset (BRCA2) mutations are at a higher risk of developing more aggressive phenotypes of prostate cancer (Mitra, Fisher et al. 2008, Castro, Goh et al. 2013). For men carrying the mutations rate of both metastatic disease and death from prostate cancer are significantly higher (Castro, Goh et al. 2013). The findings of a UK BRCA screening study (IMPACT) showed positive predictive value for biopsy using a PSA threshold of 3.0 ng/ml in BRCA2 mutation carriers was double the positive predictive value reported in population screening studies, furthermore there was a significant difference in detecting intermediate-high risk disease observed in BRCA2 carriers (Bancroft, Page et al. 2014). However, further research is needed to determine the possible differences between the impact of the two BRCA mutations however the findings do indicate germline genetic markers can be used to identify men at higher risk of prostate cancer (Bratt and Loman 2015).

There are other lifestyle related factors associated with prostate cancer. There is strong evidence to suggest a link between some prostate cancers and being overweight or obese, being tall and a high consumption of beta-carotene (WCRF-CUP 2014). Furthermore, obesity is linked with elevated incidence of aggressive disease, increased risk of biochemical failure following radical prostatectomy and external-beam radiotherapy, higher frequency of complications following ADT, and increased prostate cancer mortality (Allott, Masko et al. 2013). There is some evidence to suggest a link between prostate cancer risk and sedentary behaviour, a higher consumption of dairy products, diets high in calcium, low plasma alpha-tocopherol concentration (vitamin E) and low plasma (blood) selenium concentrations (WCRF-CUP 2014).

In England, it is also less common in men in the most deprived areas (Tweed, Allardice et al. 2018). However, this is likely linked to the rise in incidence rates since the introduction of PSA testing, where those who are in more affluent areas are more likely to have greater exposure to testing

(Shafique, Oliphant et al. 2012). This reflects the disparities of prostate cancer incidence worldwide mentioned previously.

The link between hypogonadism and the risk of prostate cancer is contentious, but there is some evidence to suggest a link with an increased risk of developing more aggressive prostate cancer with hypogonadism (Morgentaler and Rhoden 2006).

1.3 Evolution and clinical staging

A large population of men with prostate cancer are asymptomatic until the late stages of their disease. Once the prostate has enlarged to where it obstructs the urethra, known as bladder outlet obstruction, men may experience typical lower urinary tract symptoms (LUTS) (Rosier and de la Rosette 1995). This includes micturition hesitancy, nocturnal polyuria, urinary retention and haematuria. For more advanced disease where metastasis is present bone pain is a frequent symptom, particularly in the spine and pelvis.

1.3.1 Diagnostic and staging procedures

Prostate cancer screening, using blood PSA levels, has dramatically shifted the stage at which the disease is diagnosed with fewer men diagnosed showing radiographical evidence of metastasis since its introduction. There is no formal widespread population screening programme for PSA as there exists no evidence for it but the topic remains one of the most controversial in uro-oncology (Mottet, Bellmunt et al. 2017).

The European Randomised Study of Screening for Prostate Cancer study of 162,388 men with a 13 year follow up demonstrated a small absolute reduction in prostate cancer mortality (Schroder, Hugosson et al. 2009). In the screening group the relative risk (RR) of death was reduced to 0.79, an absolute risk reduction of 0.128% or 13 lives saved per 10 000 men invited for screening.

However, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which involved 76 685 men also with a 13 year follow up, concluded that the prostate cancer specific mortality in screen detected individuals very low and not significant (Andriole, Crawford et al. 2009). In addition, both of these large scale RCTs demonstrated not only a substantial risk of over

diagnosis with PSA screening but also of a lack of benefit to all-cause mortality. As a result, widespread PSA screening programmes have not been adopted. However, targeting those men who are considered at risk of developing prostate cancer such as those with a family history of those of African American origin may be appropriate (Mottet, Bellmunt et al. 2017).

PSA is a continuous parameter where a higher PSA is indicative of an increasing likelihood of prostate cancer. A PSA is accompanied with a digital rectal examination (DRE) where the prostate is felt for an abnormal morphology. Currently, the optimal intervals for PSA testing and DRE follow-up vary dependant on the individual, such as the presence of prostate cancer risk factors (e.g. family history), age and life expectancy being taken into account.

Where blood serum PSA levels or an abnormal DRE may be indicative of the presence of prostate cancer, it should be confirmed by histological assessment of a prostate biopsy. At this stage a grading system, previously the Gleason score and now Gleason grade, is used to determine the presence of prostate cancer cells defined on the histological appearance (uniformity, size and differentiation). The Gleason score is calculated according to the image (figure 1.1) below between 1 and 5 for the most prevalent pattern (primary grade), then between 1 and 5 again for the next most prevalent (secondary grade). If a small area of high grade is present, this will be attributed a tertiary grade. The primary and secondary grades are added together to provide a sum score e.g. 3+3 = 6 or 4+3 = 7 (Rezaeilouyeh and Mahoor 2016). Men with a sum score ranging from 6 to 7 have the higher chances of survival, whereas men with scores from eight to ten have the highest mortality rate (Gleason and Mellinger 1974). The development of the Gleason grading system stratifies patients in to "groups" based on the histological definitions of the original Gleason scoring system.

The Gleason grading system (Epstein, Zelefsky et al. 2016):

- Grade group 1 (Gleason score 3 + 3 ≤6): Only individual discrete well-formed glands.

- Grade group 2 (Gleason score 3 + 4 = 7): Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands.
- Grade group 3 (Gleason score 4 + 3 = 7): Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands.
- Grade group 4 (Gleason score 8)
    - Only poorly formed/fused/cribriform glands or
    - Predominantly well-formed glands and lesser component lacking glands
    - Predominantly lacking glands and lesser component of well-formed gland
- Grade group 5 (Gleason scores 9–10): Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands.

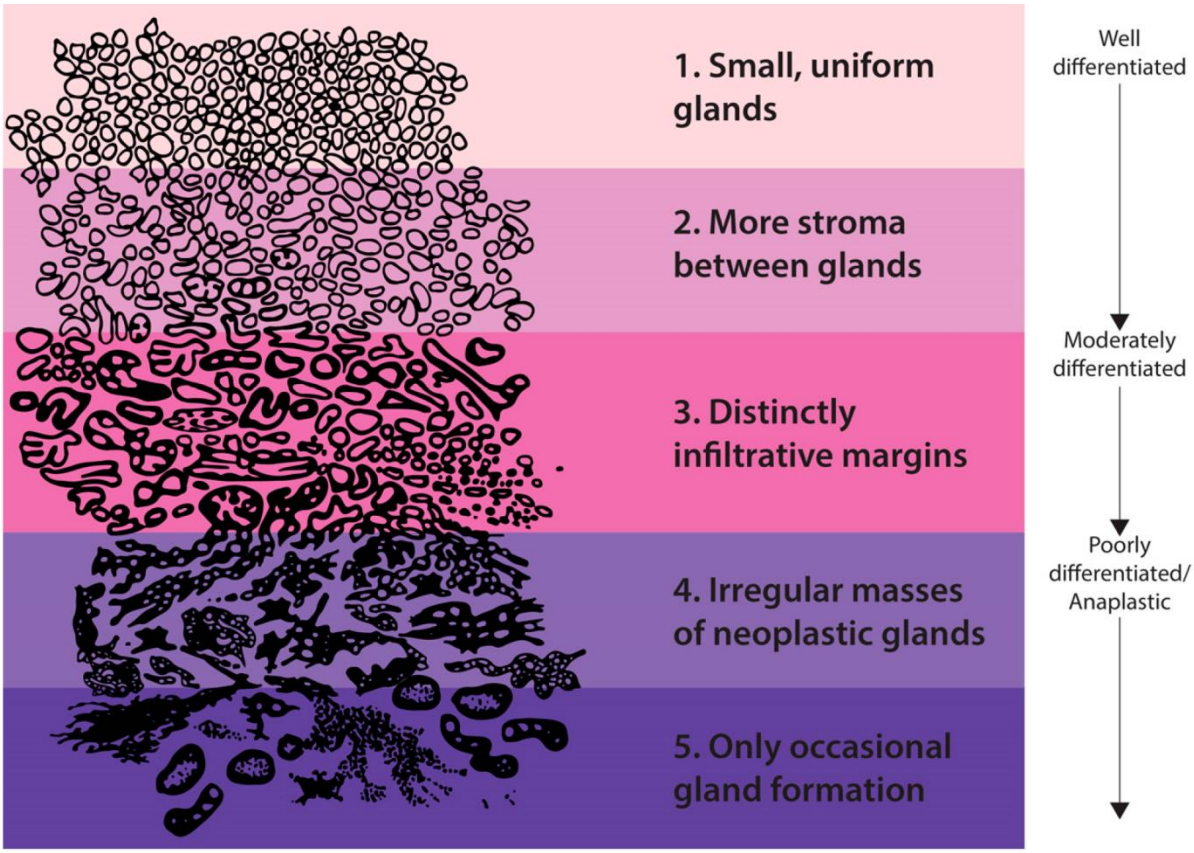

Figure 1.1 The Gleason score, the higher scores are indicative of a greater malignancy. Taken from the National Cancer Institute website

<https://training.seer.cancer.gov/prostate/abstract-code-stage/morphology.html>
public domain

Upon the histological confirmation of prostate cancer, further radiographical assessment is undertaken, inclusive of skeletal x-rays, computed tomography (CT) scanning or magnetic resonance imaging (MRI). Additionally, isotope bone scans are used to determine the extent of bone metastasis, such as Tc99 bone scan.

The most widely used staging classification is the TNM staging system. The system assesses the extent of the primary tumour (T), regional lymph nodes (N), and distant metastases (M) and provides a “stage grouping” based on T, N, and M (Edge and Compton 2010). The TNM staging system is detailed below.

Table 1.1 TNM staging of prostate cancer

TNM staging of prostate cancer	
Localised	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically apparent tumour neither palpable or visible by imaging
T1a	Tumour incidental histologic finding in ≤5% of tissue resected
T1b	Tumour incidental histologic finding in >5% of tissue resected
T1c	Tumour identified by needle biopsy
T2	Tumour confined within prostate
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than one-half of one lobe but not both lobes
T2c	Tumour involves both lobes
Locally advanced	
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour involves seminal vesicles
T4	Bladder invasion, fixed to pelvic side of wall, or invasion of adjacent structures
Metastatic	

N1	Positive regional lymph nodes
M1	Distant metastasis

Dependant on a combination of PSA, Gleason score and TNM staging the EAU risk group classification can be used to determine the risk of reoccurrence after radical local treatment for prostate cancer (table 1.2).

Table 1.2 Risk groups for biochemical reoccurrence of localised and locally advanced prostate cancer taken from (Mottet, Bellmunt et al. 2017) with permission.

	Low risk	**Intermediate risk**	**Intermediate - high risk**	**High risk**
PSA	<10 ng/ML	10-20 ng/ML	>20ng/ML	any PSA
Gleason score	AND <7	OR 7	OR >7	any Gleason score
TNM staging	AND T1-2a	OR T2b	OR T2c	T3-4 OR N+

1.4 Prostate cancer treatment

For disease localised to the prostate gland, a clinician with their patient will most likely choose to not treat at all or treatment with curative intent, opting for surgery known as radical prostatectomy or radical radiotherapy (NICE 2014). In general, surgery is more commonly adopted by North America and Europe. For more advanced disease there are a multitude of therapies which are summarised in figure 1.2 (NICE 2014). However, the cornerstone therapy for advanced, or inoperable, disease is hormone manipulation or ADT. This can be achieved with orchidectomy or the pharmacological agents - gonadotrophin-releasing hormone (GnRH) analogues. ADT manipulates circulating levels of testosterone to near negligible levels, essentially achieving castration.

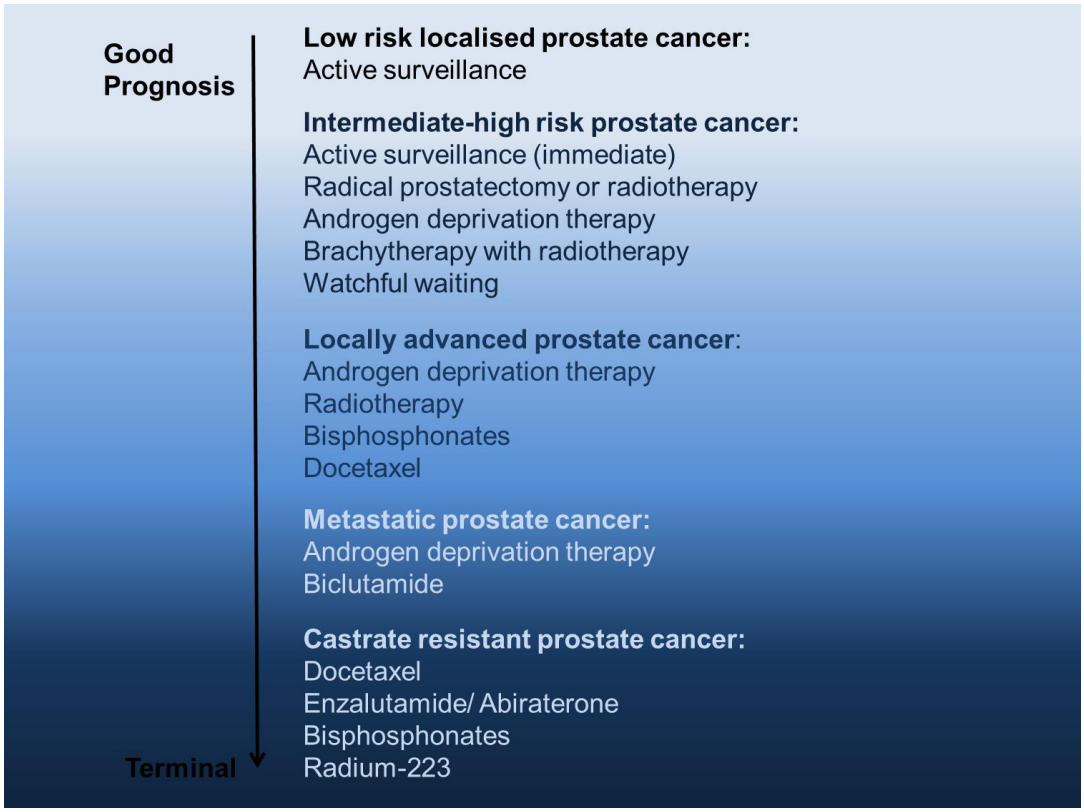

Figure 1.2 Prostate cancer treatments with advancing disease

1.4.1 Localised prostate cancer

Decisions on treatments for localised prostate cancer depend on patient fitness, comorbidities, life-expectancy and patient preference. The disease will also be risk assessed based on the Gleason score, stage and PSA. Crucially, active treatment is performed with curative intent unlike prostate cancer which is at more advanced stages.

1.4.1.1 Active surveillance and watchful waiting

Active surveillance is reserved for patients with the lowest risk prostate cancers (Gleason score 6 or 7) where it is expected that their disease will not progress to a higher grade. Active surveillance is a programme of quarterly PSA monitoring to detect a PSA doubling time of less than 3 years and planned repeat biopsies at 6–12 months from diagnosis (and thereafter 3–4 yearly), with the aim of early intervention for those who progress (Duchesne 2011, Lane, Donovan et al. 2014).

Active surveillance is not to be confused with watchful waiting, which is also a programme that omits active treatment but is reserved for those who are

considered too high risk for active treatment, such as multiple comorbidities. Older men (60-70 and older) with a higher numbers of existing comorbidities (n≥3) are more likely to die of other causes than of their prostate cancer and treatment may actually cause more harm (Lane, Donovan et al. 2014, Daskivich, Fan et al. 2015). In this case, it is unlikely that the presence of prostate cancer is going to affect OS.

1.4.1.2 Surgery

Radical prostatectomy is surgical resection of the prostate and is usually offered for the younger fitter patients. Older patients are at higher risk of incontinence with this procedure. It is conducted via an open retropubic or laparoscopic approach with or without robotic surgery (Duchesne 2011).

1.4.1.3 External bean radiotherapy

The technique for prostate radiotherapy in the UK is intensity modulated radiotherapy with image guided radiotherapy. Radiotherapy is used in both localised and locally advanced disease (Duchesne 2011).

1.4.1.4 Brachytherapy

Brachytherapy is an alternative radiation therapy which can be delivered directly into the prostate by transperineal implantation of permanent radioactive seeds (usually iodine-125, low dose rate brachytherapy), or with a temporary implant (high dose rate brachytherapy) (Duchesne 2011). A predominant advantage of this method is the low dose of radiation to the surrounding tissues. Brachytherapy can be used in conjunction with external beam radiation therapy where very high doses of radiation are warranted.

1.4.1.5 Exercise

Exercise is a promising emerging supportive therapy for cancer. This includes emerging data in localised and locally advanced prostate cancers. This is covered in more detail in the proceeding sections however a recently published multi-site feasibility RCT of aerobic exercise in men with locally advanced disease, the PANTERA trial, demonstrated that men in the intervention group had a reduction in body mass (although body composition was not measured), systolic and diastolic blood pressure and improved QoL (Bourke, Stevenson et al. 2018). However, as this study was a feasibility

study, there was no indication to the statistical significance of these findings as primary outcomes were feasibility measures.

1.4.2 Advanced prostate cancer: Androgen deprivation therapy

Hormone manipulation, or ADT, is the principle therapy for inoperable or metastatic disease. As mentioned previously, this can be achieved by either medical (GnRH analogues) or surgical castration (orchidectomy). As most prostate cancers are initially dependant on androgenic stimulation, both methods of ADT downregulate the level of prostate cancer cell proliferation compared to the rate of cell apoptosis and therefore tumour regression is achieved. About 80-90% of prostate cancers at initial diagnosis are sensitive to androgens and androgen ablation is effective at inducing regression of the disease (Heinlein and Chang 2004).

Orchidectomy is a relatively simple surgical procedure with minor surgical risks. However, despite its low physical morbidity, the development of pharmacological agents to achieve castration and the associated psychological effects of orchidectomy means it has fallen out of favour (Sharifi, Gulley et al. 2005). Medical castration has evolved from using oestrogens, to GnRH agonists and later the use of GnRH antagonists.

Oestrogens work predominantly by having anti-gonadotrophic effects however direct effects on the tumour leading to regression, including increased synthesis of SHBG, inhibition of 5α-R, and direct effects on Leydig cell function, have all been reported (Cox and Crawford). GnRH receptor agonists include drugs such as leuprolide, bruserelin and goserelin. The agonists work to inhibit LH production from the pituitary, which in turn causes a suppression of testosterone and DHT (Cook and Sheridan 2000). However, when first administered GnRH agonists can cause a surge in the release of LH, and in turn a surge in testosterone and DHT; around 5-12 days before the inhibition of LH. This surge in LH presents clinically as "tumour flare" where symptoms such as bone pain, compression of a nerve root, spinal cord compression and ureter constriction can worsen (Cook and Sheridan 2000). Tumour flare can be extremely dangerous and often leads to clinical emergencies. GnRH antagonists and anti-androgens such as

flutamide or cyproterone acetate, have been demonstrated to reduce the flare reaction and can be used instead of GnRH agonists (Cook and Sheridan 2000, Sharifi, Gulley et al. 2005).

GnRH antagonists, such as degarelix, may also be used as an alternative for medical castration. GnRH antagonists work by binding to the GnRH receptors without eliciting a response, competing with endogenous GnRH. The antagonists block GnRH and inhibits LH production, which in turn causes a suppression of testosterone and DHT (Drudge-Coates 2010). Degarelix was compared to leuprolide for achieving and maintaining testosterone suppression in a 1 year phase III trial of 610 prostate cancer patients (Klotz, Boccon-Gibod et al. 2008). The study demonstrated that degarelix was as effective as leuprolide in maintaining low testosterone levels throughout the treatment period and that it achieved testosterone and PSA suppression significantly faster than leuprolide. PSA suppression was also maintained throughout the study. Degarelix is recommended for treating advanced hormone-dependant prostate cancer in people with spinal metastasis (NICE 2016).

1.5 The prostate cancer care pathway

Established healthcare pathways are essential to facilitate the structured, multidisciplinary and high quality care of a patient from the point of diagnosis. Such pathways ensure a translation of national guidelines to implementation in local protocols and subsequently practice. Prostate cancer is no different, and The National Institute for Health and Care Excellence (NICE) have continued to provide the UK with national guidelines on how these men should be effectively managed. These recommendations are based on systematic reviews of the current evidence regarding prostate cancer treatments and cost effective data (Graham, Kirkbride et al. 2014).

As discussed earlier, there are many challenges faced when deciding on the most appropriate and effective care for a patient. Clinicians are faced with balancing the perceived benefits to the potential harm when deciding the optimal treatments, where policy makers and governing bodies must decide on the cost effectiveness of treatments. Where multiple treatment options

exist, management of patients becomes ever more complex. Such is the case in the prostate cancer care pathway. The care of men with prostate cancer is multidisciplinary spanning both urology and oncology departments. The decision making on treatments for these men becomes a team approach, crucially involving the patient themselves. The aim of this clinical pathway, like all pathways, is to ensure continuity, increase multidisciplinary integration and facilitate appropriate patient education, treatment and care for cancer patients (de Vries, van Weert et al. 2007).

Details on the treatment options for the different stage of disease have been described; however the schematic below (figure 1.3) gives a very brief indication of the prostate cancer care pathway. The boxes marked in blue indicate where a man's care will be predominantly overseen by a urologist and those in red indicate where his care is overseen by an oncologist in the UK, with the exception of radiotherapy which is overseen by a clinical oncologist. This section details the prostate cancer care pathway with a focus for men with advanced metastatic disease.

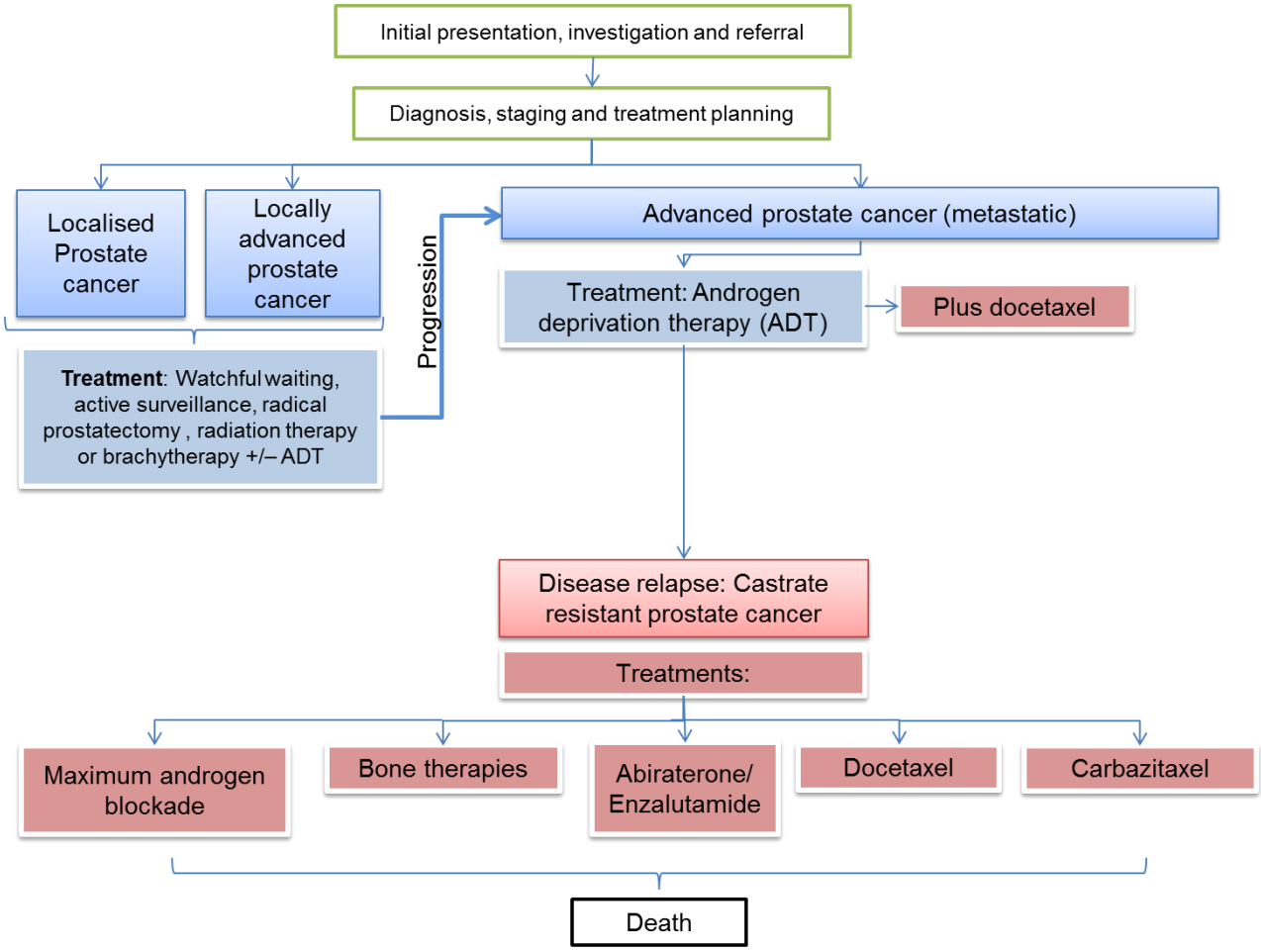

Figure 1.3 The prostate cancer care pathway. Developed from the NICE guidelines (NICE 2014)

1.6 Therapeutic changes to the pathway

The treatment of prostate cancer poses unique problems when compared to other neoplastic diseases. The natural history of prostate cancer can be very long, with some men surviving with their disease for over two decades. Men can therefore have aggressive therapies over very long periods of time and the AEs of these therapies as a result could cause more harm than good.

1.6.1 Pathway changes for hormone sensitive advanced prostate cancer

Since the development of PSA testing, 5 year survival statistics for prostate cancer have significantly increased since the early 1990s. As a result, the diagnosis of prostate cancer was occurring at much earlier stages and survival was therefore better where treatment could be offered with curative intent, but this could be due to the "lead time bias" and stage infiltration.

For advanced disease however, ADT, either alone or in combination, remains the cornerstone of treatment. However, in 2015 improvements in survival of men with the use of docetaxel at earlier (hormone sensitive) stages of metastatic (M1) prostate cancer were demonstrated in the multicentre RCTs STAMPEDE and CHAARTED (James, Spears et al. 2015, Sweeney, Chen et al. 2015). The STAMPEDE trial also evaluated two other agents, zolendronic acid and celecoxib as well as combination of the three agents in different arms (James Nicholas, Sydes Matthew et al. 2009, James, Sydes et al. 2012). Both trials demonstrated a survival benefit with the introduction of docetaxel upon initiation of ADT when compared to the ADT group alone (or standard care).

In the CHAARTED trial, in patients with hormone sensitive but higher volume disease, a survival benefit of 57.6 vs 44.0 months (docetaxel + standard care vs standard care only) (hazard ratio (HR) 95% confidence interval (CI) 0.47 to 0.81; p <0.001) (Sweeney, Chen et al. 2015). In the STAMPEDE study, men with newly diagnosed M1 hormone sensitive disease had a greater failure free survival 37 vs 20 months (docetaxel + standard care vs standard care only) (HR 0.61, 95% CI 0.53-0.70; p $=0.413 \times 10^{-13}$), median failure-free survival 37 months (HR 0.61, 95% CI 0.53-0.70; p $=0.413 \times 10^{-13}$) (James, Sydes et al. 2016). The study also addressed the use of zoledronic acid alone or in combination with docetaxel (plus standard care) and found no overall improvement in survival outcomes compared to docetaxel alone (plus standard care). Consequentially, in 2015 changes in clinical practice followed and an increasing number of men received docetaxel chemotherapy earlier in their prostate cancer care pathway (figure 1.3).

The implication of this pathway change however is yet to be evaluated. Furthermore, the predominant benefits of chemohormonal therapy was observed in those with higher volume disease in both trials, therefore the role of chemohormonal therapy for patients with N0/1 and M0 disease is still being evaluated and the benefits (or risks) of the treatment for this group is less clear. There were reports of increased fatigue and neutropenic fever observed in the CHAARTED trial although overall docetaxel plus standard care was well tolerated in both studies. However, the long-term effects of

early chemohormonal therapy have yet to be elucidated, and it is not clear how such treatments may impact on QoL, tolerance to later therapy, subsequent optimal treatment sequencing and/or cross-resistance with later treatments.

More recently, the second generation anti-androgens have been of great interest for their use earlier in the pathway where previously they have been used for castrate sensitive disease. Several new arms to the STAMPEDE have been introduced to assess the efficacy of enzalutamide and abiraterone in hormone naïve men initiating ADT (standard care) with M1 advanced prostate cancer (Attard, Sydes et al. 2014). At the point of writing this thesis the results for the enzalutamide + ADT arm in the STAMPEDE trial have not yet been published. However, in 2017 the study demonstrated that in the 3 year follow up period the failure-free survival was 75% in the abiraterone + ADT group and 45% in the ADT-alone group (HR for treatment failure, 0.29; 95% CI, 0.25 to 0.34; p <0.0001). The mean failure-free survival time was 43.9 months in the abiraterone + ADT group and 30.0 months in the ADT-alone group in the first 54 months after randomisation, a difference of 13.9 months (95% CI, 12.3 to 15.4) (James, de Bono et al. 2017).

These findings however did bring about a problem; there is no direct comparative data of docetaxel + ADT vs abiraterone + ADT. However, a sub analysis was later conducted which demonstrated no significant difference in survival between the two treatment modalities. Early measures of failure free survival, freedom from metastatic disease progression and freedom from symptomatic skeletal events favoured abiraterone, but the data was underpowered (Sydes, Mason et al. 2017, Wallis, Klaassen et al. 2017). Toxicity profiles for either regimen were similar. This may go some way to explaining why abiraterone + ADT has not been adopted in clinical practice in the NHS, more robust comparative data is needed. Once more, abiraterone is approved for use in later stages of disease (in CRPC), and the long-term effects of abiraterone will be of significant importance if its use is shifted to earlier in the pathway, similar to the concerns described for docetaxel. This too could result in problems with determining optimal

treatment sequencing at later stages of disease and potential cross-resistance of subsequent therapies.

2. Castrate resistant prostate cancer

2.1 Definition, diagnosis and prevalence

CRPC is progression of prostate cancer (clinically, biochemically or radiographically) despite the removal of testosterone of gonadal origin via ADT. Clinically, this might present as a symptomatic progression, biochemically this will present as a rise in PSA and radiographically this presents as the appearance of new metastasis or visceral disease (via imaging from computed tomography, magnetic resonance imaging, or radionuclide bone scintigraphy) or lymphadenopathy. Although other terms have been used for this stage of disease, such as hormone refractory or hormone resistant, CRPC has been adopted from the understanding that prostate cancer cells maintain androgen sensitivity via a number of mechanisms (Mostaghel, Page et al. 2007). To determine the presence of castrate resistant disease, it is imperative that testosterone levels are determined and shown to be at castrate levels (<50 ng/dl (1.73 nmol/l)), only then can a diagnosis of CRPC be made (Hotte and Saad 2010, Nishiyama 2014).

The incidence of men diagnosed with prostate cancer developing CRPC is approximately 10-20% within 5 years (Kirby, Hirst et al. 2011, Scher, Solo et al. 2015). For men diagnosed with CRPC without metastasis, about 33% will develop metastasis within 2 years (Smith, Kabbinavar et al. 2005, Kirby, Hirst et al. 2011). The epidemiological data on CRPC is spare and inconsistent but a review in 2012 estimated the mean survival time of men with CRPC at 13.5 months in the UK (Hirst, Cabrera et al. 2012). It's been estimated that about 17.8% of men with prostate cancer have castrate resistant disease (Ritch and Cookson 2016) but again these figures can vary wildly.

2.2 Pathophysiology and clinical manifestation

Clinical response to ADT, castrate responsive disease, occurs in around 80% of cases, with the remaining 20% or so of men being deemed castrate

resistant from the outset (Greasley, Khabazhaitajer et al. 2015). Where tumour regression is initially achieved, and potentially could last for several years, the disease will inevitably relapse. However the exact process by which prostate cancer cell proliferation becomes independent of ADT is unclear but several few mechanisms have been identified.

It was previously thought that the development of CRPC was due to a loss of responsiveness of the AR however it has been demonstrated that the signalling of the AR is almost never lost but in fact is maintained despite low level circulating androgens through a variety of proposed mechanisms (Feldman and Feldman 2001). These include intratumoral production of androgens via increased expression of steroidogenic enzymes, apoptosis evasion, altered AR transcriptional coregulator expression, AR posttranslational modification (phosphorylation), ligand-independent pathways activating AR, amplification, and selection of genetically modified AR with constitutive active AR splice variants summarised in figure 1.4 (Hotte and Saad 2010, Greasley, Khabazhaitajer et al. 2015). As a result, whilst androgen deprivation ceases to control disease progression, the androgen receptor remains an important target in castrate resistant prostate cancer therapies.

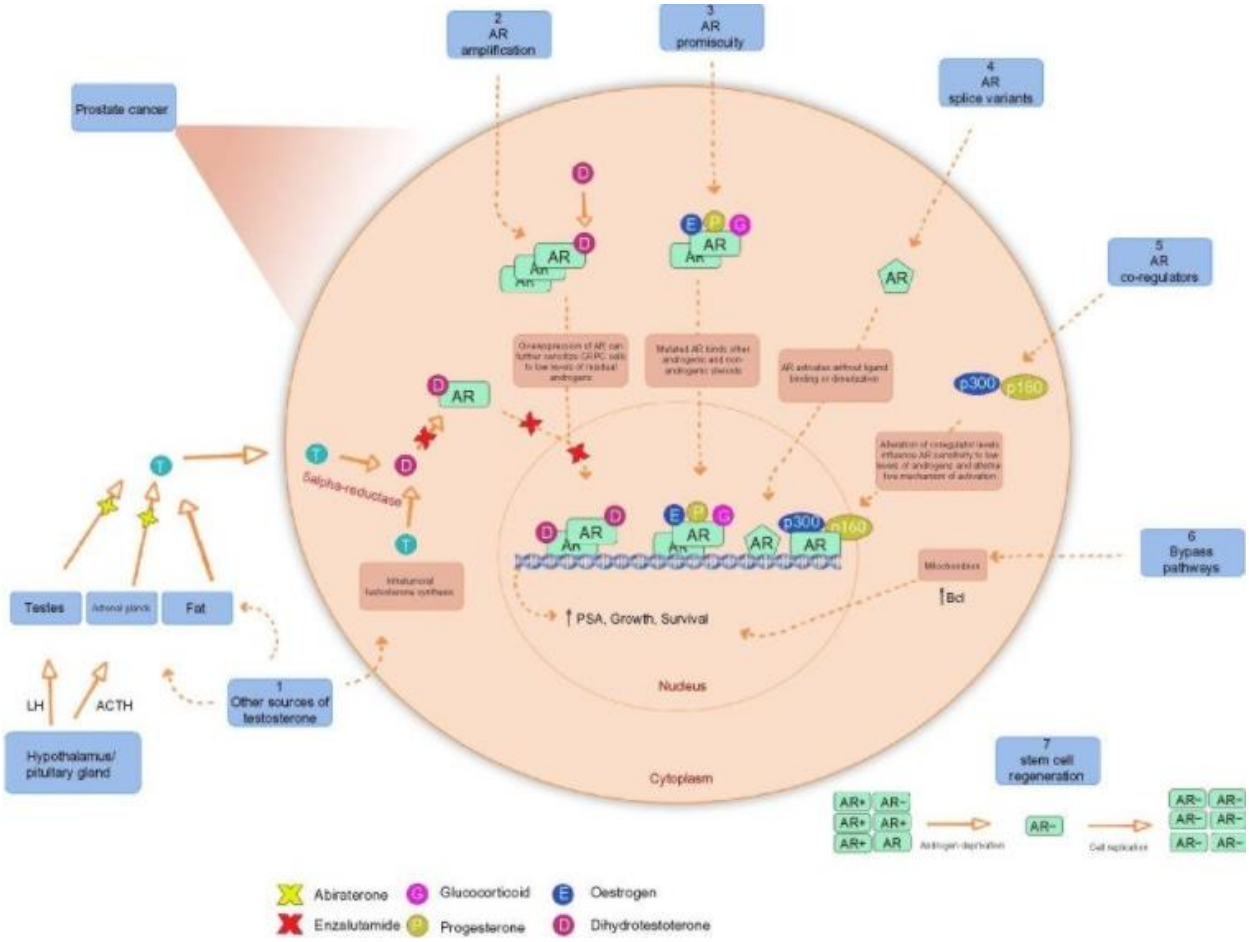

Figure 1.4 Proposed mechanisms contributing to the development of castrate resistant prostate cancer taken from (Greasley, Khabazhaitajer et al. 2015) with permission.

Unfortunately, around 90% of patients with CRPC will develop bone metastasis which can present as a bone pain, a pathological fracture or bone marrow failure (Hotte and Saad 2010).

2.3 Treatments for castrate resistant prostate cancer

2.3.1 Changing treatment paradigms in castrate resistant prostate cancer

Therapies used to treat CRPC are not curative but palliative however these agents have demonstrated not only to improve OS but also disease symptoms (table 1.3). Prior to 2010, therapeutic options for men with CRPC aimed at prolonging life remained limited to chemotherapy, specifically docetaxel, which demonstrated a significant survival benefit (18.9 months vs 16.5 months in the docetaxel groups vs mitoxantrone group) (Petrylak, Tangen et al. 2004, Tannock, de Wit et al. 2004). Previous to docetaxel,

treatments included maximum androgen blockade (MAB; using bicalutamide, nilutamide, flutamide and/or surgical castration) and oestrogens (Group. 1984, Crawford, Eisenberger et al. 1989, Dijkman, Janknegt et al. 1997). Another first generation CRPC treatment includes oral ketoconazole, which was used to suppress gonadal, as well as adrenal, androgen synthesis via inhibition of enzymes in the steroidogenesis pathway (Sanford, Drago et al. 1976).

Post 2010, great improvements in the treatment of CRPC were seen with the introduction of several new treatments (cabazitaxel, abiraterone, enzalutamide, and radium-223) (Kantoff, Higano et al. 2010, de Bono, Logothetis et al. 2011, Oudard 2011, Scher , Fizazi et al. 2012, Scher, Fizazi et al. 2012, Parker, Nilsson et al. 2013). Sipuleucel-T was also shown to demonstrate a survival benefit in phase III trials however its recommended use by NICE was withdrawn in 2015 (Lovett, George et al. 2015).

This surge in CRPC therapies brought uncertainties around the optimal sequencing of such agents. Prior to the pathway change in 2015 for men with hormone sensitive disease, there were three treatment spaces for drug development in CRPC: pre-docetaxel; docetaxel combinations; and post-docetaxel (Omlin, Pezaro et al. 2013). Since this pathway change there is a lack of data for treatments in the post-docetaxel setting. It is now the case that more men relapsing after initial ADT treatment will also have had a docetaxel regimen and therefore data on optimal treatment regimens becomes pivotal.

Unfortunately, preclinical data suggest that use of additional treatments might confer resistance to further therapies where they allow expansion of prostate cancer clones with resistant mutations (Baca, Prandi et al. 2013). Details on the incremental survival benefits of further post docetaxel + ADT treatment as well as toxicity profiles and QoL benefits are critical. Although there are a number of approved agents in CRPC post docetaxel, we do not know how the timing of the docetaxel regimen at much earlier stages of disease will affect the disease evolution. At such a late and advanced stage

of disease, treatment decisions aimed to balance survival and the maintenance of QoL are paramount.

The severity of disease symptoms and the AEs which can impede QoL are essential considerations when considering the initiation and sequencing of treatment. In trials which addressed newer agents such as abiraterone, enzalutamide and sipuleucel-T, these men were minimally symptomatic with a good performance status (PS) (Kantoff, Higano et al. 2010, de Bono, Logothetis et al. 2011, Scher, Fizazi et al. 2012). In these trials the above agents were very well tolerated and therefore it is the case that the use of these agents is in patients with minimal symptoms or a good performance status (PS 0-1). For patients with symptomatic disease or with a poorer performance status it is less clear how these agents may be tolerated and therefore the direct impact to QoL. Therefore treatment options for this group remain limited.

2.4 Treatments for castrate resistant prostate cancer: Adverse events and quality of life

Improvement or the maintenance of QoL is of fundamental importance to men with CRPC. Multiple studies have addressed the impact of the pharmacological agents used to treat CRPC on QoL. The four predominant treatments for CRPC in the UK are discussed.

2.4.1 Docetaxel

Docetaxel has been associated with numerous AEs known to negatively impact QoL and is one of the most commonly used agents in CRPC (Al-Batran, Hozaeel et al. 2015). Studies which have evaluated the impact of docetaxel on QoL have suggested that minimally symptomatic patients with good QoL scores at baseline tended to respond better to treatment (Caffo, Sava et al. 2011). The landmark study of docetaxel for advanced prostate cancer reported ≥ 1 serious adverse events (SAEs) occurred in 26% of the patients that received three weekly docetaxel and two treatment related deaths (Tannock, de Wit et al. 2004). Furthermore, grade 3/4 neutropenia was significantly more common those who received three weekly docetaxel (32%) than for those patients receiving weekly docetaxel or mitoxantrone (2% and 22%). In addition, nausea and vomiting were common with all

regimens but diarrhea was significantly more frequent in the docetaxel schedules. Discontinuation of treatment with docetaxel was due to fatigue, musculoskeletal events, nail changes, sensory neuropathy, and infection. However this study showed when compared to the mitoxantrone and standard care, the HR for death in the three weekly docetaxel arm was 0.76 (95% CI 0.62 to 0.94, p =0.009) indicating a statistically significant improvement in OS (Tannock, de Wit et al. 2004). A cochrane review demonstrated that overall, studies which evaluated the OS benefit of a docetaxel regimen compared to best standard care in men with CRPC was <2.5 months, however the review evaluating these landmark studies was published in 2006 and the standard of care has evolved since then as discussed (Shelley, Harrison et al. 2006).

2.4.2 Enzalutamide

The AFFIRM trial, one of the landmark phase III trials evaluated enzalutamide in men with CRPC post-chemotherapy in 1199 men. The study showed the incidence of grade≥ 3 AEs was lower in the enzalutamide group (45.3%) than in the placebo group (53.1%) (Scher, Fizazi et al. 2012). In the enzalutamide group, AEs included fatigue (34%), diarrhea (21%), hot flashes (20%), musculoskeletal pain (14%), headache (12%), cardiac disorder (6%), seizure (<1%), and myocardial infarction (<1%). AEs leading to death occurred in 3% (n =23) of the patients in the enzalutamide group. Enzalutamide was superior to a placebo in terms of QoL measured by the FACT-P questionnaire (43% in the enzalutamide group vs 18% in placebo arm had a 10 point improvement in FACT-P scores).

However, in the PREVAIL phase III study of 1,717 CRPC randomly assigned to receive enzalutamide or a placebo, toxicity profiles were not quite as good compared to placebo (Beer , Armstrong et al. 2014). Grade≥ 3 AEs occurred in 43% of the patients in the enzalutamide group vs 37% of those in the placebo group. Common AEs experienced in the enzalutamide group included fatigue (36%), back pain (27%) and constipation (22%). AEs leading to death occurred were similar in each group (4%).

2.4.3 Abiraterone

The double-blind phase III trial of abiraterone plus prednisolone (n =791) and a placebo plus prednisolone (n =394) demonstrated that both groups had a similar toxicity profiles (de Bono, Logothetis et al. 2011). The most common AE of was fatigue (abiraterone plus prednisolone: 44% vs placebo plus prednisolone: 43%). The other common AEs were back pain, nausea, constipation, bone pain, and arthralgia which were similar across both groups. In another study, AEs were more common in the abiraterone plus prednisolone group for fluid retention/edema, and hypokalemia (31 and 17% vs Placebo: 22 and 8% respectively). Mortality was also similar in both groups (abiraterone group: 13% vs placebo group: 16%) (Fizazi, Tran et al. 2017). Although both studies assessed QoL using the FACT-P questionnaire, neither reported on changes in scoring for men in the studies.

2.4.4 Carbazitaxel

The phase III study a large-scale compared cabazitaxel plus prednisone (n =371) to mitoxantrone plus prednisolone (n =371) (the TROPIC trial) (de Bono, Oudard et al. 2010). The most common grade≥ 3 AEs described in the cabazitaxel arm were neutropenia (82%), leukopenia (68%), anaemia (11%), and thrombocytopenia (4%). The most common non-haematological AE was diarrhoea (47% for all grades). 5% patients in the cabazitaxel group died due to AEs.

Unfortunately the above study also failed to report on QoL outcomes. Another study addressed the safety of carbazitaxel and its impact on QoL (Bahl, Masson et al. 2015). QoL was measured using the EQ-5D-3L questionnaire and the visual analogue scale, the study showed a trend towards improvement in QoL and in pain scores during treatment however neither of these findings were significant (Bahl, Masson et al. 2015).

Table 1.3 Current treatment options for CRPC taken from (Greasley, Khabazhaitajer et al. 2015) with permission

Therapeutic agent	Mechanism of action	Clinical trial status	Therapeutic efficacy
Docetaxel	Stabilization of tubulin, induction of cell cycle arrest and inhibition of cell proliferation	FDA approved	Overall survival benefit vs mitroxantrone (2.0–2.9 month) and palliation of cancer-associated symptoms
Cabazitaxel	Stabilization of tubulin, induction of cell cycle arrest and inhibition of cell proliferation	FDA approved for men after failure of docetaxel	Overall survival benefit vs mitroxantrone (2.3 months) and palliation of cancer-associated symptoms.
Sipuleucel-T (provenge)	Enhancement of men's autologous antigen-presenting cells to induce cytotoxic response against prostate cancer cells	FDA approved	Increase in overall survival (4.4 months) but not progression-free survival
Abiraterone acetate	Irreversible inhibition of CYP17 and subsequent androgen synthesis	FDA approved in the pre- and post-docetaxel settings	Increase in overall survival (almost 4 months), radiographic progression-free survival, time to PSA progression, and palliation of cancer- associated symptoms
MDV3100 (enzalutamide)	AR antagonist preventing nuclear translocation and binding to chromatin	FDA approved in the post-docetaxel setting Phase III clinical trial in comparison with placebo in chemotherapy-naïve men	Increase of overall survival (4.8 months), radiographic progression-free survival and time to PSA progression. Similar benefits reported
BEZ235	Inhibition of PI3K	Phase I/II clinical trials in combination with	Results pending

		Abiraterone acetate (NCT01717898)	
RAD001 (everolimus)	Inhibition of mTOR	Phase II clinical trial in combination with bicalutamide (NCT00630344)	Failure to show increase in time to progression
Alpharadin (Radium-223)50	An alpha emitter which selectively targets bone metastases with alpha particles	Phase III clinical trial in men who had received, were not eligible to receive, or declined Docetaxel	Increase of overall survival (median, 14.0 months vs 11.2 months [placebo]; HR 0.70).
Dovitinib (TK1258)	Inhibition of FGFR	Phase II clinical trial in men after failure of docetaxel-based chemotherapy (NCT01741116)	Results pending
Cabozantinib (XL184)	Inhibition of c-MET	Phase II clinical trial in men with mCRPC (NCT01428219) Phase III clinical trial in comparison with prednisone in men previously treated with docetaxel and abiraterone or MDV3100 (COMET-1, NCT01605227) Phase III clinical trial in comparison with mitoxantrone and prednisone (COMET-2, NCT01522443)	Reduction of soft tissue lesions, resolution of bone scans, increase of progression-free survival Results pending

Abbreviations: CRPC, castration resistant prostate cancer; FDA, Food and Drug Administration; PSA, prostate-specific antigen; mCRPC, metastatic castration resistant prostate cancer; PSA, prostate-specific antigen; AR, androgen receptor; vs, versus.

2.5 Treatment decisions: balancing quality of life and survival

The debate regarding sequencing of treatment is weighted heavily in prolonging OS. However, CRPC patient preferences regarding treatments have shown a greater concern for the potential loss of QoL due to treatment AEs than the prolonging of survival (Uemura, Matsubara et al. 2016). In addition, the relationship between disease progression and the emergence of worsening symptoms is not well defined and there is limited data on predicting worse outcomes for patients with progressive disease. Given the AEs associated with treatments for CRPC, balancing QoL and survival is a pivotal issue.

ADT has long been associated with detrimental effects to QoL (Lubeck, Grossfeld et al. 2001, Green, Pakenham et al. 2002, Dacal, Sereika et al. 2006). As these men will have remained on ADT for a number of years they are a risk of developing significant AEs, worsening with time. Studies have demonstrated that for some of these men, there is significant regret in treatment choices made at earlier stages of their disease due to the significant impact on their QoL (Clark, Wray et al. 2001). Some of this is associated with problematic communication with the treating clinician.

Although QoL is of fundamental importance to these men there appears to be a significant lack of data in research with a large amount of clinical studies failing to report QoL outcomes. Clinicians are therefore faced with the difficult task of balancing unknown effects on QoL with survival benefit, which as discussed can also be uncertain. This can be compounded further by the fact these men are faced with more complications and comorbidities. In addition, shared decision making on therapy is a very individual approach, with some patients desiring minimal input, delegating this to the clinician, and others wanting to take the reigns over their care (Edwards and Elwyn 2009).

It is clear however that as a key aspect of patient and clinician decisions on treatment, maintenance of QoL throughout prostate cancer care becomes integral to successful outcomes. Interventions involving the maintenance or improvement in QoL for men with CRPC are therefore essential.

2.5.1 Hypogonadism: A therapeutic minefield

The landmark publication by Huggins and Hodges stated there was a symptomatic relief in patients with clinical prostate cancer (Huggins, Stevens et al. 1941). The study led to the widespread use of bilateral orcidectomy and acceptance of the androgen hypothesis, which supports the role of androgens in prostate cancer growth, proliferation, and progression; however the ADT palliative effects were confused with cure or permanent cancer control. The androgen hypothesis was further supported by animal studies which demonstrated induced prostate tumours with testosterone administration (Pollard, Luckert et al. 1982). Two historical studies in prostate cancer patients with metastatic or advanced prostate cancer reported tumour growth and/or recurrence (Prout and Brewer 1967, Fowler and Whitmore 1981).

Since, ADT achieved through surgery or from pharmacological agents, has demonstrated to result in numerous significant physiological and psychological AEs. Physiological AEs include a loss of muscle mass, increasing fat mass, hot flashes, fatigue, sexual dysfunction, insulin resistance, increased cardiovascular disease (CVD) and detrimental effects to bone mineral density (BMD) increasing bone fracture risk (Basaria, Lieb et al. 2002, Galvão, Spry et al. 2008, Bagrodia, DiBlasio et al. 2009, Sountoulides and Rountos 2013, Cheung, Zajac et al. 2014). QoL is greatly affected by this and is compounded by the negative psychological effects also associated with treatment (Green, Pakenham et al. 2002, Dacal, Sereika et al. 2006). A summary of the AEs of ADT is given in table 1.4.

Table 1.4 Adverse effects associated with ADT

Adverse effect	Type of study	Measures	Findings	Conclusion	Evidence
Sexual function	**Potosky 2002:** A population-based random sample of 661 men undergoing ADT. **Elliot 2010:** A multidisciplinary working group (21 clinicians and researchers).	**Potosky 2002:** Medical Outcomes Study 36-item generic health status questionnaire **Elliot 2010:** Expert opinion of the side effects of ADT that affect the QoL of men with prostate cancer and their partners.	**Potosky 2002:** Decline in multiple attributes of sexual function, including libido, erectile function, and frequency of sexual activity in men receiving ADT **Elliot 2010:** Side effect identified included body feminization (gynecomastia, weight gain and loss of muscle mass, genital shrinkage, hot flashes), sexual changes (erectile dysfunction, loss of sexual desire, absent orgasm, infertility).	Castration levels of circulating testosterone results in a loss of potency, decreased genital size, sexual dysfunction and loss of libido.	(Potosky, Reeve et al. 2002, Elliott, Latini et al. 2010)
Fatigue	**Stones 2000:** population based study of 62 men starting ADT. **Pirl 2008:** Cohort of men with advanced or recurrent prostate cancer (n =52) were randomly assigned to receive either leuprolide or bicalutamide. **Cherrier 2009:** A cohort of (n-=20) hormone naïve men with prostate cancer were treated with intermittent ADT.	**Stone 2000:** Fatigue Severity Scale (FSS) **Pirl 2008:** Fatigue Severity Scale questionnaire. **Cherrier 2009:** Profile of Mood States questionnaire.	**Stone 2000:** A significant increase in subjective fatigue in patients with prostate cancer after treatment with LHRH analogues. Overall 66% of men reported an increase in fatigue severity. **Pirl 2008:** Mean FSS scores increased significantly from baseline (μ:24.43, SD:11.75) to 6 months (μ:27.93, SD:13.52) remaining steady at 12 months. **Cherrier 2009:** A significant increase fatigue in the ADT group at month 9 compared to baseline, and a trend for increased fatigue in month three compared to baseline ($p < 0.08$).	Fatigue worsens over time following ADT initiation after only a short period of treatment, as little as 3 months. As many as 66% of men treated with ADT have been reported to experience clinically significant fatigue.	(Stone, Hardy et al. 2000, Pirl, Greer et al. 2008, Cherrier, Aubin et al. 2009)
Body composition	**Basaria 2002**: cross-sectional study: 20 men undergoing medical castration for at least 12 months prior to the onset of the study (ADT group); 18 men with non-metastatic disease who were post prostatectomy and/or radiotherapy but had not undergone ADT (non-ADT	**Basaria 2002**: DEXA **Berutti 2002**: DEXA **Smith 2002**: DEXA	**Basaria 2002**: BMD was significantly lower in men on ADT. The ADT group had higher fat mass compared to the other groups ($p = 0{\cdot}0001$) and significantly reduced upper body strength ($p = 0{\cdot}001$). **Berutti 2002**: At baseline 46% (at spine) and 40% (at hip) of cases were classified as osteopenic and 14% (at spine) and 4% (at hip) as osteoporotic. ADT significantly decreased BMD either at the lumbar spine or the hip. Lean body mass decreased	ADT is associated with significant decreases in LBM and increases in visceral and total body fat mass. This also associated with a decline in muscle	(Basaria, Lieb et al. 2002, Berruti, Dogliotti et al. 2002, Smith, Finkelstein et al. 2002)

	group); and 20 age-matched normal men (control group). **Berutti 2002**: Prospective cohort study of 35 patients with prostate cancer who received ADT for 12 months. **Smith 2002:** RCT of men with prostate cancer (n =40) locally advanced, node-positive or biochemically recurrent prostate cancer and no prior ADT were treated with leuprolide or leuprolide and pamidronate (plus biclutamide).		whereas fat body mass consistently increased with ADT. **Smith 2002**: Weight increased by μ=2.4%. Percentage fat body mass increased by μ=9.4%, and percentage lean body mass decreased by μ=2.7%. Cross-sectional paraspinal muscle area decreased by μ=3.2%.	strength, fitness and physical function. The increase in fat mass is associated with increasing body weight, BMI, increased insulin resistance and metabolic dysfunction.	
Cardiovascular morbidity	**Keating 2006**: Observational study of a population-based cohort of 73,196 diagnosed with locoregional prostate cancer treated with GnRH agonists or orchiectomy. **Saigal 2007**: A cohort of newly diagnosed men (n = 22,816 subjects). **Tsai 2007:** Data from the Cancer of the Prostate Strategic Urologic Research Endeavor database of 3262 patients treated with radical prostatectomy and 1630 patients treated with external beam radiation therapy, brachytherapy, or cryotherapy for localized prostate cancer. **Jespersen 2014:** A national	**Keating 2006:** Surveillance, Epidemiology and End Results Medicare data was used for analysis. **Saigal 2007**: Using a multivariate model, the risk of subsequent cardiovascular morbidity in men with prostate cancer who were treated with ADT was calculated. **Tsai 2007:** Risk regression analyses assessed whether use of ADT was associated with a shorter time to death from cardiovascular causes.	Keating 2006: GnRH agonist use was associated with significant increased risk of incident diabetes (HR: 1.44), coronary heart disease (HR: 1.16), myocardial infarction (HR: 1.11), and sudden cardiac death (HR, 1.16). **Saigal 2007**: Newly diagnosed prostate cancer patients who received ADT for at least 1 year were found to have a 20% higher risk of serious cardiovascular morbidity compared with similar men who did not receive ADT. Subjects began incurring this higher risk within 12 months of treatment. **Tsai 2007**: ADT use (HR: 2.6) was associated with statistically significant increased risk of death from cardiovascular causes in patients treated with radical prostatectomy. Among patients 65 years or older treated with radical prostatectomy, the 5-year cumulative incidence of cardiovascular death was 5.5% in those who received ADT and 2.0% in those who did not. Among patients 65 years or older treated with external beam radiation therapy,	ADT is associated with an increased risk of myocardial infarction with HR of 1.09. CVD is still the most common cause of death in men diagnosed with prostate cancer and men are 2.6 times more likely to die from a cardiovascular event then men not receiving ADT. Some evidence suggests that men on ADT have a 20-25% higher risk of coronary artery	(Keating, O'malley et al. 2006, Saigal, Gore et al. 2007, Tsai, D'Amico et al. 2007, Jespersen, Norgaard et al. 2014)

	cohort study of all patients with incident prostate cancer registered in the Danish Cancer Registry from January 1, 2002, through 2010 (n = 31,571).	**Jespersen 2014**: Cox regression analysis to estimate HR of myocardial infarction and stroke for ADT users.	brachytherapy, or cryotherapy, ADT use was associated with a higher cumulative incidence of death from cardiovascular causes. **Jespersen 2014**: Men treated with ADT had an increased risk for mycocardial infarction and stroke with adjusted HRs of 1.31 and 1.19 respectively, compared with nonusers of ADT.	disease compared to men not receiving ADT. Risk factors for CVD are metabolic syndrome, diabetes and sarcopenic obesity.	
Bone health	**Morote 2007**: A cross-sectional study that included 390 patients with prostate cancer who were free of bone metastases. **Hamilton 2010:** 12 month prospective observational study of 26 men with non-metastatic prostate cancer during the first year of ADT. **Beebe-Dimmer 2012:** Data from a cohort of the Surveillance, Epidemiology, and End Results–Medicare linked database, for fracture incidence related to the exposure and dose among prostate cancer patients of GnRH.	**Morote 2007:** DEXA **Hamilton 2010:** High-resolution peripheral quantitative computed tomography. **Beebe-Dimmer 2012:** Adjusted HRs using time-dependent Cox regression	**Morote 2007:** The osteoporosis rate was 35.4% in hormone-naive patients, 42.9% after 2 years of ADT, 49.2% after 4 years, 59.5% after 6 years, 65.7% after 8 years, and 80.6% after 10 or more years. Conversely, the rate of normal BMD decreased from 19.4% in hormone-naive patients to 17.8% after 2 years of ADT, 16.4% after 4 years, 10.8% after 6 years, 5.7% after 8 years, and 0% after 10 or more years of ADT **Hamilton 2010:** After 12 months of ADT, total bone density decreased by 5.2% at the distal radius and 4.2% at the distal tibia. Total testosterone levels were independently associated with decreased total and corrected cortical volumetric BMD at the tibia. **Beebe-Dimmer 2012:** ADT was associated with an increased rate of fracture in both non-metastatic patients (HR: 1.34) and metastatic patients (HR: 1.51). Fracture rates increased with increasing cumulative GnRH dose but decreased with increasing number of months since last use in each dose category. The mortality rate doubled for men experiencing a fracture after their diagnosis compared with that for men who did not experience a fracture (HR: 2.05).	Within the first year of ADT, absolute BMD loss is ≈5%. The temporal relationship of ADT and incidence of osteoporosis is demonstrated over 4 and 10 years at 49.2% and 80.6%, respectively. In a large observational study, ADT was associated with increased rate of fracture (HR, 1.34), and mortality risk doubled after a fracture.	(Morote, Morin et al. 2007, Hamilton, Ghasem-Zadeh et al. 2010, Beebe-Dimmer, Cetin et al. 2012)

Quality of Life	**Green 2002**: RCT or men with extraprostatic prostate cancer (n =82) assigned to receive continuous leuprorelin, goserelin, cyproterone acetate or close clinical monitoring. **Llorente 2005**: A population-based, retrospective cohort review age 65 and older, residing in South Florida between 1983 and 1993. **Cherrier 2009:** A cohort of (n-=20) hormone naïve men with prostate cancer were treated with intermittent ADT.	**Green 2002**: cognitive assessments measuring memory, mood, attention and executive function. **Llorente 2005**: Average annual suicide rate was calculated for prostate cancer-related suicides **Cherrier 2009:** Profile of Mood States questionnaire.	**Green 2002**: Men receiving ADT per-formed worse in two of 12 tests of attention and memory; 24 of 50 men randomized to active treatment and assessed 6 months later had a clinically significant decline in one or more cognitive tests but not one patient randomized to close monitoring showed a decline in any test performance. **Burke 2005:** Of 667 completed suicides, 20 were prostate cancer-related (3% of the total male suicide sample). The risk of suicide in men with prostate cancer was 4.24 times that of an age- and gender-specific cohort. **Cherrier 2009:** A significant decline in spatial reasoning, spatial abilities and working memory during treatment for men on ADT. Significant changes in self-rated mood such as increased depression, tension, anxiety, fatigue and irritability were evident during treatment compared with baseline.	In a survey of men newly diagnosed with metastatic disease, about a third of patients were identified as highly distressed increasing over the first 12 months with a 4 fold risk of suicide compared to controls. ADT has been found to impair memory, attention and executive functions resulting in a decline of cognitive performance in as little as 6 months from initiating ADT.	(Green, Pakenham et al. 2002, Llorente, Burke et al. 2005, Cherrier, Aubin et al. 2009)

2.5.2 The Saturation Model

More recently, the widespread acceptance of the "androgen hypothesis" has been challenged, arguing the link between Huggins' castrated men over 70 years ago and current hypogonadal men treated with ADT is tenuous, with no direct evidence of increased risk of recurrence for men successfully treated for primary prostate cancer (Morgentaler 2008, Morgentaler 2008, Isbarn, Pinthus et al. 2009). There exists an argument to move beyond the historical data given the profound AEs of hypogonadism resulting from ADT.

The saturation model is an alternative to the androgen hypothesis. It suggests that physiological concentrations of testosterone provide an excess of testosterone and of DHT for optimal prostatic proliferation. By reducing testosterone concentrations to below a critical concentration threshold (the saturation point) it creates a intracellular milieu and the availability of androgens becomes rate limiting to prostate tissue growth (Morgentaler and Traish 2009). This model accounts for the observation that prostate cancer growth is extremely sensitive to blood testosterone concentrations at or below the castrate level (<50 ng/dl (1.73 nmol/l)). In an in vitro cell model of prostate cancer cells in a study by Bologna demonstrated that testosterone and DHT were able to stimulate growth in prostate cancer cells (LnCaps) in only the lowest tested concentrations of testosterone and DHT (0.001 μM). At higher concentrations, they show a moderate inhibition effect, but was is most cases is not statistically significant (Bologna, Muzi et al. 1995). The saturation model could also explain why at peak lifetime level of testosterone young men do not develop BPH or prostate cancer despite the presence of prostate cancer microfoci (Sakr, Grignon et al. 1994). This study showed frequency of cancer in prostates without high grade prostatic intraepithelial neoplasia (HGPIN) was 24%. HGPIN was found in 0, 5, 10, 41 and 63% of men in the 3rd, 4th, 5th and 7th decades of life, respectively (Sakr, Grignon et al. 1994). In addition, it offers an explanation for the lack of an increased rate of prostate cancer or significant changes in PSA in testosterone therapy trials (Morgentaler 2008). Some of the most compelling evidence for the saturation model came in a trial published in 2012 which demonstrated no association between prostate cancer and testosterone and DHT (Muller,

Gerber et al. 2012). The Reduction by Dutasteride of Prostate Cancer Events trial of 8122 men showed that prostate cancer detection was similar among men with low compared with normal baseline testosterone levels (25.5% and 25.1%; p =0.831). Prostate cancer risk was unrelated to testosterone and DHT levels. However, among men with low baseline testosterone levels (n =596; 18%), those with the lowest baseline testosterone had the lowest prostate cancer risk. This risk increased as baseline testosterone levels approached normal levels; thereafter, prostate cancer risk stabilized regardless of higher testosterone levels. At the higher end of baseline testosterone levels, prostate cancer detection decreased (Muller, Gerber et al. 2012).

Furthermore, prostate cancer appears to be more prevalent in hypogonadal men (Morgentaler and Rhoden 2006, Shin, Hwang et al. 2010). The Morgentaler et al study involved 345 men diagnosed with hypogonadism and showed cancer was detection was higher in men in the lowest tertile compared with the highest tertile for total testosterone (OR: 2.15; 95% CI 1.01 - 4.55) and for free testosterone (OR: 2.26; 95% CI 1.07 - 4.78). The Shin et al observational study involved a slightly larger cohort of 568 men, and showed a low serum testosterone level was associated with a higher risk of prostate cancer (OR=1.99, 95% CI=1.25-3.16, p =0.001) but had no association with the risk of high grade prostate cancer. However, both of these studies were observational studies within select populations of men. Conversely, another study found men with higher Gleason scores ranging from 7 to 10 had lower serum testosterone levels at baseline with respect to men with lower Gleason scores (2 to 6) (Garcia-Cruz, Piqueras et al. 2012). However this study was a retrospective cohort study of 183 men and was therefore lower level evidence. A published abstract of 671 hypogonadal men also showed that those who had received testosterone had a lower incidence of prostate cancer than those men who did not, however the full manuscript data was not available for this study (Haider and Haider 2017). In contrary to the androgen hypothesis, these studies potentially evidence the saturation model proposed.

2.5.3 Hormone replacement therapy

2.5.3.1 Hypogonadism: Testosterone replacement therapy

Physiological hypogonadism, which is circulating androgens below normophysiological levels not resulting from ADT, is associated with decreased muscle mass, decreased energy, depressed mood, decreased libido, gynecomastia and erectile dysfunction (Bhasin, Cunningham et al. 2010, Basaria 2014). Physiological hypogonadism can result from impaired testosterone production and in rare cases mutations of the androgen receptor. Testosterone replacement therapy has been used to treat the secondary effects of hypogonadism (Byrne and Nieschlag 2003, Kalra, Agrawal et al. 2010). A 2016 systematic review suggested that testosterone replacement therapy in four RCTs (involving 1779 participants) improved libido, erectile function and sexual satisfaction (Ponce, Spencer-Bonilla et al. 2018).

Despite the potential therapeutic benefits, its use is not recommended in men with prostate cancer; men with a palpable prostate nodule or PSA greater than 4 ng/ml; or in men at high risk for prostate cancer (Bhasin, Cunningham et al. 2010). This is due to predominantly historical data supporting the "androgen hypothesis" stating: androgens play a key role in the etiology of prostate cancer; high testosterone levels is a risk factor for prostate cancer; low levels of testosterone are protective against prostate cancer; and administering testosterone to men with existing prostate cancer universally causes rapid tumour growth (Gravina, Di Sante et al. 2015). Furthermore, concerns over the potential promotion of prostate cancer with testosterone replacement therapy have led to reservations in prescribing in hypogonadal individuals. Despite this, three RCTs which have addressed testosterone replacement therapy on normal prostate tissue have shown no increase in PSA, prostate tissue levels or in dihydrotestosterone (Cooper, Perry et al. 1998, Marks, Mazer et al. 2006, Bhasin, Cunningham et al. 2010). These studies were all conducted in normal healthy men and the study by Marks et al evaluated testosterone replacement in hypogonadal men. As a result, the saturation theory described is the proposed model offering to explain these lack of prostate cancer progression in these trials,

which contradict what would be expected based on the androgen hypothesis (Warburton, Hobaugh et al. 2015).

However, all of these studies have been conducted in very small numbers of men (between 31 and 44 participants), and so the conclusions regarding testosterone administration and prostate safety are limited and further large scale studies are needed. Furthermore, a systematic review of the use of testosterone in hypogonadal men determined that there was a lack of evidence demonstrating therapeutic effects on cardiovascular outcomes, erectile dysfunction, libido, physical function and psychological wellbeing, in contrast to previous studies (Huo, Scialli et al. 2016). The findings of the review did suggest however, there to be improvements in muscle strength (Huo, Scialli et al. 2016).

2.5.3.2 Testosterone replacement and prostate cancer

As one might expect, the controversy surrounding the use of testosterone replacement therapy for men with treated or untreated prostate cancer has led to a lack of research. But in 2009 a case study was published which demonstrated treatment with testosterone for two years in a hypogonadal men with untreated prostate cancer (but without HGPIN) resulted in a drop in PSA with no prostate cancer progression reported (Rhoden and Morgentaler 2003). However, this study was a small cohort intervention study of 75 men with only a small follow up period of 1 year. As a result, the level of evidence is limited from this study, and data on long-term safety was not obtained.

Another study in 2004 documented that testosterone therapy for hypogonadal men who had been previously treated with curative radical prostatectomy had no evidence of biochemical or clinical evidence of cancer recurrence (Kaufman and Graydon 2004). This study was a small retrospective review of 7 hypogonadal men, so once more definitive conclusions from this limited level of evidence cannot be drawn. Furthermore, the study determined further cautious use of testosterone in a carefully selected population given the study limitations.

Similarly, a study in 2008 demonstrated that testosterone therapy in hypogonadal men who had undergone radical prostatectomy or radical

radiotherapy for localised prostate cancer had no significant difference in PSA compared to the control and that symptoms of hypogonadism had improved (Davilla, Arison et al. 2008). Like previous studies, this study was limited by a small sample size of 20 men who were retrospectively studied in a cohort study and therefore no determinant conclusions can be drawn.

A larger and more recent study involving 103 hypogonadal men with prostate cancer treated with testosterone after prostatectomy too demonstrated that although a rise in PSA was observable, no clinical signs of cancer reoccurrence were reported even for those with high risk disease (Pastuszak, Pearlman et al. 2013). Although there was a small but statistically significant increase in PSA was observed in the high risk and non-high risk treatment groups, the increase was not supportive of prostate cancer recurrence, i.e. no consecutive increases in PSAs and patient referral for salvage radiotherapy. In addition, the biochemical reoccurrence rate in the high risk men treatment with testosterone remained lower than in the high risk men not treated (Pastuszak, Pearlman et al. 2013). Another study in 2014 involving 1181 men received exogenous testosterone following a prostate cancer diagnosis which was not associated with increased overall or cancer-specific mortality (Kaplan, Trinh et al. 2014). Both of these studies were retrospective cohort studies therefore the data is limited to the population of men studied, which lacked randomisation and therefore a selection bias exists. Given both trials did not have placebo groups it is not possible to objectively compare those who had not received testosterone replacement therapy in the same time frame.

The lack of clinical disease progression demonstrated in these studies suggests that the use of testosterone replacement therapy may be of therapeutic benefit where symptoms of hypogonadism have been alleviated. The data conflicts with the "androgen hypothesis" where you would expect a progression of prostate cancer with the reintroduction of androgens. However, there is a significant lack of high level evidence pertaining to placebo controlled RCTs of large cohorts in the given data. Much of the data is in small cohort and retrospective studies which limits the conclusions which can be drawn given the lack of high quality evidence.

2.5.3.3 Castrate resistant prostate cancer and androgen replacement therapy (clinical and preclinical)

In vitro CRPC cell models involving prostate cancer cells (LnCap) cultured in androgen free medium for 2 years resulted in progression to a different phenotype of cell, with slow growing and fast growing characteristics (Kokontis, Hay et al. 1998). The new phenotype was not responsive to the anti-androgen therapy Casodex. In fact the proliferation of the androgen-deprived cells was mitigated by the addition of androgens. The cells when continuously passed through androgen rich growth medium actually reverted cells back to the androgen dependant phenotype (Kokontis, Hay et al. 1998).

Another study used the same cell phenotype, cultured the cells similarly and implanted them into castrated mice models where tumours were allowed to form. When treated with testosterone, LnCap cell proliferation was mitigated and tumour regression was observed (Umekita, Hiipakka et al. 1996). This effect was not observed however in tumours derived from LnCap cells which were not androgen deprived or from androgen receptor negative prostate cancer (PC3) cell lines. In addition, the removal of testosterone or implantation of finasteride, a 5α-R inhibitor, caused regrowth of these tumours in these mice (Umekita, Hiipakka et al. 1996). A very similar study in mice models demonstrated similar effects and testosterone treatment resulted in tumour regression. The suppression of LnCap proliferation was caused by G1 cell cycle arrest via reduction of Skp2 and c-Myc and induction of p27Kip1 (Chuu, Kokontis et al. 2011).

One of the few studies to address the use of high dose exogenous testosterone in men with CRPC was conducted in 2009 (Morris, Huang et al. 2009). The trial took small cohorts of patients and administered testosterone for a week (cohort 1), a month (cohort 2) or until disease progression (cohort 3). The trial found that even at supraphysiologal levels of testosterone, its administration was safe. One participant achieved a >50% drop in PSA and the median time on testosterone treatment was 84 days (range: 23–247 days) for cohort 3 (Morris, Huang et al. 2009). Interestingly, the exogenous testosterone levels given were three times the normophysiological levels but

despite this replacement dose, blood testosterone levels did not exceed normal levels.

Another phase I study treated 15 men with endogenous testosterone doses of 2.5, 5.0, or 7.5 mg/day with discontinuation of treatment for significant toxicity, clinical progression, or a 3-fold increase in PSA (Szmulewitz, Mohile et al. 2009). The study demonstrated that testosterone was well tolerated and the median time to progression was 9 weeks (range: 2-96 weeks). The AEs included one discontinuation of the study due to grade 4 cardiac toxicity at 53 weeks and minimal grade 2 toxicities. Symptomatic progression was seen in one patient and 20% (n =3) of patients had a decrease in PSA.

The preclinical studies to exogenous testosterone have demonstrated the potential for testosterone to have a therapeutic effect. In addition, the safety of testosterone treatment has been demonstrated in early clinical studies however there is a significant lack of evidence in human studies for its use therapeutically. Although the use of testosterone in symptomatic hypogonadal men with or cured of their prostate cancer is theoretically underpinned, there is still a reluctance to explore its use in research where historically it has always been contraindicated. There is a huge void of evidence and a need for larger scale, multi-arm RCT to establish the potential therapeutic benefit of testosterone and therefore challenge the androgen hypothesis. It may be the case that we have the potential to alleviate some of the highly detrimental effects of ADT for these men, and this question is fundamentally worth investigating.

2.6 Summary: Prostate cancer and castrate resistant prostate cancer

Prostate cancer is the most common malignancy amongst men in the UK. CRPC is defined by disease progression despite ADT. Men with CRPC are an extremely complex and heterogenous population, potentially with a very long history of disease.

ADT has long been the cornerstone of therapy for men with advanced prostate cancer and men with CRPC can remain on ADT for over a decade. ADT is associated with a tirade of adverse effects which can significantly impact on QoL including detrimental effects to sexual function, body

composition, cardiovascular (CV) morbidity, bone health and increased fatigue. Furthermore the advancement and development in treatments for CRPC has presented further difficulty. Since the introduction of docetaxel, numerous other agents have been introduced and have significantly changed the treatment landscape for CRPC such as Enzalutamide and Abiraterone. The data surrounding the optimum sequencing of these therapies however is lacking with no consensus on the optimal sequencing of approved agents for CRPC and the potential for cross resistance of pharmacological agents. Furthermore, there is some doubt over the tolerability and impact on these treatments in men with symptomatic disease or with a poorer performance status.

There is critical debate over the widespread use of ADT as a treatment for prostate cancer, with doubt over the accepted "androgen hypothesis". Some emerging data is suggested to support and alternative model, the "saturation model", whereby androgens such as testosterone are no longer thought to be the driving force in prostate cancer progression in androgen sensitive disease. This is supported by the lack of disease progression observed in men with prostate cancer treated with testosterone replacement therapy. There is some suggestion that testosterone replacement therapy could be used in men with prostate cancer to alleviate symptoms of hypogonadism, although extremely controversial.

3. Muscle matters: conditions causing skeletal muscle loss

Whole lean body mass (LBM) contributes to around 30-40% and 20-30% of a healthy adult male and female body mass respectively (Nedergaard, Karsdal et al. 2013). Skeletal muscle functions not only to enable locomotion, ventilation and prevention against trauma; it critically acts as the main glycogen store in humans and mammals, therefore regulating glucose metabolism and energy utilization (LeBrasseur, Walsh et al. 2010, Jensen, Rustad et al. 2011). For this reason skeletal muscle is implicated in critical homeostatic and physiological mechanisms such as insulin sensitivity as well as providing the key amino acids for cellular and neuronal development (Wai and Langer 2016).

A significant loss in LBM can have catastrophic effects not only on functionality but on general health and wellbeing. The primary causes of LBM loss are natural processes such ageing, starvation or inactivity; however, it can also be a common comorbidity accelerated in chronic disease (Evans 2010, Nedergaard, Karsdal et al. 2013). It results from the imbalance in protein metabolism to favour more catabolic than anabolic processes and is an accurate predictor of a poorer QoL and an increased risk of morbidity and mortality (Mei, Batsis et al. 2016, Vanhoutte, van de Wiel et al. 2016).

The nature of LBM loss can be complex and multifactorial making it increasingly difficult to determine the origin. As a result, particularly in chronic disease, there has been great difficulty in accurately defining and recognising it's causation in both the clinic and in research. Often terminology is incorrectly used to define LBM loss in these conditions; such as sarcopenia (which is accelerated LBM loss associated with ageing) a term often used regardless of the age and disease status of the individual (Hepple 2012). There is an ongoing need to have a wide-spread acceptance of the correct terms for these conditions in order for the development of accurate diagnostic criteria as well as effective treatments, particularly as we risk the false impression that all muscle atrophy is mediated by the same processes. In addition to this, the lack of clear definitions or understanding of these conditions can hinder the ability to gain epidemiological information and recruit to clinical trials (Vanhoutte, van de Wiel et al. 2016).

In research, progress has been made in determining the pathophysiology behind chronic disease associated with LBM loss and this has subsequently fed into the development of tools to help accurately screen, diagnose and treat. However, both recognition and treatment or prevention of LBM loss is still a clinically unmet need. It is vastly underestimated as a driving factor in numerous pathologies accelerating metabolic dysfunction and bone loss.

3.1 Cancer related muscle loss

A multitude of studies have demonstrated increased treatment toxicity and poorer OS with a decline in LBM in cancer patients (and its association with a decline in PS). In some cases, dose limiting toxicities can lead to

compromising therapy. The findings associating a decline in both LBM and PS and the associated detrimental treatment and survival effects are detailed in table1.5.

3.2 Chemotherapy and muscle loss

Cancer therapeutics have been associated with muscle wastage contributing to LBM loss and cancer cachexia (section 3.1.3) (Barreto, Mandili et al. 2016). Although the association of chemotherapy with cancer cachexia is not completely clear, there are profound side effects associated with chemotherapy are thought to be contributory to cachexia such as nausea, diarrhoea, anorexia and fatigue (Barreto, Mandili et al. 2016). There is evidence to suggest that chemotherapy promotes the onset of cachexia regardless of tumour growth (Garcia, Garcia-Touza et al. 2005, Damrauer, Stadler et al. 2008). Some studies have shown that where chemotherapeutics have been able to indeed reduce the tumour burden the symptoms of cachexia persist, in one study this was attributable to the induction of NF-κB activity (Damrauer, Stadler et al. 2008).

3.3 ADT and body composition

The effect of testosterone in promoting muscle protein synthesis is well established (Griggs, Kingston et al. 1989). In hypogonadal men, testosterone replacement results in an increase in fat-free mass (predominantly associated with increased skeletal muscle mass) and a decrease in fat mass (FM) (Brodsky, Balagopal et al. 1996).

Smith et al demonstrated that within 48 weeks of treatment with ADT for men with locally advanced non-metastatic prostate cancer, men experienced a 2.4% ±0.8% increase in body weight and an increase in FM by 9.4% ±0.4% (Smith, Finkelstein et al. 2002). In addition, LBM decreased by 2.7% ±0.5% and cross-sectional paraspinal muscle area decreased by 3.2% ±1.3% (Smith, Finkelstein et al. 2002).

In a retrospective analysis conducted by Boxer et al, men who had received 6 months of ADT were compared to age-matched controls. The study showed that men who had received ADT had a higher body FM vs controls (29.8 ± 6.3 vs 26.3 ± 4.6, respecively). Men on ADT also had a lower

appendicular skeletal muscle mass compared to controls, where skeletal muscle mass decreased from baseline to by 2.3%(± 0.03; p ⩽0.001) (Boxer, Kenny et al. 2005).

A cross-sectional study assessed three patient groups; men with prostate cancer on ADT for at least 12 months, age-matched men with non-metastatic prostate cancer who were post prostatectomy and/or radiotherapy with no previous ADT and age-matched healthy normal men (control group). The study showed the long-term ADT group had a lower BMD (lumbar spine BMD (p ≤ 0·0001) and total body BMD (p =0·03), a higher FM and a reduced upper and lower body strength (although lower body strength did not reach statistical significance, p =0.022) (Basaria, Lieb et al. 2002).There was however no statistically significant difference in LBM between the groups.

A multisite study also followed men with stage M0 prostate cancer initiating ADT to 12 months follow up. With the concurrent fall in blood testosterone levels (79.7% ± 3.0%) a decrease in LBM of 3.8% ± 0.6% and increase in FM 11.0% ± 1.7% was observed (Smith 2004).

Galvao also demonstrated upper limb, lower limb, trunk and whole-body LM decreased by a mean (standard error, SE) of 5.6 (0.6)%, 3.7 (0.5)%, 1.4 (0.5)% and 2.4 (0.4)% (p <0.01), respectively in men after 36 weeks of ADT (Galvão, Spry et al. 2008). Indeed, FM had also significantly increased (upper limb 20.7 (3.3)%, lower limb 18.7 (2.7)%, trunk 12.0 (2.5)% and total 13.8 (2.3)% (p <0.001)). Hip, spine, whole-body and upper limb BMD decreased by 1.9 (0.3)%, 3.3 (0.4)%, 1.6 (0.3)% and 1.3 (0.3%) (p <0.001) respectively.

Table 1.5 Treatment and survival outcomes associated with performance status and lean body mass

Author	Type of study	Patient population	N	Median age	Performance status outcomes	LBM outcomes	Treatment and survival outcomes
(Wu, Liu et al. 2015)	Retrospective review	Prostate cancer, Docetaxel	333	60-70 for different chemo regimens		CT: iSKM	Those with a high skeletal muscle index (iSKM) had a median **survival of 5.4 months longer** than those with a low iSKM.
(Antoun, Baracos et al. 2010)	RCT phase III	Renal cell carcinoma, sorafenib	55 - sorafenib; 41 – placebo	59		CT: iSKM	8 males with dose limiting toxicity (DLT) had a iSKM index 48.6 vs no DLT 54.1 [0.02, SS] and 4 females with DLT iSKM 38.4 vs no DLT 38.0 (Not significant). None significant association for iSKM DLT for all participants.
(Prado, Lieffers et al. 2008)	Cross-sectional study	Solid tumours of the respiratory and gastrointestinal tract	250	63.9	ECOG scores of >2 median **survival** 13·7 months [1·7–15·8] vs scores of 0–1 24·0 months [16·1–32·5]	CT: iSKM	15% of obese patients had sarcopenia (iSKM 43·3 (6·3) vs non-sarcopenic (iSKM =56·4 (9·9). Sarcopenic obesity vs non-sarcopenic **survival HR = 2·4** [SS] **Median 10.3 longer survival** for non-sarcopenic.
(Aslani, Smith et al. 1999)	Longitudinal	Breast cancer; cyclophosphamide, methotrexate, and 5-fluorouracil based chemotherapy	31	47		Total body Nitrogen and total body protein	A **nitrogen index of <0.89 was associated significantly with risk for neutropenia** (85% of courses of chemotherapy in populations with <0.089 lead to neutropenia) **RR = 1.14**

(Prado, Baracos et al. 2009)	Prospective study	Metastatic breast cancer resistant to anthracycline and/or taxane treatment; capecitabine	55	54.8	ECOG 0-1 vs ECOG >2 was not significantly different between sarcopenic and non-sarcopenic	CT: SKM and LBM (kg)	25.5% were sarcopenic and 74.5% were non-sarcopenic. **DLT present in 50% of sarcopenic vs 20% of non-sarcopenic individuals (p = 0.03)**. Lumbar iSKM in sarcopenic individuals was lower (35.0 vs non-sarcopenic 47). Whole LBM in sarcopenic individuals was lower (34.0 vs non-sarcopenic 42.5). The dose of mg capecitabine/kg LBM in sarcopenic individuals was 104.2 vs non-sarcopenic 86.9 . Diarrhoea and stomatitis was significantly worse in the sarcopenia group. **RR of Time to progression in sarcopenic individuals 1.9.**
(Prado, Baracos et al. 2007)	Prospective study	Stage II/III colon cancer patients; 5-FU and leucovorin.	62	60.3		CT: LBM	Patients who had DLT had a mean of 5-FU/kg LBM of 17.9 versus 16.3 mg/kg in patients who did not have any DLT. Neutropenia was the most common toxicity. Women with 5-FU/kg LBM >20 mg/kg had a statistically significant lower total muscle cross-sectional area and LBM (-15%) and higher 5-FU/kg LBM (+ 24%) compared with women <20 mg/kg. Logistic regression showed that 20 mg/kg as cut-off for 5-FU/kg LBM was a significant predictor of overall toxicity OR = 16.73 for women.
(Barret, Antoun et al. 2014)	Prospective, cross-sectional study	metastatic colorectal cancer; oxaliplatin, irinotecan, fluoropyrimidine	51	65	WHO score, n (%) 0: 13 (25.5) 1: 31 (60.8) 2: 5 (9.8) 3: 2 (3.9)	CT: iSKM	Sarcopenia [n (%)] women [5 (38.5)] Men [31 (81.6)]. In multivariate logistic regression analysis the only factor associated with **Grade 3-4 toxicity was sarcopenia: OR = 13.55**.

(Cousin, Hollebecque et al. 2014)	Prospective study	various cancer types and stages	93	57	ECOG: n (%) 0: 32 (34) 1: 59 (64) ≥2 : 2 (2)	CT: iSKM	**10% of patients experienced DLT** and had a lower iSKM: 40.8±4.6 vs. 48.1±9.6 cm2 /m2 (p =0.01). Severe toxicity events (STE) occurred in 14 %. STE was associated with low iSKM: 42.4±5.8 vs. 48.4±9.7 cm2/m2 (p =0.02).
(Huillard, Mir et al. 2013)	Retrospective review	Metastatic renal cell carcinoma; sunitinib	61	60	ECOG: n (%) 0: 19 (31.2 1: 31 (50.8) ≥2: 11 (18)	CT: iSKM and LBM	Sarcopenic patients with a **BMI <25kgm2 experienced more DLTs** (p = 0.01; OR = 4.1), more cumulative grade 2 or 3 toxicities (p = 0.008), more grade 3 toxicities (p = 0.04) and more acute vascular toxicities (p = 0.009). LBM of those with early DLT = 37.7 (9.7) vs those without early DLT = 45.6 (9.4). iSKM of those with early DLT = 43.5 (10.3) vs those without 48.7 (8.2) [SS, P = 0.02].
(Choi, Oh et al. 2015)	Retrospective review	Pancreatic cancer; palliative chemotherapy	484	60.4	ECOG: n (%) 0–1: 393 (81.2) ≥2: 91 (18.8)	CT: iSKM	**Sarcopenia and low iSKM during chemotherapy were poor prognostic factors for OS**. While the OS of male patients was affected with sarcopenia and decreased iSKM, the OS of female patients was influenced with overweight at diagnosis, decreased BMI and decreased iSKM.
(Massicotte, Borget et al. 2013)	Phase III RCT	Advanced medullary thyroid cancer.	33	54		CT:iSKM	Without DLT vs with DLT had lower iSKM (37.2 vs 44.3 cm2/m2) and a higher blood vandetanib level (1091 vs 739 ng/mL). **Lower BMI and low muscle mass may be associated with vandetanib toxicity**; 83% of the patients with normal or low BMI and low muscle mass experienced DLT. Normal or low BMI and low muscle mass had a higher probability of DLT (10 of 12, 83%) vs patients with BMI > 25 or SM index > 43.1 (3 of 17, 18%).

(Tan, Brammer et al. 2015)		oesophago-gastric cancer; neoadjuvant chemotherapy	89	65.8		CT: iSKM	DLT occurred in 37 (41.6%) undergoing chemotherapy. **Sarcopenia (OR: 2.95; p = 0.015) was associated with DLT. Median OS** for patients who were **sarcopenic was 569 days vs. 1013 days for patients who were not sarcopenic (p = 0.04).**
(Iwase, Sangai et al. 2016)	Retrospective study	Advanced breast cancer; neoadjuvant chemotherapy	172	54	Whole group ECOG of 0−1	CT:iSKM	No significant relation between muscle mass and survival. May result from the threshold value for iSKM being higher than previous studies, ranging from 38.5 to 41.0 cm2/m2.

iSKM - Skeletal muscle mass; OR - Odds ratios; DLT - dose limiting toxicity; STE - Severe toxicity events

3.4 Cancer Cachexia: Definition, diagnosis and prevalence

3.4.1 Definition

Cachexia is defined as "a complex metabolic syndrome associated with underlying illness and characterized by a loss of muscle with or without loss of FM"(Evans, Morley et al. 2008). It is a multifactorial syndrome with a complex pathology and clinical presentation making it difficult to accurately diagnose. There is no single adopted operational definition to characterise cachexia in patients and, almost self-fulfilling, is therefore infrequently identified, diagnosed and treated (Fox, Brooks et al. 2009). This lack of definition is equally problematic for healthcare professionals in that they are therefore unable to adequately plan appropriate resources and treatment for the cachectic patient. It is important that cachexia is not to be confused with simple starvation or sarcopenia, an age related loss of lean body mass. There are a few hallmark symptoms associated with cancer cachexia and include anorexia, fatigue, metabolic and endocrine alterations, and loss of LBM.

The National Cancer Institute has graded cancer cachexia via the common toxicity criteria: Grade 1 is defined as 5% loss from baseline body weight; Grade 2 is a 10% weight loss; Grade 3 is a 20% weight loss; Grade 4 is defined as life threatening (Gullett, Mazurak et al. 2011). The criteria is limited with its predominant focus on weight loss without any evaluation of inflammation, fatigue, weakness or the loss of muscle mass which are predominant detrimental effects of cancer cachexia.

Recent efforts in the scientific and clinical community to properly define cachexia have developed a three stage classification: pre-cachexia, cachexia and refractory cachexia (Fearon, Strasser et al. 2011). The classification aimed to aid healthcare providers in the recognition and therefore correct diagnosis and treatment of the syndrome. Conflicting and varying definitions underline the importance of working on the diagnostic framework for cachexia in order to allow not only a true representation of the prevalence of the condition but equally to aid in the development of therapeutics.

3.4.2 Clinical manifestation and diagnosis

There is indeed a spectrum in cancer cachexia, ranging from non-symptomatic alterations with minimal weight and muscle loss at early stages, to severe muscle wasting and poor PS in more advanced stages (Madeddu, Maccio et al. 2012).

In 2006, a meeting organised by Society for Cachexia and Wasting Disorders, saw a consensus group made up of international experts conclude the agreed definition of cachexia which has predominantly been adopted (Evans, Morley et al. 2008). The consensus group agreed that a diagnosis of cachexia can be made on the following criteria: "a weight loss of at least 5% or more in 12 months or less (or BMI <20 kg/m^2) in the presence of underlying illness, plus three of the following criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, abnormal biochemistry (increased inflammatory markers (C-reactive protein >5.0 mg/l), IL-6 >4.0 pg/ml), anaemia (<12 g/dl), and low blood albumin (<3.2 g/dl)) (Evans, Morley et al. 2008). Other diagnostic modalities such as physical performance can also be very valuable.

However, this has not been consistently translated in research. Fox et al, demonstrated that the proportion of cancer patients with cachexia, from 8541 cancer patients identified from a retrospective database study, varied between 0.8% and 25.5% (for various cancer types) dependant on which of four possible definitions of cachexia were employed (table 1.6) (Fox, Brooks et al. 2009). For prostate cancer specifically, 3354 patients were identified from the study and proportions varied from 0.8% to 15.1% (Fox, Brooks et al. 2009).

It has been recognised that there is a need for a robust set of clinical identifiers by which patients can be successfully classified in to cachectic stages and therefore receive the necessary and effective treatments. A few attempts have been made to address this gap (Muscaritoli, Anker et al. 2010, Fearon, Strasser et al. 2011, Blum, Stene et al. 2014). More recently Argilés et al put forth a model which not only addressed the issue surrounding identification and diagnosis of pre-cachexia but equally defined the

classification domains within cancer cachexia (Figure 1.5) which is termed "The cachexia score" (CASCO) (Argilés, López-Soriano et al. 2011).

Although issues with diagnosis and identifying the different stages of cachexia are recognised internationally, it is likely that even whilst attempts are made to rectify this by researchers, it will take significantly longer for new approaches in diagnosis to be adopted routinely in clinics. Patients are therefore still at risk of going unrecognised and not receiving the best care available.

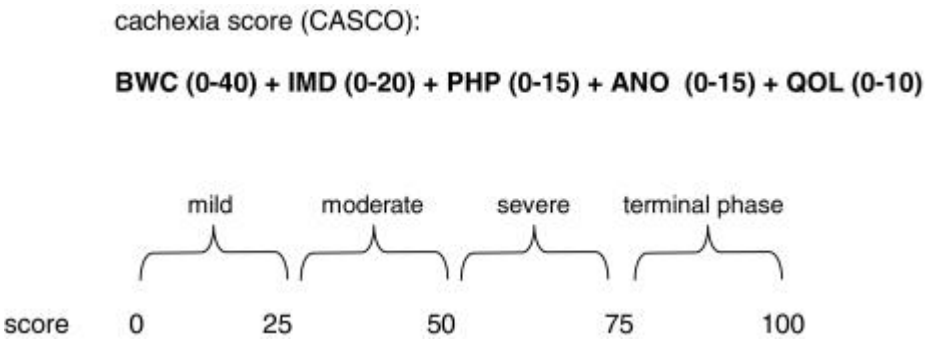

Figure 1.5 The CASCO staging scale: BWC body weight loss and composition, *IMD* inflammation/metabolic disturbances/immunosupression, *PHP* physical performance, *ANO* anorexia, *QOL* quality of life. Taken from (Argilés, López-Soriano et al. 2011)

3.4.3 Prevalence

Cachexia is thought to be experienced by up to 80% of advanced stage cancer patients and estimated to be responsible for 20-40% of immediate cancer related death (Fox, Brooks et al. 2009, Gullett, Mazurak et al. 2011). As previously discussed, a lack of standard definition of cachexia has made it increasingly difficult to estimate the prevalence of the condition, and therefore to accurately plan appropriate resources and treatments for patients (table 1.6).

However, more recently von Haehling and Ankler estimated that around 1 million of cancer patients within Europe had cachexia, stating that these figures were in fact most likely an underestimate (von Haehling and Anker 2014). Details of the estimated clinical impact are given in table 1.7. These

estimates are based on the cachexia criteria determine by the consensus group.

Unfortunately, until a standard definition is routinely adopted internationally there can be no accurate data on prevalence.

Table 1.6 Proportion of cancer patients with cachexia by cancer type. Adapted from (Fox, Brooks et al. 2009)

Cancer type	*Cancer patients with cachexia ICD-9 code only*	*Cancer patients with cachexia ICD-9 code only*	*Cancer patients taking prescription medication indicative of cachexia*	*Cancer patients with ≥5% weight loss*	*Cancer patients with any one of the cachexia definitions*
Breast, n =2112	0.80%	3.10%	5.30%	18.60%	24.80%
Colorectal, n =905	2.50%	6.10%	6.20%	16.40%	25.50%
Oesophagus, n =117	12.80%	20.50%	13.70%	16.20%	41.90%
Gastric, n =142	8.40%	15.50%	19.00%	19.70%	41.50%
Head/neck, n =246	6.10%	17.10%	6.10%	19.90%	37.00%
Liver, n =153	3.30%	6.50%	3.90%	17.00%	24.20%
Lung, n =1291	6.40%	9.70%	14.20%	15.20%	31.10%
Pancreas, n =221	3.60%	7.20%	19.50%	12.70%	34.80%
Prostate, n =3354	0.80%	3.20%	2.60%	11.00%	15.10%

Table 1.7 The Estimated clinical impact of cachexia in cancer in Europe 2014. Estimates are assumed to be rather conservative. Adapted from (von Haehling and Anker 2014)

	Prevalence in population (%)	Patients at risk (%)	Prevalence in patients at risk (%)	Absolute number of patients with cachexia*	1-year mortality of patients with cachexia (%)
Cancer, All types	0.5	90	30	1.0m	20-60

*assupmtions are based on a total population of 742 million in Europe.

3.5 Cancer Cachexia: Pathophysiology and aetiology

Significant weight loss through the catabolism of skeletal muscle and adipose tissue leads to increased morbidity, loss of muscle function, fatigue, impaired QoL and ultimately death occurring with 25-30% of total body mass loss from baseline pre-treatment weight. The respiratory failure from

hypostatic pneumonia is the consequence of loss of respiratory muscle function, i.e. the degradation of the diaphragm (Windsor and Hill 1988).

The degradation of proteins and decreased protein synthesis contributes to catabolism of skeletal muscle while loss of adipose tissue results mainly from enhanced lipolysis. These mechanisms are most likely predominantly mediated through systemic inflammation and involve both interactions of the host and the tumour.

The host hepatic acute phase protein response (APPR) is stimulated by an increase in inflammatory cytokines, predominantly IL-6 but others such as Tumour necrosis factor-α (TNF-α), Interleukin-2 (IL-2), IL-8, interferon-γ IFN-γ and parathyroid hormone related peptide (PTHrP), can play an important role in the pathophysiology of cachexia (Moshage 1997). It encompasses a variety of pathophysiological responses such as pyrexia, leukocytosis, hormone alterations, and muscle protein depletion in an attempt to minimize tissue damage while enhancing the repair process. It consequentially leads to a multitude of metabolic abnormalities, including increased insulin resistance, elevated synthesis of acute phase proteins and altered nutrient utilization (Ladner, Caligiuri et al. 2003, Figueras, Busquets et al. 2005, Skipworth, Stewart et al. 2007).

The tumour contributes by increasing the local secretion of pro-inflammatory cytokines that then lead to the initiation of the APPR by activating the host inflammatory cells as they pass through the tumour (Deans, Wigmore et al. 2006, Deans, Tan et al. 2009). This subsequently leads host cells initiating or triggering their own cytokine cascade and therefore the production of pro-cachectic factors that have direct catabolic effects on host tissues e.g proteolysis inducting factor (PIF) and lipid mobilising factor (LMF) (Todorov, Cariuk et al. 1996, Hirai, Hussey et al. 1998). Both the systemic inflammatory response and the neuroendocrine response become activated.

Although a variety of mechanisms leading to the development of cachexia are likely to exist, its full nature is not well understood. However, some of the predominant processes which are established in research are described in further detail.

3.5.1 Muscle metabolism

Reductions in muscle mass are as a result of a whole body net increase in protein catabolism. This is not always purely a result of processes increasing protein catabolism, decreased protein anabolic processes result from decreased plasma insulin levels and insulin sensitivity in the skeletal muscle. The metabolism of amino acids is altered from the reduction in insulin sensitivity reducing their movement into striated muscle promoting protein synthesis and inhibiting degradation (Manchester and Wool 1963, Gelfand and Barrett 1987, Ardies 2002).

The proteolytic pathways are numerous and complex, however the predominant pathway implicated in cancer cachexia is the ubiquitin proteasome pathway (UPP).

3.5.1.1 Ubiquitin-proteasome pathway

Muscle proteolysis in cancer cachexia is predominantly attributed to the UPP, occurring as the muscle atrophies and is dependent on ATP to dissemble and degrade muscle myofilaments (Lecker, Solomon et al. 1999). Proteins are marked for degradation by ubiquitin chained molecules via covalent bonds, or polyubiquitination (figure 1.6). Polyubiquitination requires the action of the ubiquitin-activating enzyme (E1), ubiquitin-conjugated enzyme (E2) and ubiquitin protein ligase (E3) where E3 is the key enzyme in the process (Lecker, Solomon et al. 1999, Wing 2005).

E1 has a relatively low expression in skeletal muscle; E2 expressed in multiple mammalian cells, although only a few are expressed in muscle wasting, and interacts with E3, which recognises specific protein substrates and forms the largest family (although a limited number are upregulated in muscle wasting) (Burckart, Beca et al. 2010). The target protein is subsequently degraded by a large tube like proteasome, 26S proteasome (figure 1.6).Two specific genes encoding E3s have been found to be upregulated in catabolic conditions: atrogin-1/MAFbx (muscle atrophy F-box protein) under control of FoxO- forkhead box O and MuRF-1 (muscle specific ring-finger) under transcription of NF-KB. Studies have demonstrated that mice lacking either of these ligases are resistant to proteolysis suggesting it as a potential target in the UPP (Bodine, Latres et al. 2001).

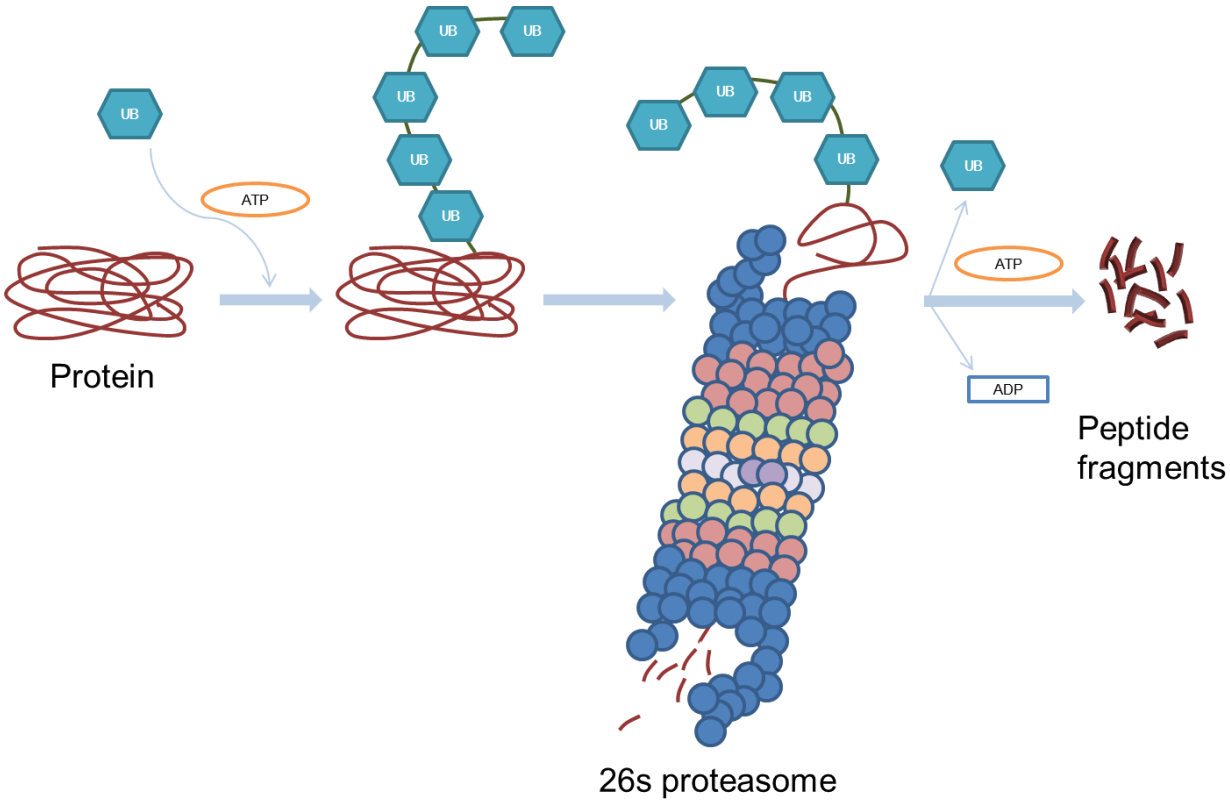

Figure 1.6 Ubiquitin proteasome pathway. The protein is tagged for degradation by an ubiquitin molecule via covalent attachments. The protein is subsequently polyubiquitinated by a chain of ubiquitin molecules (conjugation) which is then recognised by the 26S proteasome (a large multi-subunit catalytic complex). The proteasome then degrades the protein into peptide fragments.

3.5.1.2 TNF-alpha

TNF-α is one of the first known mediators of cancer cachexia and is produced by the host immune system and some tumours. As well as being implicated in the UPP, it is also thought to reduce muscle uptake of glucose and amino acids key to reducing insulin sensitivity (Tuca, Jimenez-Fonseca et al. 2013).

3.5.1.3 IL-6

Blood serum IL-6 levels 7 pg/mL or greater was associated with a reduction in total protein, albumin, and cholesterol levels, haemoglobin levels, and body mass index in one study involving prostate cancer patients (Kuroda, Nakashima et al. 2007). IL-6 was also associated with increased tumour

size, greater weight loss and poorer prognosis (Kuroda, Nakashima et al. 2007). Anti-IL-6 antibodies were effective in attenuating cachectic response (Strassmann, Fong et al. 1993).

3.5.1.4 Autophagic-lysosomal System

More recently, the autophagic-lysosomal pathway has demonstrated its increasing importance in cancer cachexia. In autophagy small ubiquitin like molecules are involved in the formation of a double membrane vesicle. This vesicle engulfs cellular constituents (autophagosome) and then fuses with lysosomes where there content is degraded (figure 1.7) (Sandri 2010). Cathepsins (B, L, D, and H) are proteolytic enzymes present within the lysosomes which determine its proteolytic capacity (Bechet, Tassa et al. 2005).The level of lysosomal protease cathepsin B was found upregulated in patients with lung cancer and suggested an inverse relationship with fat free mass (Jagoe, Redfern et al. 2002).

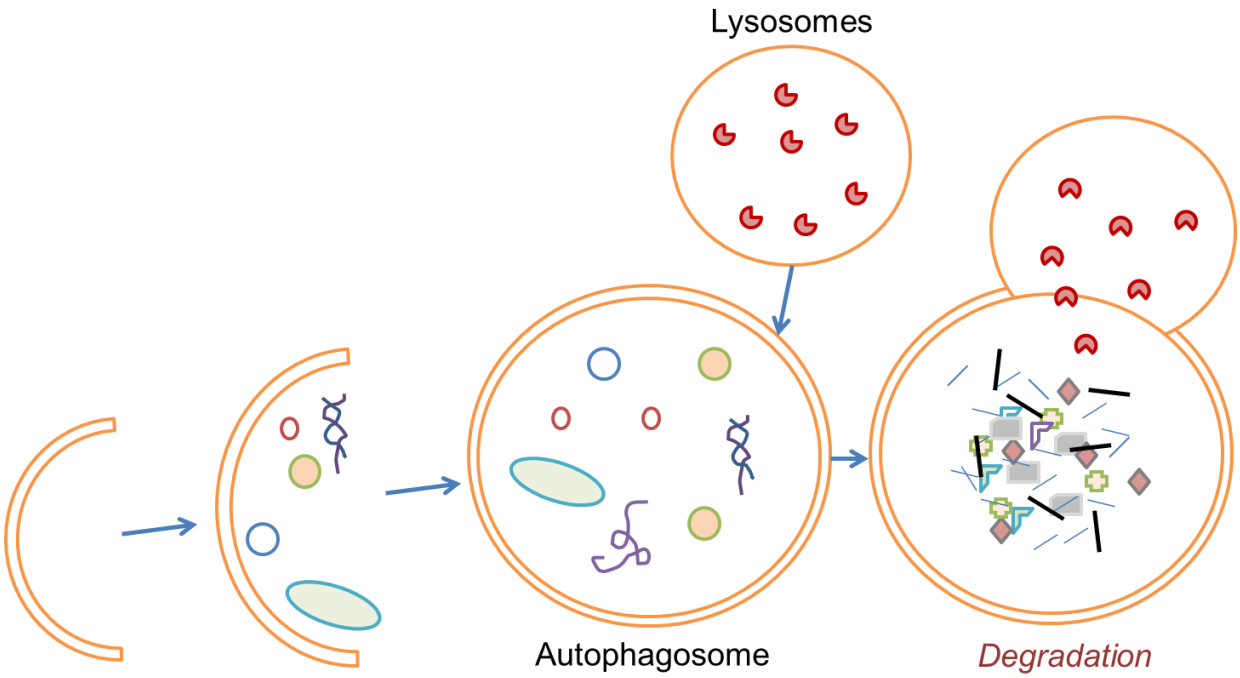

Figure 1.7 Autophagic-lysosomal System. The autophagosome engulfs the cellular components when it then fuses with the lysosome and degrades its contents.

3.5.1.5 Calcium Dependant (Calpain) Pathway

Cytosolic calcium derived system can be activated by PIF. Calpains are cysteine proteases and are activated by calcium. They are implicated in

muscle wasting by initiating digestion of individual myofibrillar proteins (Huang and Forsberg 1998). PIF was first identified as glycosylated polypeptide isolated from mice models transplanted with the MAC16 adenocarcinoma (McDevitt, Todorov et al. 1995). It has been detected in the urine of cachexia patients which demonstrates a significantly greater weight loss than those whose urine does not contain PIF (Cariuk, Lorite et al. 1997). Additionally, injection of PIF which was isolated from the urine of cachectic cancer patients into mice induced cachexia (Cariuk, Lorite et al. 1997).

3.5.2 Adipose metabolism

Unlike muscle and protein metabolism in cachexia, the factors relating to adipose tissue loss have been much less well researched. Studies into the mechanisms underlying adipose tissue loss have led to the discovery of a LMF, which was purified from the urine of cachectic patients (Masuno, Yamasaki et al. 1981, Masuno, Yoshimura et al. 1984). LMF is a tumour induced catabolic factor, working on adipose tissue to release free fatty acids and glycerol via oxidation (Rydén, Jocken et al. 2007). LMF also binds with high affinity to β3-adrenergic receptor which is thought to play a key role in the regulation of lipolysis, energy expenditure and triglyceride-fatty acid cycling (Russell, Hirai et al. 2002).

As mentioned previously, cancer induces an upregulation of pro-inflammatory cytokines which stimulates the APPR. This can reduce lipogenesis and circulating lipid uptake whilst also activating lipolysis and triglyceride mobilisation by inhibiting lipoproteinlipase (Tuca, Jimenez-Fonseca et al. 2013).

3.5.3 Neuroendocrine response

When it comes to homeostasis, the hypothalamus is the principle co-ordinator and is fine tuned in energy balance. Therefore, it is only logical that it is critically implicated in functions relating to the development of cachexia, stimulating or repressing food intake and energy expenditure. The hypothalamus is constituted by neurons that co-ordinately secrete anorexigenic or orexigenic neuropeptides to control food intake with different lesions of hypothalamus, such as ventromedial and lateral regions, inducing either hyperphagia or promoting anorexia (Anand and Brobeck 1951, Hervey

1959). Research has implicated the melanocortin system as a key driver in the development of cancer cachexia. The system primarily consists of pro-opiomelanocortin neurons that exert anorexigenic effects (Balthasar, Dalgaard et al. 2005, Cone 2005, Silva, de Almeida et al. 2014).

3.5.4 Patient demographic

It may also be the case that the individual patient demographic plays an important role in the development of cachexia as well as the response (and therefore reversibility of the condition) to therapeutics. Age, level of physical activity and specific patterns of metabolism of ingested protein are likely to have an effect (Skipworth, Stewart et al. 2007). Elderly muscle appears to be less anabolically sensitive to amino acids, which are key to protein synthesis via post-prandial increase in plasma amino acid concentration (Tessari, Inchiostro et al. 1987).

3.6 Treatments for cancer cachexia

The multi-faceted aetiology of cancer cachexia makes it a complex and difficult disorder to treat and requires a multimodal approach. In early stage or pre-cachexia, therapy is primarily prophylactic, and it is generally accepted that the only way to completely cure cachexia is to cure the cancer (Suzuki, Asakawa et al. 2013). At advanced stages of cancer, usually the time at which patients have evolved in to cachexia and refractory cachexia stages, the treatments predominantly palliative (Suzuki, Asakawa et al. 2013). In addition, the classifications of cachexia are not adequately described in most trials which aim to assess the effectiveness of treatments, preventing the graded recommendations for the different stages and dimensions of cachexia.

Physiotherapy, psychological and nutritional support is a part of the management of cachexia in patients; however table 1.8 predominantly focuses on the pharmacological approach to cachexia treatment. Pharmacological treatment may be inappropriate in contexts where therapy offers more of a burden than relief, particularly for patients at end stages of disease. Treatments are focused on alleviating the consequences of cachexia and their risk may outweigh the potential benefit. Equally, treatments which may take weeks for effect will likely be inappropriate where patients may have an extremely poor prognosis and short life expectancy. For these reasons, a comprehensive patient assessment and ensuring the patient is well informed is key to determine the most effective treatment, if any treatment at all.

The tolerance of chemotherapy and radiation therapy can be dramatically affected by weight loss and therefore impact on a patients survival benefit. Sub-optimal dosage of anti-cancer therapies and a greater number of AEs have been associated with cachexia (Andreyev, Norman et al. 1998, O'Gorman, McMillan et al. 1998). Refractory cachexia is characterised by a poor performance score (PS; WHO 3-4) (Radbruch L 2010) and at this stage, men with prostate cancer would not be eligible to receive either ADT or chemotherapy for their disease. Currently, there is no globally effective or accepted treatment for cachexia; however there are multiple therapies

currently under investigation. The data is lacking however, and as a result oncologists may find themselves reluctant to prescribe pharmacological agents without further research.

Table 1.8 highlights the use of novel, emerging and established cachexia therapeutics, with detail of their use for men with prostate cancer where data is available. This includes a description of whether the agents have androgenic activity, indicated by androgen receptor activity. Many of the agents have androgenic activity, indicative of the therapeutic role of androgens in the mitigation of LBM loss and maintenance of LBM. In addition, the studies below have demonstrated other therapeutic benefits in reducing symptoms of hypogonadism such as improvements bone health, libido, decreased FM, the reduction of hot flashes and improvements in QoL for example. Treatments such as testosterone have also been shown to have increased efficacy when used alongside exercise (Lenehan 2003, Kanayama, Hudson et al. 2008).

Table 1.8 Cachexia treatments

Type of agent	Name of agent	Mode of action and metabolic effects	AR+	Physiological effect	Benefits	Harms and Disadvantages	Cancer risks	Evidence
SERM	Gtx-758	Selective oestrogen receptor (ER) alpha agonist: Rapidly increases sex hormone binding globulin (SHBG) and reduces circulating free testosterone	N	Suppress secretion of luteinizing hormone (LH) by feedback inhibition on the pituitary, thereby inhibiting the production of androgens by the testes.	The potential to prevent and/or ameliorate bone loss and hot flashes in men on ADT. 125 mg and 250 mg doses have demonstrated dose dependent increases in s SHBG, reductions in free testosterone, and a reduction in PSA.	Phase 2 clinical trials in men with CRPC was terminated. Higher incidence of venous thromboembolic events vs placebo.	none recorded	(Clinicaltrials .gov 2011, GTx 2012, Yu, Getzenberg et al. 2015)
SARM	Gtx-024	Tissue selective anabolic and androgenic activity: Binds with high affinity and selectivity to the AR, does not bind the ER, and cannot be converted to estrogenic metabolites.	Y	Tissue selective anabolic effects on muscle and bone whilst sparing androgenic tissue related to hair growth in women and prostate effects in men.	Statistically significant increase in lean body mass, improved physical function, enhanced libido, decrease in bone turnover (potentially resistant to metastasis), decreased total FM and increased QoL. Reduction in blood insulin.	In development, was not FDA approved for treatment of wasting diseases. AE include nausea, alopecia, anaemia and vomiting. Decreases in HDL in a dose dependant manner.	none recorded	(Dalton, Barnette et al. 2011, Dobs, Boccia et al. 2013)
SARM	MK-4541	Tissue selective anabolic and androgenic activity: Gene selective agonist that induces AR-conformations results in a ligand that maintains some of the actions of DHT such as musculoskeletal anabolic activities but lack effects on skin and prostate.	Y	Inhibit proliferation and induce apoptosis of AR+ prostate cancer cell line that grows in an androgen-independent manner.	Inhibits the growth of the prostate in rats and mice while maintaining significant anabolic activity of androgens on bone and muscle. Reduction in seminal vesicle weight by 96%. Induced bone formation. Maintains some of the beneficial anabolic activity such as musculoskeletal benefits. Reduced prostate tumour size in animal models.	Only studied in animal models. No change in LBM in animal models.	none recorded	(Schmidt, Meissner et al. 2014)

A highly selective ghrelin receptor agonist	Anamorelin	Non-peptidic, orally-active, centrally-penetrant, selective agonist of the ghrelin/growth hormone: Increases plasma levels of growth hormone (GH), IGF-1, and IGF-binding protein 3 (IGFBP-3) in humans.	N	Appetite-enhancing and anabolic effects with significant increases in overall body weight, LBM, and muscle strength.	Improves appetite and body mass in patients with advanced lung cancer who are suffering cancer anorexia and cachexia. Improvements in LBM.	Most frequently occurring AEs were hyperglycaemia and nausea. Patients did not experience improvements in their muscle strength in phase 2 and 3 trials .	none recorded	(Garcia, Boccia et al. , Temel, Abernethy et al.)
Polypeptide hormone	GH/IGF-1	Hepatic/extra hepatic target tissues: stimulates release of IGF-1. Anabolic effects on protein synthesis. Insulin-like properties: increased glucose uptake and protein synthesis (particularly in liver and muscles) and inhibition of lipolysis in adipose tissue. Retention of nitrogen and improved nitrogen balance increasing protein synthesis.	N	Longitudinal growth of bones. Stimulation of myoblast differentiation, increases in muscle mass and glomerular filtration rate. Mobilisation of lipids from adipose tissue and increases oxidation, sparing muscle glycogen improving body composition.	Sustained increases in LBM and weight. Decrease in fat mass. Improvements in physical functioning. Well tolerated in HIV wasting . AEs resolve with symptomatic treatment or dose reduction. Improvements not seen in patients <90% of ideal body weight. Benefits can be transient.	Hypoglycaemia, intracranial hypertension, myalgia, visual changes, headache, nausea, vomiting, peripheral oedema, carpal tunnel syndrome, arthralgia, myalgia, acromegalic features, hypertension, cardiomegaly, cardiovascular risk, glucose intolerance and diabetes.	IGF-1 implicated in cell proliferation, apoptosis angiogenesis , metastasis and chemo resistance Some evidence connecting it to leukaemia.	(Cohen, Clemmons et al. 2000, Mulligan and Schambelan 2002, Lenehan 2003)
Testosterone Propionate	Testosterone Propionate	Androgenic, anabolic: Bind to the androgen receptor or is converted to DHT by 5α-reductase activating gene expression.	Y		Shorter duration of action than testosterone cypionate. Protein anabolic effects may be augmented with resistance exercise training, efficacy in women uncertain. Significant gains in LBM, weight, muscle mass and muscle strength. Improvement in QoL and indices of depression.	Decreased HDL cholesterol. Fluctuations in circulating levels of testosterone. Lower anabolic effects in comparison to anabolic steroids.	Tumours on liver and kidneys in animal models given doses equivalent to body-builders/athletes.	(Lenehan 2003, Kanayama, Hudson et al. 2008)

Testosterone Cypionate	Testosterone Cypionate	Androgenic, anabolic: Bind to the androgen receptor or is converted to DHT by 5α-R activating gene expression.	Y		Protein anabolic effects may be augmented with resistance exercise training, efficacy in women uncertain.	Decreased HDL cholesterol. Can aromatise easily (high doses): gynaecomastia. Fluctuations in circulating levels of testosterone. Lower anabolic effects in comparison to anabolic steroids	Tumours on liver and kidneys in animal models given doses equivalent to body-builders/athletes.	(Lenehan 2003, Kanayama, Hudson et al. 2008)
Cannabinoid	Dronabinol	Partial agonist activity at the cannabinoid receptor CB1, located mainly in the central nervous system, and the CB2 receptor, expressed in cells of the immune system. Psychoactive effects mediated by its activation of CB1G-protein coupled receptors, which result in a decrease in the concentration of the second messenger molecule cAMP through inhibition of adenylate cyclase.	N	Antiemetic and appetite stimulant.	Improvements in mood and appetite.	Common AE: tiredness, dizziness, cardiovascular and psychoactive effects. Overdose usually presents with lethargy, decreased motor coordination, slurred speech, and postural hypotension. Politically and socially controversial.	none recorded	(Gullett, Mazurak et al. 2011, Tuca, Jimenez-Fonseca et al. 2013)

Steroidal Progestin	Megestrol Acetate	Anti-anabolic effects, the mechanism of action of progestagens in cachexia has not been completely elucidated. Agonist of the progesterone receptor. Behaves as an anti-androgen no affinity for the ER. Antigonadotropic effects at sufficient doses, decreasing circulating androgen and oestrogen concentrations to castrate levels in both sexes.	Y	Appetite stimulant.	Appetite stimulation, increased fat deposition and weight gain. Improved wellbeing and QoL. Lower circulating levels of IL-1α, IL-1β and TNF-α .	Ankle oedema, mild hyperglycaemia, thrombophlebitis (doses exceeding 800mg/d). Little or no improvement in LBM. 30% of patients treated experience short-term appetite stimulation, although weight and appetite improve, there is no demonstrated improvement in QoL or OS.	none recorded	(Gullett, Mazurak et al. 2011)
Corticosteroid	Prednisolone	Synthetic glucocorticoid, a derivative of cortisol. Agonist of the progesterone receptor. Behaves as an anti-androgen no affinity for the ER. Antigonadotropic effects at sufficient doses, decreasing circulating androgen and oestrogen concentrations to castrate levels in both sexes.	Y	Appetite stimulant	Improves appetite and QoL compared with placebo.	Long-term use: progressive muscle wasting and weakness, especially in proximal gravity opposing muscles. Mental status changes, diabetes, osteoporosis, cataract formation and immunosuppression. It has been shown that prednisolone plasma levels in patients with CRPC were sufficiently high to activate mutant AR.	none recorded	(Richards, Lim et al. 2012)
Fish oil supplement	Eicosapentanoic acid	Omega-3 fatty acid that acts as a precursor for prostaglandin-3 (which inhibits platelet aggregation), thromboxane-3, and leukotriene-5 eicosanoids. May support the anabolic potential of muscle through sensitising skeletal muscle to insulin. May inhibit several catabolic stimuli that promote	N	May decrease muscle breakdown via a protective role in skeletal muscle differentiation. Immune: down-regulate acute phase response.	Significant gains in LBM, weight gain, appetite and QoL.	Phase III clinical trials reported minimal benefits of supplementation. Previous studies were small, non-randomised and uncontrolled.	none recorded	(Gullett, Mazurak et al. 2011, Murphy, Yeung et al. 2011)

		muscle degradation during the cachectic process						
Anabolic steroid	Oxymetholone	Anabolic agent: Block tumour necrosis factor alpha. Nitrogen balance is improved. Enhances the production and urinary excretion of erythropoietin.	Y	Increased LBM via protein anabolism	Orally available. Weight gain and improvements in LBM. Self-reported appetite and QoL improved.	Elevations in liver enzymes. Potential liver toxicity. At higher doses: depression, lethargy, headache, swelling, rapid weight gain, priapism, changes in skin colour, urination problems, nausea, vomiting, stomach pain (if taken on an empty stomach), loss of appetite, jaundice, breast swelling in men, feeling restless or excited, insomnia, and diarrhoea. No studies performed for treatment of PCa). Gains not possible without weight/resistance training and better with strenuous exercise.	Liver cell tumours are also reported. Most often these tumours are benign and androgen-dependent, but fatal malignant tumours have been reported. Withdrawal of drug often results in regression or cessation of progression of the tumour.	(Hengge, Baumann et al. 1996, Kanayama, Hudson et al. 2008)

AR+: Y- Indicates the agent as an effect on the androgen receptor; N- the agent has no effect on the androgen receptor.

3.6.1 Protein and creatine supplementation, and changes in lean body mass

The effect of protein in promoting the maintenance or gain in LBM is well established, including in ageing or chronically ill populations (Burke, Chilibeck et al. 2001, Frestedt, Zenk et al. 2008, Gullett, Mazurak et al. 2011, Chalé, Cloutier et al. 2012). Protein supplementation has also been shown to be useful in mitigating some of the effects of cancer cachexia by preserving LBM (Fearon, von Meyenfeldt et al. 2003, Fearon 2008, Gullett, Mazurak et al. 2011). In addition it has been shown to improve total energy expenditure and physical activity in cachectic patients with pancreatic cancer (Fearon, von Meyenfeldt et al. 2003). In breast cancer, a higher protein intake has also been associated with better survival (Borugian, Sheps et al. 2004). Protein supplementation has also been demonstrated to have greater gains in LBM in combination with resistance exercise vs resistance exercise alone in frail elderly adults (Tieland, Dirks et al. 2012).

A combination of protein and creatine supplementation has been demonstrated to further increase LBM gains (Burke, Chilibeck et al. 2001). Creatine alone has also demonstrated to have beneficial effects on LBM such as improved performance and strength, LBM gains and changes in GLUT-4, a marker of insulin sensitivity (Burke, Chilibeck et al. 2001, Derave, Eijnde et al. 2003, Cermak, Res et al. 2012). In parallel to exercise training, creatine supplementation in older adults has been reported in a meta-analysis to improve both total body mass, fat-free mass, upper and lower body muscle strength and functional outcomes such as the 30 second chair sit-to-stand test, compared with exercise training without creatine. (Devries and Phillips 2014)

3.7 Summary

LBM loss is associated with a tirade of poor outcomes for patients with cancer. This includes reduced treatment tolerability from increased dose limiting toxicities, poorer survival, poorer PS and increased morbidity. In addition, a low LBM is associated with increased metabolic disorders such as decreased insulin sensitivity. In addition, prostate cancer treatments including chemo and ADT can contribute to LBM loss.

Cancer cachexia is a multifactorial syndrome with a complex pathology and clinical presentation making it difficult to accurately diagnose. Therefore, the true data on the prevalence and incidence of cachexia is not clear. However, it is estimated to be prevalent in about 80% of all advanced cancer patients at varying stages of cachexia. Some data suggest the proportion of cachexia in prostate cancer patients can be up to 15%.

So far treatments for cachexia have been palliative and there are no known cures for cachexia, unless the cancer itself is cured. However, therapeutics for cachexia have the potential to be of greater benefit if cachexia is caught at earlier stages.

Many of the therapeutics have some androgen receptor activity, which further demonstrates the potential therapeutic role of androgens. This includes not only the alleviation or mitigation of LBM loss, but also of other hypogonadal symptoms such as decreased hot flashes, improved bone health and increased libido in some agents. Given that testosterone replacement therapy has not been shown to result in disease progression, further detail is given in section 2.5, there could be a rationale the use of agents with androgenic activity for men with significant side effects from ADT detrimental to QoL. Furthermore, nutritional intervention with supplementation of protein and creatine has also demonstrated success in the preservation and improvement in LBM, including for that of cachexia patients. Both whey and creatine supplementation and testosterone replacement therapy have also demonstrated superior effects when combined with exercise training.

A combination of a nutritional/pharmacological intervention alongside exercise training has the potential to improve symptoms of hypogonadism such as LBM loss, declining bone health and increased fat mass. This is of particular significance for men with CRPC, who have a long history of disease and a poor QoL.

3.7.1 ADT body composition and cancer cachexia

LBM loss and its associated skeletal dysfunction as a result of ADT has also been suggested to potentially exacerbate cachexia in men with prostate

cancer, facilitating a proinflammatory state and decreasing survival (Del Fabbro, Hui et al. 2010). The patient demographic described in section 3.3.4 in this chapter describes how factors such as inactivity, age and patterns of metabolism may potentiate cachexia in cancer patients. Given the known metabolic effects of ADT, and the some evidence with demonstrates a link with hypogonadism in cachexia, there may potentially be a mechanism as to ADT predisposing these men at later stages in disease to developing cachexia (Wiechno, Poniatowska et al. 2017). Furthermore, hypogonadism has also been associated with appetite loss and thus potentially forming a vicious circle and exacerbating the cachexia (Garcia, Li et al. 2006, Wiechno, Poniatowska et al. 2017). At present however, there exists no established mechanism for this.

Furthermore, the prevalence of cachexia is in fact lower in prostate cancer than other cancers given the data in table 1.6, which would suggest that ADT does not predispose these men to the onset of cachexia. However, given the associated LBM loss with ADT, and potentially pre-existing sarcopenia (given that this population of men is older) it may be that cachexia remains undiagnosed in this cohort, and is in fact mistaken for LBM loss associated with cancer treatments. As described in section 3.2 in the present chapter, there are ongoing difficulties with the diagnosis of cachexia in all cancer types, and therefore a missed diagnosis of cachexia could be possible. Furthermore, ADT could potentially mask the development of cachexia due to adverse effects such as increased central obesity. Equally, the lower numbers of cachexia in men with prostate cancer may indicate a potentially protective effect of ADT. Regardless, it is clear that the accurate diagnosis, prevalence and clinical significance of cachexia in men with prostate cancer requires further research.

Subsequently, interventions aimed in men who are undergoing or continue to undergo long-term ADT may gain significant benefit from interventions to promote LBM accrual. Such interventions may include exercise and/or dietary programmes with an aim to improve or maintain LBM whilst these men continue through their cancer journey. The following chapter includes a literature review to address the current body of evidence surrounding

exercise and dietary interventions for men with CRPC with the aim to improve outcomes in these men.

Chapter 2 Literature review of exercise and dietary interventions as a supportive therapy for cancer and thesis overview

1. Introduction

With an expanding cancer population expected to live 5 years or longer (White, Holman et al. 2014), the adoption of healthy lifestyle behaviours to reduce all cause morbidity and mortality have become increasingly important. A cancer diagnosis has long been regarded as "a teachable moment" by which cancer patients are motivated to make behaviour changes associated with a healthy lifestyle to reduce their risk of adverse health outcomes. This encompasses a "self-help" approach to mitigating the long and short term effects of cancer and its treatments. This approach can include adopting regular exercise and a healthy diet, maintaining a healthy weight and other practices such as attending support groups and undertaking mindfulness training for example (Jones and Demark-Wahnefried 2006). Adoption of such lifestyle behaviours has been demonstrated to improve QoL and physical function in cancer patients (Morey, Snyder et al. 2009, Demark-Wahnefried, Morey et al. 2012).

As discussed previously, the AEs associated with the treatment of prostate cancer can be debilitating. As a result, healthy lifestyle behaviours have the potential to help alleviate some of these debilitating effects unique to these men.

2. Cancer and diet

There are dual concerns when it comes to cancer patients and maintaining a healthy weight and diet. As previously discussed, cancer patients can be faced with anorexia and/or cachexia as a result of their cancer therapy and disease (in advanced cancer) and this is of significant concern. But much more prevalent in cancer populations is obesity and overweight problems (Brown Jean, Byers et al. 2009, Rock, Doyle et al. 2012). Obesity is an established risk factor for cancer such as breast, oesophagus, colon, prostate and kidney cancer (Bianchini, Kaaks et al. 2002, Vucenik and Stains 2012). In addition, excess weight has been associated with increased cancer mortality (Calle, Rodriguez et al. 2003). For this reason, changes in body composition during the natural history of cancer can be convoluted and complex to treat but the metabolic effects can be devastating. Therefore,

establishing a nutritional balance is a clinical need in cancer patients to ensure favourable body composition and therefore reduce the risk of functional decline, comorbidity, and cancer recurrence.

Multiple pre-clinical and clinical studies, including observational cohort studies, have demonstrated anti-tumour effects of a low carbohydrate and high protein diet (Slattery, Benson et al. 1997, Terry, Jain et al. 2003, Fung, Hu et al. 2011, Ho, Leung et al. 2011, Fokidis, Yieng Chin et al. 2015). A high fibre diet has also been associated with chemoprotective effects, lowering the risk of colorectal cancer (Bingham, Day et al. 2003, Peters, Sinha et al. 2003).

2.1 Prostate cancer and diet

In prostate cancer, there are some studies which suggest a link between certain food groups and increased cancer risk or chemopreventative effects. However, there is great complexity surrounding studies which demonstrate a causal relationship with isolated foods or food groups due to the highly variable nature of the human diet.

2.1.1 Eggs

A meta-analysis of nine cohort studies and 11 case-control studies has demonstrated there is no association with prostate cancer incidence or mortality and egg consumption (Xie and He 2012). This meta-analysis included 5791 cases of prostate cancer, and most studies suggested a non-significant relationship.

However, a prospective cohort study (Cancer of the Prostate Strategic Urologic Research Endeavor) by Richman et al of 1294 men with prostate cancer also showed a greater consumption of eggs was associated with 2-fold increases in risk of prostate cancer recurrence or progression in a comparison of extreme quantiles (HR: 2.02; 95% CI: 1.10, 3.72; p =0.05) (Richman, Stampfer et al. 2010). Furthermore, in the Health Professional Follow-up study, involving 27,607 men followed from 1994–2008, men who consumed 2.5 or more eggs per week had an 81% increased risk of lethal prostate cancer compared with men who consumed less than 0.5 eggs per week (HR: 1.81; 95% CI: 1.13-2.89; p =0.01) (Richman, Kenfield et al. 2011).

Therefore, the data suggests that although egg consumption may not increase the risk of developing prostate cancer, there is an associated risk of a more aggressive prostate cancer phenotype, prostate cancer reoccurrence or progression.

2.1.2 Fish

Fish consumption has been associated with a lower risk of death from prostate cancer. A meta-analysis of cohort studies demonstrated that for men with the highest consumption of fish a there was a 63% reduction in prostate cancer-specific mortality [4 cohort studies (n =49,661), RR: 0.37; 95% CI: 0.18, 0.74] (Szymanski, Wheeler et al. 2010). The meta-analysis did not demonstrate an association with a reduction in prostate cancer incidence. In particular, fish that is high in omega-3 such as salmon, sardines and mackerel, may reduce risk of clinically significant prostate cancer. Furthermore, the study of 1294 men by Richman et al did not find an association with fish consumption and prostate cancer recurrence or progression (Richman, Stampfer et al. 2010). But the findings did show that men who consumed the highest levels of fish also consumed more cruciferous vegetables and tomato products and less processed meat.

These findings suggest that although consumption of fish products does not affect the incidence of prostate cancer, there may be a lower risk of prostate cancer mortality with high levels of fish consumption. However, it may be that these findings reflect overall healthier dietary behaviours in those who eat larger amounts of fish than those who do not.

2.1.3 Poultry

Studies suggest that skinless poultry is not associated with prostate cancer progression but poultry with skin has shown some association (Richman, Kenfield et al. 2011). The 2010 study by Richman et al did demonstrate that poultry with skin (about 3 servings/week) after prostate cancer diagnosis had a 2.26-fold increased risk of recurrence compared with men who consumed 0 servings/week (Richman, Stampfer et al. 2010). Conversely, poultry intake was inversely associated with advanced prostate cancer risk (p =0.009), with an odds ratio of 0.7 (95% CI: 0.6–1.0) for highest versus lowest quartile of intake for poultry that was baked (Joshi, Corral et al. 2012). This study

included 1096 controls, 717 localised and 1140 advanced prostate cancer cases from the California Collaborative Prostate Cancer Study.

The findings suggest that there is tentative evidence a relationship between prostate cancer risk and poultry consumption. However, there may be an association in how poultry is prepared and prostate cancer risk.

2.1.4 Processed and red meat

There have been several reports highlighting processed and/or meat increases prostate cancer risk. A large cohort study of 175,343 US men demonstrated an increased risk with red and processed meat consumption for total (red meat: HR: 1.12, 95% CI: 1.04-1.21; processed meat: HR: 1.07, 95% CI: 1.00-1.14) and advanced (red meat: HR: 1.31, 95% CI: 1.05, 1.65; processed meat: HR: 1.32, 95% CI: 1.08, 1.61) prostate cancer (Sinha, Park et al. 2009). The CLUE II study, involving 3892 men, demonstrated that processed meat (but not red meat or total meat consumption) was associated with a non-statistically significant higher risk of total (5+ vs. ≤1 servings/week: HR: 1.53, 95% CI: 0.98–2.39) and advanced (HR: 2.24; 95% CI: 0.90–5.59) prostate cancer (Rohrmann, Platz et al. 2007).

However, a meta-analysis published in 2010 demonstrated that no significant association between red meat or processed meat and prostate cancer was observed (Alexander, Mink et al. 2010). This meta-analysis included prospective cohort studies; 15 studies of red meat and 11 studies of processed meat were included in the analyses, which included the CLUE II study but not the Sinha et al 2009 study. The summary results for processed meat were slightly elevated however, the association across the more recently published studies that were adjusted was attenuated and not statistically significant. The authors concluded there was evidence of publication bias across the cohort studies of processed meat. Despite this, this study and the authors of this meta-analysis were partially funded by the Cattlemen's Beef Board, through the National Cattlemen's Beef Association which presents a serious conflict of interest.

The findings suggests that while some large scale studies do report an association between red and processed meat and prostate cancer the data is

tentative with a meta-analysis data of complied studies suggesting no association (although this meta-analysis had a serious conflict of interest). Furthermore, the World Cancer Research Fund - Continuous Update Project (WCRF-CUP) has determined that there is inconclusive evidence of the relationship between red and processed meat and prostate cancer, however the authors still recommended to limit the consumption of red and processed meat (WCRF-CUP 2014).

2.1.5 Cruciferous vegetables

The greater consumption of cruciferous vegetables is associated with a lower risk of developing aggressive prostate cancer. In one study, risk of prostate cancer (stage III or IV tumours) decreased with increasing vegetable intake (RR: 0.41, 95% CI: 0.22-0.74, for high versus low intake; p =0.01). The study demonstrated this association was considered to be predominantly explained by intake of cruciferous vegetables (RR: 0.60, 95% CI: 0.36-0.98, for high versus low intake; p =0.02) (Kirsh, Peters et al. 2007). Similarly, a 2000 study of 1619 cases of prostate cancer demonstrated the inverse relationship (Kolonel, Hankin et al. 2000).

Overall the studies suggest there to be an inverse relationship with the consumption of cruciferous vegetables and prostate cancer risk. Furthermore, the WCRF-CUP suggest a diet high in fruit, vegetables and legumes as part of cancer prevention recommendations (WCRF-CUP 2014).

2.1.6 Dairy products

The Prostate Cancer Systematic Literature Review (SLR) 2014 by the WCRF-CUP identified a total of 21 studies which addressed the association of dairy products and prostate cancer risk (WCRF-CUP 2014).

Of 15 studies examining total prostate cancer incidence, 13 reported a positive association with dairy products, four of which were significant. Two studies reported a non-significant inverse association. Fifteen of the 21 studies were included in the dose-response meta-analysis, which showed a statistically significant 7% increased risk per 400 g of dairy products per day (RR 1.07). However, when stratified by prostate cancer type, there was no significant association for non-advanced, advanced, or fatal prostate cancer.

The report concluded that for a higher consumption of dairy products, the evidence suggesting an increased risk of prostate cancer is limited.

2.2 Supplementation and cancer

Similarly, with specific food groups, decades of extensive research has attempted to clarify the role of dietary supplementation in cancer groups. In the previous chapter the effect of whey protein and creatine supplementation on LBM in cancer and non-cancer populations was discussed. However, there are a number of other dietary supplements which have been studied in cancer populations. The primary aim of many of these studies has been to demonstrate some level of anti-tumour effect of dietary supplementation as a complementary therapy alongside usual cancer treatments. In general, these studies have demonstrated limited effects, and the role of dietary supplements in cancer is still contentious. This is in part due to the difficultly in conducting robust research studies relating to diet. Most of the evidence which exists is in retrospective, case control and prospective cohort studies as RCTs are much more difficult to perform but provide the most robust level one data. However, some RCT studies and their findings have been summarized in table 2.1 reproduced from (Vernieri, Nichetti et al. 2018).

Table 2.1 RCTs testing supplements for cancer prevention. In the column "Results", relative change in tumour incidence in the intervention arm compared with the control arm of each trial is indicated. * indicates statistically significant results (p <0.05). Reproduced from (Vernieri, Nichetti et al. 2018) with permission (23 May 2018; licence 4354810177315)

Study	Participant group	Tumour	Supplement	Results (Incidence)
CARET (Omenn, Goodman et al. 1996)	High risk of developing lung cancer	Lung	Beta-carotene plus retinyl palmitate	+28%*
The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (1994)	Male smokers	Lung	Beta carotene	+18%*
SELECT (Lippman, Klein et al. 2009)	Men	Prostate	Vitamin E	+17%
Linxian (Blot, Li et al. 1993)	Men/women Chinese, including poorly nourished	All tumors	Molibden plus vitamin C	+6%
SELECT (Lippman et al., 2009)	Men	Prostate	Selenium	+4%
SU.VI.MAX. (Hercberg, Galan et al. 2004)	Healthy French adults	All tumors (women)	Low-dose vitamin plus mineral mix	+4%
Linxian (Blot et al., 1993)	Men/women Chinese, including poorly nourished	All tumors	Zn plus retinol	No difference
The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (1994)	Male smokers	Lung	Vitamin E	−1%
PHS (Hennekens, Buring et al. 1996)	Male U.S. physicians	All tumors	Beta carotene	−2%
WHI (Cauley, Chlebowski et al. 2013)	Postmenopausal Women	Colorectal	Ca^{2+} plus vit D	−5%
Linxian (Blot et al., 1993)	Men/women Chinese, including poorly nourished	All tumors	Selenium plus Beta carotene plus vitamin E	−7%
SU.VI.MAX. (Hercberg et al., 2004)	Healthy French adults	All tumors (men)	Low-dose vitamin plus mineral mix	- 31%

2.2.1 Prostate cancer and dietary supplementation

The data presented below has been taken from the WCRF-CUP meta-analysis (Prostate Cancer SLR 2014) of the evidence for supplements for prostate cancer (WCRF-CUP 2014).

2.2.1.1 Calcium supplementation

The Prostate Cancer SLR 2014 included a total of nine cohort studies in the CUP on calcium supplements. Dose-response meta-analysis of four studies on total, advanced, and non-advanced prostate cancer showed no significant association to prostate cancer risk (Ahn, Albanes et al. 2007, Park, Murphy et al. 2007, Park, Mitrou et al. 2007, Kristal, Arnold et al. 2010). Two studies were included in the dose-response meta-analysis on fatal prostate cancer and calcium supplements, which showed a significant positive effect (RR: 1.27) (Giovannucci, Liu et al. 2006, Park, Mitrou et al. 2007). One RCT was included in the CUP, which showed a non-significant inverse association to prostate cancer risk (Kristal, Arnold et al. 2010). The report findings suggested that no conclusion could be drawn for calcium supplements.

2.2.1.2 Beta-carotene supplementation

The Prostate Cancer SLR 2014 identified five cohort studies (three articles) (Cook, Stampfer et al. 2000, Wu, Erdman et al. 2004, Kirsh, Hayes et al. 2006, Ahn, Moslehi et al. 2008, Ambrosini, de Klerk et al. 2008, Roswall, Larsen et al. 2013). All five studies reported no significant association between beta-carotene supplements and total prostate cancer. The report concluded that consuming beta-carotene in supplements is unlikely to have a substantial effect on the risk of prostate cancer.

2.2.1.3 Vitamin E

The Prostate Cancer SLR 2014 conducted dose-response meta-analyses for vitamin E supplements, and total prostate cancer. No significant associations were found at a dose of 100 IU/day (RR 1.00 95% CI 0.99-1.01) from seven studies in 21,862 cases (WCRF-CUP 2014). This meta-analysis included the findings mentioned in table 2.1 of the SELECT study which did demonstrate an association, however when the evidence was compiled with other studies no associations were found.

2.2.1.4 Selenium

The Prostate Cancer SLR 2014 included a total of five studies in the CUP on selenium supplements, but no meta-analysis was possible. The SELECT trial reported that selenium supplements, taken alone or with vitamin E, did not reduce risk of prostate cancer (Stratton and Godwin 2011). The findings of

the SELECT trial relating to selenium exposure given in table 2.1 were not related to selenium supplementation but other exposures (such as diet).

3. Physical activity, exercise and cancer

The goal of a sustained exercise programme is that over time cardiovascular, musculoskeletal, respiratory, neurophysiological and metabolic adaptations occur. For cancer patients living with or beyond the disease, there is sound theoretical rationale that such adaptations have the potential to confer a range of benefits specific to this population. Increasing evidence demonstrates that exercise may represent a useful stand alone or supportive therapy for the treatment of cancer, improving physiological and psychosocial outcomes (Segal, Reid et al. 2003, Knols, Aaronson et al. 2005, Ornish, Weidner et al. 2005, Galvao, Nosaka et al. 2006, Courneya, Segal et al. 2007).

This thesis refers to the terms "physical activity" and "exercise" throughout and are defined below, as has previously been described in (Caspersen, Powell et al. 1985):

"Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure…Physical activity in daily life can be categorized into occupational, sports, conditioning, household, or other activities. Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness."

The current UK public health physical activity recommendations for adults states, weekly activity should add up to at least 150 minutes of moderate intensity physical activity, undertaken in bouts of 10 minutes or longer or 75 minutes of vigorous intensity activity a week (Rock, Doyle et al. 2012, Sparling, Howard et al. 2015). Compared to healthy adults, cancer patients are more likely to be inactive (defined as not meeting these recommendations) as well as being more sedentary after a cancer diagnosis, rarely returning to pre-diagnosis activity levels (Brown Jean, Byers et al. 2009).

In this body of work, sedentary was determined as less than 90 minutes of moderate intensity exercise per week. This criterion was chosen because less than this refers to under three 30-minute exercise sessions or less per week, which is substantially less than the Centre for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) recommendation (Bennett, Wolin et al. 2009) and therefore those men would be considered sedentary or inactive. This criteria has also been described as sedentary in a previous systematic review of exercise interventions in sedentary cancer patients (Bourke, Homer et al. 2013). However, in research any definitions of sedentary have been adopted; furthermore many studies have failed to report on what was deemed as sedentary (Pate, O'Neill et al. 2008, Tremblay, Aubert et al. 2017).

In comparison to that of studies which focus on early stage cancer, the effect of exercise on advanced cancer is less understood except the need to adequately adapt exercise programmes on an individual basis for these patients (Brown Jean, Byers et al. 2009). These patients are faced with a different set of clinical problems in comparison to those at earlier stages of disease. They tend to be older and can have bone disease or significant impairments such as arthritis or peripheral neuropathy, where there may be a higher risk of falls and injures as a result. Equally, there may be occasions where the disease or treatment necessitates periods of bed rest, such as major surgery, and a result a reduced fitness and strength may follow. As discussed previously, for these patients, LBM loss and a gain in visceral FM can also be of significant clinical concern. This is compounded with being on long-term anti-neoplastic therapies. However, exercise is a promising intervention strategy for these patients given its ability to reduce inflammation, increase protein anabolism and protein synthesis and decrease fatigue (Gould, Lahart et al. 2013) and the beneficial effects of exercise training for improving or preserving LBM are well established (Galvao, Nosaka et al. 2006, Galvão, Taaffe et al. 2010, Hvid, Winding et al. 2013). Studies investigating the effectiveness of resistance training and cancer have shown positive effects demonstrating an increase in

chemotherapy completion rate (Courneya, Segal et al. 2007, van Waart, Stuiver et al. 2015).

3.1 Prostate cancer and exercise

Multiple systematic reviews have demonstrated that exercise interventions have a beneficial effect specific to improving outcomes in men with prostate cancer. These results have been summarised in table 2.2. The studies represented in the systematic reviews and single meta-analysis represent effects of exercise on prostate cancer patients at a range of stages in their treatment from interventions during irradiation, ADT and with inpatients prior to and/or shortly after surgery.

The findings of the reviews and meta-analysis suggest that exercise for men with prostate cancer is safe and can alleviate some of the symptoms of ADT. This includes potential benefits to QoL, fatigue, functional performance and muscle strength. In addition, the findings suggest that resistance exercise (with or without aerobic training) in particular potentially confers a greater benefit for outcomes such as QoL, muscle strength/endurance and LBM.

However, the strength of this evidence varied between reviews dependant on the quality of the trials. Where some reviews excluded based on trial design, such as the inclusion of only RCTs, others included non-randomised trials and cohort studies. This meant that there were differing levels of evidence between studies. Studies which included solely RCT, or stratified studies for higher level evidence, found little or no evidence of benefit for disease progression, cardiovascular health, or sexual function. There was also inconclusive evidence for blood lipids, BMD and immune response.

There is a stronger body of evidence, from the most robust studies (RCTs with a low risk of bias) to suggest improvements in QoL, fatigue and muscular strength and endurance. There is moderate level evidence to suggest improvements in body composition, sexual function and functional performance. Overall it was clear that the most promising results were from studies which involved supervised exercise as opposed to home-based programmes. In addition, the evidence suggested that group-based programmes were also more effective. It was also felt that a mix of both

aerobic and resistance exercise was most likely to confer the largest beneficial effects. One review assessed studies which examined whether trials involving resistance exercise (Hasenoehrl, Keilani et al. 2015) which demonstrated beneficial effects on muscle strength and performance (more strongly correlated with resistance exercise only studies) and QoL, however there were inclusive results on body composition and BMD.

Only one review conducted a meta-analysis which determined no significant effect of exercise to QoL in contrast to the other reviews (Bourke, Smith et al. 2015). However, the authors concluded this was potentially due to the poor adherence reported in the trials. This was predominantly due to the finding that those trials with poor adherence did not find clinically significant changes in trial outcomes. In addition there was no significant effect of exercise on disease progression, cardiovascular health, or sexual function where other systematic reviews had suggested a beneficial effect.

Observational data and early pilot trials have linked exercise behaviour after diagnosis to favourable disease progression and cancer specific mortality outcomes in men with prostate cancer (Ornish, Weidner et al. 2005, Frattaroli, Weidner et al. 2008, Kenfield, Stampfer et al. 2011, Richman, Kenfield et al. 2011, Magbanua, Richman et al. 2014). However, the findings from the study by Bourke et al did not determine an association with exercise and disease progression in a meta-analysis data of only RCTs, which considers only higher level evidence (Bourke, Smith et al. 2015). Given the limitations described in the Bourke et al study (i.e. low adherence) the data regarding disease progression and mortality is not conclusive.

However, due to the level one evidence in multiple published RCTs, special recommendations for prostate cancer patients, have been published. NICE in the UK (NICE-CG175) and the European Association of Urology (EAU) have both recommended supervised exercise training as part of standard treatment for men with prostate cancer on long-term ADT (NICE 2014). The NICE guidance states to offer men who are starting or having ADT supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue and improve QoL. EAU guidelines recommend to

offer men on ADT, 12 weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.

Table 2.2 Prostate cancer and exercise interventions reviews

Author	Review	Quality of studies	Findings	Conclusions
(Baumann, Zopf et al. 2012)	A systematic review of RCTs in men with prostate cancer including 25 studies involving 2590 patients. The trials involved both supervised and unsupervised exercise studies published up until 2010	Most studies ranked evidence level "2b." Only four studies, all conducted during medical treatment, reached the level "1b."	Supervised exercise was deemed more effective than non-supervised exercise. Resistance training during irradiation showed significant improvement in fatigue, aerobic fitness, muscle strength, and quality of life. Similar results could be observed in prostate cancer patients performing aerobic endurance training during irradiation. Toxicity scores also decreased. However, resistance training brings about more positive effects than endurance training. Significant improvements in quality of life, fatigue, and fitness seem to only be accomplished by isolated resistance training during ADT.	The data suggested that incontinence, fitness, fatigue, body composition and QoL can be improved by exercise in patients during and after prostate cancer.
(Bourke, Smith et al. 2015)	A systematic review and meta-analysis of 16 RCTs involving 1574 men with prostate cancer published up to March 2015.Studies included aerobic and/or resistance exercise.	Level 1 evidence. Sensitivity analysis of studies that were judged to be of high quality indicated a moderate positive effect estimate (standardised mean differences (SMD) 0.33, 95% CI 0.08-0.58; median follow-up 12 wk). The most common issues effecting high risk of bias that would impact on study quality were level of study attrition during at least one follow-up point, poor intervention adherence, lack of investigator blinding, and selective reporting bias.	Analysis of the 7 trials which measured QoL revealed no significant effect (SMD 0.13, 95% confidence interval [CI] -0.08 to 0.34, median follow-up 12 wk). Similar beneficial effects were seen for cancer-specific fatigue, submaximal fitness, and lower body strength. There was no evidence of benefit for disease progression, cardiovascular health, or sexual function.	These results supported the hypothesis that exercise interventions improve cancer-specific quality of life, cancer-specific fatigue, submaximal fitness, and lower body strength.
(Gardner, Livingston et al. 2014)	A systematic review of 10 studies published between January 1980 and June 2013. Studies involved	Risk of bias was addressed from the downs and black checklist of methodological	Exercise training demonstrated benefits in muscular strength, cardiorespiratory fitness, functional task performance, lean body mass, and fatigue, with	Among patients with prostate cancer treated with androgen-

	men on ADT with prostate cancer. Studies included both aerobic and/or resistance exercise. 10 studies were included involving a total of 565 patients. 5 studies were RCTs and 5 studies were uncontrolled trials.	quality. All studies ranked good or excellent for risk of bias (>20).	inconsistent effects observed for adiposity. However, the impact of exercise on bone health, cardiometabolic risk markers, and quality of life are currently unclear.	deprivation therapy, appropriately prescribed exercise is safe and may ameliorate a range of treatment-induced adverse effects.
(Hasenoehrl, Keilani et al. 2015)	A systematic review of studies published between 1966 and September 2014 involving resistant exercise in men undergoing adjuvant therapy and rehabilitation of prostate cancer. The study included 13 studies involving 876.	Of the 13 studies 2 studies were categorized Leve IIb and the remainder at level Ia. Risk of bias was measured by the downs and black checklist. The scores of the rated studies ranged good to excellent (23-30 of a maximum of 32 points). The study subjects could not be blinded to the interventions. In 7 of the 13 studies, no attempt was made to blind those measuring the main outcomes.	The majority of studies demonstrated resistance exercise as an effective and safe intervention to improve muscular strength and performance, fatigue and QoL. There is inconclusive evidence concerning cardiovascular performance, body composition, blood lipids, BMD and immune response.	Resistance exercise appears to be safe in prostate cancer patients with beneficial effects on physical performance capacity and QoL.
(Keogh and MacLeod 2012)	A systematic review of 12 studies including 8 RCTs and 4 non-RCTs in men with prostate cancer. Studies included aerobic and/or resistance exercise.	Of the 12 eligible studies, three were categorized as being Level I, five as Level II, and four as Level III–V. The most common issues effecting high risk of bias that would impact on study quality were level of study attrition and lack of investigator blinding.	High level evidence was observed for the benefits of exercise in improving muscular endurance, aerobic endurance, and overall QoL, as well as reducing fatigue. Moderate level evidence also suggested that exercise may improve muscle mass, muscular strength, functional performance (walking and sit to stand speed), as well as health-related, social and physical QoL. These effects appeared greater for group, rather than home-based, exercise, especially if these programs included resistance training.	It is recommended that most prostate cancer patients be encouraged to exercise regularly by their clinicians and significant others. Where possible, this exercise should be group-based and include some resistance training.

3.2 Men on androgen deprivation therapy and exercise

Reviews have demonstrated that men on long-term ADT with prostate cancer will gain specific benefit from interventions of aerobic and/or resistance exercise related to their treatment and therefore hypogonadal state. A summary of the available evidence which has evaluated exercise in these men are given below.

3.2.1 Body composition

Galvao et al demonstrated an increased in LBM in a combined programme of aerobic and resistance exercise of 1% to 5% vs usual care (Galvão, Taaffe et al. 2010). However, his earlier 2006 study of resistance exercise showed no significant benefit (Galvao, Nosaka et al. 2006). Although both studies had a 12-week intervention period, the 2006 study did involve only 10 men compared to the 57 men recruited in the 2010 study, which is likely to account for the inconsistencies in these findings.

Similarly, Segal et al showed a 12-week resistance exercise intervention did not improve body composition significantly including body weight, BMI, waist circumference, or subcutaneous skinfolds (Segal, Reid et al. 2003). Conversely, his later study showed that whilst both control and aerobic exercise arms showed no effect on body fat percentage over 24 weeks only the resistance exercise arm was able to prevent increases in body fat (Courneya, Segal et al. 2007).

Hanson et al also reported a significantly increased total body muscle mass of 2.7% and thigh muscle volume 6.4% with a 12-week resistance exercise intervention in black African men (Hanson, Sheaff et al. 2013). The study also demonstrated a significant decreased percentage body fat by 2.2% but not in subcutaneous or intermuscular fat.

3.2.2 Bone health

Of the RCTs mentioned in the reviews, Galvao et al investigated whole-body bone mineral calcification and hip BMD in 10 men over 20 weeks of resistance exercise and found no significant change (Galvao, Nosaka et al. 2006). However, the intervention may have mitigated further detrimental changes to bone health as opposed to increasing BMD.

3.2.3 Physical function

Numerous studies have demonstrated a significant beneficial change in physical performance defined as cardiorespiratory fitness, muscular outcomes and functional tasks. Bourke et al showed significant improvements in cardiorespiratory fitness with a 12-week aerobic and resistance exercise intervention which was maintained at six months of follow up (Bourke, Doll et al. 2011). The Hanson et al study demonstrated strength training significantly increased chair sit to stand tests and six-minute walk test (6MWT) ($p < 0.001$) as well as timed up and go, stair climbs and 400m walk ($p < 0.05$) (Hanson, Sheaff et al. 2013). However another study involving a 16-week physical activity intervention showed no significant changes in 6MWT or the sit and reach test (Culos-Reed, Robinson et al. 2010) but did show improvements in systolic and diastolic blood pressure.

A 2012 study by Alberga et al failed to demonstrate significant changes in $V\dot{O}_2$ peak in the aerobic and resistance exercise group in a 24-week intervention, although aerobic fitness decreased in the control group ($p = 0.044$) (Alberga, Segal et al. 2012).

3.2.4 Fatigue

Both the 2011 study by Bourke and the 2003 study by Segal showed significant reductions in fatigue with exercise training (Segal, Reid et al. 2003, Bourke, Doll et al. 2011). The Segal 2003 study, involved 155 men in a 16-week resistance exercise trial. However the trial by Bourke et al involved 50 men undertaking a programme of aerobic activity so the findings are limited by a small sample size. The later study by Segal in 121 patients showed only a borderline significant improvement in fatigue with the resistance training group and no difference in the aerobic training group (Segal, Reid et al. 2009). Furthermore, the study demonstrated greater long-term improvements in fatigue in the resistance exercise group (Segal, Reid et al. 2009). Culos-Reed et al showed no benefit to fatigue with a home-based exercise intervention vs control (Culos-Reed, Robinson et al. 2010). The Culos-Reed study involved 100 men and included a mix of aerobic and some light resistance training. This may indicate that a 16-week programme of resistance exercise confers a more robust beneficial effect on fatigue when compared to aerobic training.

3.2.5 Cardiovascular health

ADT is associated with significant cardiovascular morbidity and mortality (Zhao, Zhu et al. 2014). This has been evidenced by the reduction in flow-mediated dilatation (FMD)

of the brachial artery in men treated with long-term ADT (Gilbert, Tew et al. 2013). An inverse relationship between relative FMD and the risk of future cardiovascular events exists. It has been suggested that a reduced cardiovascular risk of 13% per 1% higher relative FMD in individuals with any pre-existing cardiovascular risk factor (Ras, Streppel et al. 2013).

Gilbert et al demonstrated an improvement in FMD in a 12-week supervised exercise intervention of aerobic, resistance and balance exercises (Gilbert, Tew et al. 2016). At 12 weeks, the difference in FMD was 2.2% favouring the intervention group. The study estimated that the changes in FMD could translate clinically to a significant risk reduction in cardiovascular events by 39%, with a 4.1% absolute risk reduction.

Galvao et al showed a decrease in C-reactive protein after a 12-week supervised exercise intervention, but the findings were not supported by any other improvements in cardiovascular health outcomes (Galvão, Taaffe et al. 2010). Another study of a home based exercise programme, by Culos-Reed et al, failed to show any clinically significant change in systolic and diastolic blood pressure, although there was a reduction in both the non-exercising and exercising groups (Culos-Reed, Robinson et al. 2010).

3.2.6 Quality of life

A number of studies have reported on QoL outcomes. Cormie et al there was a significant improvement in perceived general health, vitality and physical health composite domains of the Short-Form Health Survey (SF-36) (Cormie, Newton et al. 2013). The 2003 and 2009 Segal studies too showed significant benefits of resistance exercise training to QoL measures (Segal, Reid et al. 2003, Segal, Reid et al. 2009).

Conversely, a non-significant improvement in the Functional Assessment of Cancer Therapy- Prostate (FACT-P) QoL questionnaire score was demonstrated in the Bourke study (Bourke, Doll et al. 2011). The Culos-Reed study also demonstrated no significant benefit of the home based exercise intervention vs control in the QoL measures (Culos-Reed, Robinson et al. 2010).

3.3 Supplementation and exercise in men with prostate cancer

There is evidence to suggest that supplements taken alongside a programme of exercise is of some therapeutic benefit regarding LBM loss associated with cancer, either from the disease itself or from its associated treatments (Fearon 2008, Penna,

Busquets et al. 2011, Madeddu, Maccio et al. 2012). Exercise, whey protein and creatine supplementation to promote muscle protein synthesis through stimulation of anabolic processes in men with castrate levels of testosterone is therefore an attractive therapeutic choice.

Two studies published recently have evaluated the effect of dietary supplementation and resistance exercise on musculoskeletal health for men with prostate cancer on long-term ADT (Hanson, Nelson et al. 2017, Dawson, Dorff et al. 2018).

Hanson et al examined the effect of whey supplementation and resistance exercise on acute muscle protein synthesis response for men undergoing ADT for advanced prostate cancer (Hanson, Nelson et al. 2017). The findings demonstrated that men on ADT are still able to initiate a robust response increasing muscle protein synthesis following resistance exercise and whey protein supplementation, despite basal protein synthesis being compromised by ADT. The study involved 18 participants, 8 men undergoing treatment for prostate cancer and 10 healthy age-matched controls. The average duration of ADT in these men was 18 months. The resistance exercise consisted of unilateral knee exercises followed immediately by consuming 40g of whey protein isolate; the unilateral model enabled the participants to serve as their own resting controls (where one leg was not performing any knee exercise). The findings suggest that men on ADT for prostate cancer had a reduced basal and protein induced rises in muscle protein synthesis. However, when the protein ingestion followed resistance exercise, the increase in muscle protein synthesis exceeded that of the protein alone (resting leg), with the magnitude of the increase not statistically significantly different to that of the healthy age-matched controls.

A pilot four arm RCT assessed the effect of protein supplementation, resistance exercise or the combination of both vs control in men with advanced prostate cancer undergoing ADT (Dawson, Dorff et al. 2018). The study involved 32 prostate cancer patients over a 12-week period and the aim was to counter obesity associated sarcopenia and cardiometabolic markers in men on current or adjuvant ADT. Individual resistance exercise was undertaken with a personal trainer, three times per week lasting approximately 45 minutes and the supplementation was 50g a day of whey protein isolate. The study demonstrated that 12 weeks of resistance exercise training significantly countered ADT related LBM loss and fat gain. Approximately 44% of the

participants in this study were classified as sarcopenic at baseline (appendicular skeletal mass (kg)/height (m^2)) < 7.26 kg/m^2, no differences between the groups at baseline) with the prevalence increasing in the non-exercising groups vs a significant reduction in the exercising groups. However, a comparison between the groups receiving protein demonstrated the protein did not enhance the effects of resistance training.

4. Castrate resistant prostate cancer and exercise: A systematic review of the literature

4.1 Methods

A literature search was carried out to describe the current knowledge base for CRPC and exercise interventions. The search engines used were Web of Science, Medline via EBSCO, Scopus and SportsDiscus. The key search terms are given in table 2.3 and literature was filtered by human studies and English language. Papers were assessed at abstract and title and subsequently full text. Exclusions were made if the papers were reviews, not specific to men with CRPC or non-primary literature (ie, study or trials). Figure 2.1 summarises the search strategy.

Table 2.3 Search terms and the number of literature retrieved from the databases (Search date: 23/06/2018)

Search term number	Medline	Scopus	Web of Science	SportsDiscus
1	"castrat* resistant"			
	6152	8083	7845	22
2	"hormone refractory"			
	2753	3161	3189	13
3	"prostate cancer"			
	99828	156,345	174873	1244
4	prostat* N3 neoplasm*			
	114738	105841[1]	7354[2]	7
5	prostat* N3 carcinoma*			
	18037	26676[4]	19449[3]	23
6	physical* N3 activ*			
	106441	167844[6]	183872[5]	57495
7	"motor activity"			
	100656	109941	15200	1338
8	physical* N3 exercis*			
	21904	20734[8]	34422[7]	10069
9	"aerobic exercis*"			
	7972	15698	12486	9513
10	"resistance training"			
	10056	15090	8048	6856
11	lifestyle			
	81369	103508	87833	18087
12	walking			
	69954	141284	164202	21482
13	kinesi*			
	39389	53068	15561	29541
14	"strength training"			
	4356	6539	5521	9180
15	"exercise therap*"			
	35928	34231	3365	6197
16	1 OR 2			
	8763	10992	10891	34
17	3 OR 4 OR 5			
	224283	190486	188238	57521
18	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14			
	392525	605014	462995	140631
19	16 AND 17			
	6987	10890	10723	0
20	17 AND 18			
	107198	3280	2650	57497
21	19 AND 18			
	23	56	33	0

[1] "prostat* neoplasm*"; [2] prostat* NEAR neoplasm*; [3] prostat* NEAR carcinoma*; [4] "prostat* carcinoma*"; [5] physical* NEAR activ*; [6] "physical* activ*"; [7] physical* NEAR exercis*; [8] "physical* exercis*"

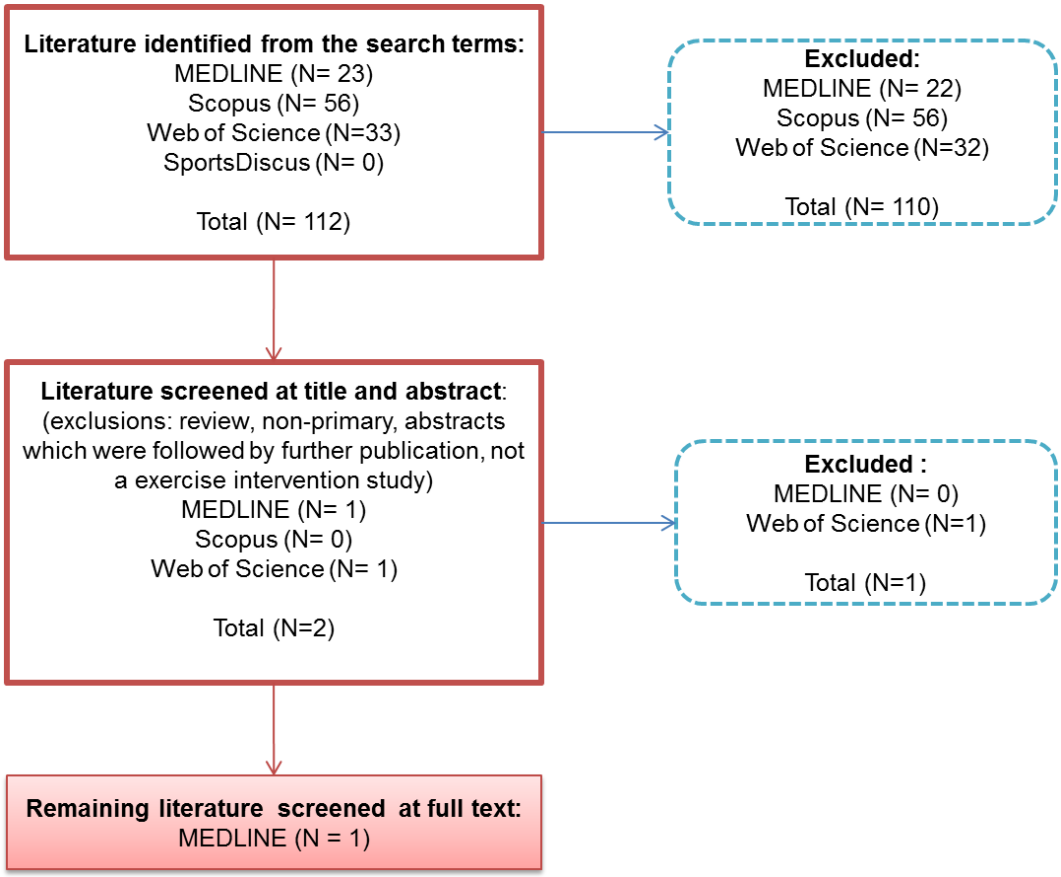

Figure 2.1 Summary of literature review search strategy

4.2 Results

Post exclusion, only two texts were available an abstract and a protocol, both for the ongoing INTERVAL-MCRPC (ClinicalTrials.gov Identifier: NCT02730338) (Newton, Hart et al. 2017, Newton, Kenfield et al. 2018). The phase III RCT will determine if supervised high-intensity aerobic and resistance exercise with psychosocial support increases OS compared with printed exercise recommendations (self-directed exercise) with psychosocial support in men with CRPC. The study aims to recruit 866 men with no prior chemotherapy or evidence of progression of their disease at enrollment. After written informed consent, confirmation of clinical eligibility and successful completion of screening assessments, men will be randomised on a 1:1 ratio to either the supervised exercise or self-directed exercise.

Secondary endpoints include time to disease progression, occurrence of a skeletal-related event or progression of pain, and degree of pain, opiate use, physical and emotional quality of life, and changes in metabolic biomarkers (Newton, Kenfield et al. 2018).

This study has extensive exclusion criteria, however such exclusions could lead to poor recruitment. Given that some clinicians may preferentially treat with docetaxel early whilst men have good PSs, such exclusion criteria including no previous docetaxel regimen for metastatic disease will likely limit the timeframe by which men can be eligible for recruitment. In addition, another exclusion is the presence of progressive disease whilst undergoing treatment with enzalutamide or abiraterone. These exclusion criteria will exclude a proportion of patients who otherwise may be very keen to take part in the study. Men must also have a good PS (ECOG ≤ 1). Given that these men have a long history of disease and treatment, many suffer with adverse effects which impact on PS. In addition, the proportion of men at such advanced stages of disease who have maintained a good PS is not clear, but it is likely to be much less compared to earlier stages of disease where the literature for exercise interventions for prostate cancer patients exists.

The need for a good PS in these men may be explained by the intensity of the supervised exercise programme proposed. The period of the study intervention period is 2 years (24 cycles with each cycle spanning 28 days). Given that upon the diagnosis of CRPC life expectancy in the UK is around 13.5 months, to ensure the participants have the best chance of completing the intervention it would be necessary to choose those with the best PS at baseline. However, a long period of intervention and the reported 3 year follow up, would give a great deal of data on survival and disease progression for those recruited. The applicability of these findings on the CRPC population however may be brought into question as those with the best PSs are recruited and therefore reflect only a select population.

The programme consists of structured resistance exercise and combinations of high-intensity interval training and moderate-intensity continuous training aerobic exercise. Although, the programme is stated to be "individualised, periodised, progressive and autoregulated" there may be issues with adherence with exercise of high-intensity, particularly with consideration to adverse effects such as fatigue. However, once more such criteria risk the exclusion of a large proportion of CRPC and therefore may bring into question the applicability of the findings of this study.

The study offers a gradual tapered transition to self-management, with the subsequent 48 weeks of the programme (year 2) self-managed with one exercise visit required.

Such an approach could be a successful way to empower these men to a "self-care" approach to managing the symptoms of their cancer. In addition, the trial includes behavioral and psychological support which could improve adherence and long-term behavior change.

Finally, the study also encompasses both patient and public involvement. Such data will provide a unique viewpoint and experience of participants to ensure that the study protocol engages participants and addresses the needs of men with CRPC. In addition, the study also includes urologists and medical oncologists as part of the research team who work with men with CRPC on a daily basis. The inclusion of these clinicians will help inform the study of patient priorities, experience and preferences to help inform the development of the research questions and outcome measures.

4.3 Castrate resistant prostate cancer and exercise: Unmet supportive care needs

The significant lack of data suggests that there is an unmet clinical need for supportive interventions of exercise in men with CRPC. It is likely that due to the advanced stage at which these men present they have been negated in their inclusion to the plethora of exercise intervention studies that exist for men with prostate cancer. However, the advanced stage at which these men present mean they indeed stand to gain a great deal from such interventions. The associated benefits of exercise to LBM, BMD, QoL, fatigue and physical function to name a few are the heavily burdened by this population of men. Their long-term ongoing cancer therapies involving ADT and chemotherapy mean a potential specific benefit to treatment based outcomes, such as increased chemotherapy completion rate and reduced dose-limiting toxicity. Due to the nature of complex lifestyle intervention studies, such complex men with multiple comorbidities are likely to be seen as less desirable when looking for evidence of efficacy. Therefore, there is a significant gap in the research for such beneficial supportive programmes in men with CRPC.

Although the ongoing INTERVAL-MCRPC is a supervised exercise intervention for men with CRPC with an aim to improve survival, it replicates the limitations of previous cancer and exercise studies in some aspects (Newton, Hart et al. 2017, Newton, Kenfield et al. 2018). The study negates the inclusion of men with a poorer performance status, those with progressing disease on second line ADT as well as

those who have received a previous docetaxel regimen for metastatic CRPC. Such exclusions will likely mean that a very large proportion of men with CRPC will not be eligible for the study and therefore, those who although may have complex needs and potentially stand to gain a great deal from supportive interventions are neglected.

5. Thesis overview

The current prostate cancer treatment pathway is evolving and therefore so is the care of these men; the effects of new therapies, changes to treatment sequencing and access to treatments are unclear. Subsequently, with such uncertainties, it is not known how exercise may be feasible in the current treatment pathway. Despite the existing NICE recommendations for exercise training for men undergoing or initiating ADT, there is a significant lack of data as to show how exercise has been implemented and what a successfully implemented exercise programme may look like. It is also clear that given the severe and detrimental effects of long-term ADT, there is a clinical need for such interventions. Such lifestyle interventions have the potential to improve both physical and psychological wellbeing in men with CRPC; reducing the burden of treatment and disease. Furthermore, the specific barriers these men may face engaging in exercise given their advanced stage of disease, both treatment and disease related, is not documented. No studies exist which have evaluated an RCT of a lifestyle intervention of resistance exercise alone or in combination with a dietary/nutritional intervention for men with CRPC. Despite the theoretical rationale for such a study, this group of men have remained neglected in research studies of lifestyle interventions for prostate cancer.

A lifestyle intervention of resistance exercise, whey protein and creatine supplementation in men with CRPC has the potential not only to confer some of prostate specific benefits (such as QoL, fatigue, sexual function, muscle strength and endurance demonstrated in previous studies) but also offer a supportive therapy where currently nothing is offered. In addition, LBM loss associated with long-term ADT and advanced cancer could be mitigated or potentially reversed with such an intervention. A lifestyle intervention to alleviate some of the symptoms of hypogonadism and advanced cancer could significantly improve outcomes in these men and therefore QoL but at present, no such intervention has been conducted.

For the reasons described, the following body of work in this thesis is presented. This includes a national survey and interviews of healthcare professionals involved in prostate cancer care (chapter 3); a feasibility RCT of a lifestyle intervention involving exercise, whey protein and creatine supplementations for men with CRPC (chapter 4) and finally post-study focus groups of the RCT participants (chapter 5). This body of work is proposed to address the following research question.

Research question: Can a lifestyle intervention of resistance exercise, dietary supplementation and dietary guidance improve outcomes in men with CRPC?

5.1 Objectives

- Describe exercise in the usual care pathway for men in the UK with prostate cancer who have undergone ADT; including if, how and in which trusts exercise is part of "usual care".

- Explore the perspectives of health care professionals (HCP) on the use of exercise training for the management of CRPC.

- Determine the feasibility and participant acceptability of a 16-week programme of resistance exercise training, dietary supplementation and dietary guidance as a novel supportive therapy in men with CRPC.

5.2 Choice of methods

5.2.1 A multi-method approach

The importance of drawing on multiple sources of evidence to provide public health guidance, using a spectrum of sources and methodologies is widely recognised in healthcare research (Pawson 2006). Although, RCTs are considered the optimal study design giving an accurate estimate of the effect of an intervention (Craig, Dieppe et al. 2008); both NICE and The Medical Research Council (MRC) recognise the need for qualitative methods to support and inform guidance for complex health interventions and development of public health guidance (NICE 2012, Craig, Dieppe et al. 2013). In public health, it is no longer enough to identify the efficacy of a prescribed intervention with only quantitative methods, the complexity of healthcare pathways and causal chains in public health means that often RCTs must be enhanced by qualitative studies to further understand the context, mechanisms underpinning their external validity. Multiple methodological designs provide robust evidence which enable the

implementation of such interventions successfully in real-life situations (Webber 2014). Furthermore, it may not be possible or ethical to undertake an RCT alone to test theory in complex interventions inclusive of multiple social interactions (Hawkins 2016) or where interventions are too large to implement or where it is impossible to manipulate exposure to the intervention.

In public health, there is more than just the need for recommendations on what may be effective and/or cost effective. Social scientific, epidemiological and clinical evidence is needed to examine the context, process and implementation of an intervention and how this may affect outcomes. Essentially this multi-focus approach enables researchers to address when, why, how and for whom an approach does work (Pawson 2006). For example, the method of using interviews to obtain practitioners' views, experiences and working methods (including any barriers and facilitators to supporting implementation of the intervention) was fundamental to the development and design of the feasibility study of a complex lifestyle intervention (NICE 2012). Therefore, a multi-method approach to collecting evidence should be utilised and findings synthesised to comprehensively answer the research aims of complex interventions.

5.3 Philosophical approaches

This research in this thesis is based on the pragmatic paradigm using abductive processes that combine both qualitative and quantitative methods driven by the research questions (Neuman 2013). The range of methodological approaches routed in different philosophical positions overcomes the limitations of using a single methodological approach. Methods such as the RCT are routed in more positivist philosophical underpinnings, where positivist social science is deemed:

"an organised method for combining deductive logic with precise empirical observations of individual behaviour in order to discover and confirm a set of probabilistic causal laws that can be used to predict general patterns of human activity" - (Neuman 2013) *Chapter 4 page 95*.

However, realism assumes the existence of an empirical world outside of our inner thoughts and perceptions of it, which refers to underlying processes and mechanisms, and therefore the "real world" exists regardless of whether or not it is observed (Bonell, Fletcher et al. 2012, Neuman 2013). Qualitative methods are tools which can provide

emphasis and value on the human experience of the social world and the significance of both the participant and investigator interpretations. A realist approach can utilise these methods to explore the mechanism of change, the aspects of the intervention components and how pathway variables mediate intervention effects (Bonell, Fletcher et al. 2012).

5.4 Summary

Despite the evidence for the benefits of exercise and dietary interventions in men with prostate cancer or those with advanced cancer of any type, to the authors knowledge there have been no studies which have explored the effects of such interventions to improve outcomes in men with CRPC. Particularly as these men are afflicted with the AEs of long-term castration, they have the potential to gain specific health benefits from a supportive lifestyle intervention, such as improvements in LBM, physical fitness and physical performance. The following body of work was conducted to investigate if supportive resistance exercise training, dietary supplementation and dietary guidance intervention would be feasible for men with CRPC using the research methods described.

Chapter 3 Exercise training provision for prostate cancer patients - a survey and interviews of healthcare professionals in the UK

1. Introduction

NICE published a set of guidelines (CG175, 1.4.19) around diagnosis and treatment of prostate cancer stating specifically to *"Offer men who are starting or having androgen deprivation therapy (ADT) supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue and improve quality of life"* (NICE 2014). There is very little known about the current provision of exercise services in the NHS and how (if at all) exercise programmes or referral schemes have been provided. This includes information on whether current provision for exercise support is integrated as part of current prostate cancer care, who it is delivered by and how men are referred to supportive exercise services.

National campaigns aimed to improve physical activity and exercise behaviour in cancer patients run by cancer charities such as Macmillan's "Move More" and "Active Everyday" working alongside local authorities and in some cases community based local referral programmes have been implemented (Macmillan 2018). Although it is not clear exactly what is available for these patients and what these referral programmes are offering. Both Macmillan and Prostate Cancer UK (PCUK) have recommendations on physical activity for all cancer and prostate cancer patients respectively (Prostate Cancer UK 2015, Macmillan Cancer Support 2018). However, whilst both organisations recognise the importance of an active lifestyle, neither offered specific guidelines on the type, frequency, volume or intensity of activity. Furthermore, this results in a lack of clarity as to whether the aim of such programmes are to improve physical activity or to promote exercise training which is goal orientated and possibly disease specific. Cancer patients are an extremely heterogeneous population and therefore a safe and effective programme for one individual can look very different for another. For some, a community based programme may not be appropriate and therefore maintenance or increased activity or encouraging those to engage in an exercise training programme remains a challenge.

In addition, guidelines set out by The American College of Sports Medicine (ACSM) recommend that cancer survivors should be supervised with a certified exercise professional when undertaking a new exercise programme (Wolin, Schwartz et al. 2012). Yet the ASCM recognised that circumstances such as finance and location could pose significant barriers. Where this is the case the key take home message from the ACSM was "avoid inactivity", a far cry from what the recommendations are

actually advocating i.e. 150 minutes of aerobic activity with at least 2 sessions of resistance exercise a week (Wolin, Schwartz et al. 2012), guidelines similar to those set out by NICE.

The variability on available information, established programmes and advice for exercise in prostate cancer patients risks a significant lack of consistency of exercise advice present between clinicians and patients. In the UK, The National Cancer Survivorship Initiative (NCSI) recognised in 2011 that health and social care professionals are likely to need support to help cancer survivors to make lifestyle changes which will optimise their health and wellbeing (National Cancer Survivourship Initiative 2013). It has been demonstrated that endorsement by HCPs to participate in physical activity is key to improving physical activity behaviours in patients (Craike, Livingston et al. 2011) and that a clinician referral into an exercise programme significantly improves exercise levels (Damush, Perkins et al. 2006, Livingston, Craike et al. 2015). However, despite evidence to suggest that there are benefits associated with structured exercise for men with prostate cancer, such supportive exercise programmes nor lifestyle advice is routinely discussed at follow-up appointments (Bourke, Sohanpal et al. 2012). The study by Bourke et al showed that none of the men with advanced prostate cancer who took part in an exercise trial had been offered information on lifestyle changes during their standard care.

While a lack of available exercise referral schemes may be a barrier, for some HCPs there might also be concerns regarding safety to exercise, inhibiting the discussion of physical activity and exercise training with cancer patients. A survey of 102 oncologists and surgeons found that 55.9% did not discuss physical activity with their patients routinely (Daley, Bowden et al. 2008). However, the survey also demonstrated a strong association between the physical activity status of the clinician and the likelihood of such discussions taking place with their patients, where those who participated in more physical activity themselves were more likely to discuss (Daley, Bowden et al. 2008). Furthermore, those HCPs with more experience of dealing with potential contraindications (such as fatigue, anaemia or risk of infection) have higher levels of physical activity recommendations in patients undergoing cancer treatment (Tsiouris, Ungar et al. 2018).

For survivors who require supervision or who may need guidance on how to exercise safely, referral to an exercise programme under the supervision of an exercise specialist may help. There is evidence to suggest that a clinician referral and 12-week exercise programme significantly improved vigorous exercise levels and had a positive impact on mental health outcomes for men living with prostate cancer (Livingston, Craike et al. 2015).

The implementation of physical activity guidelines in the UK poses a challenge given the ever evolving pathway as described in chapter 1. A better understanding of the clinical pathways patients follow provides timely and accurate information as to how an exercise programme may be successfully implemented into the care pathway with the support of key stakeholders, such as clinicians, allied HCPs, CCGs and local authorities. Without the adequate support of key stakeholders for exercise programmes it is unlikely that exercise support services can be successfully implemented within the care pathway.

In order to better understand the context for implementing exercise programme as part of the prostate cancer care pathway, it is important to establish what is currently being offered across the UK, defining what exercise support as part of "usual care" looks like. For this reason, a survey of UK HCPs involved in prostate cancer care was conducted. Interviews were undertaken with clinicians to establish their views on embedding a supervised, individually tailored exercise intervention in the prostate cancer care pathway for men with CRPC. It was important to understand the perspective of clinicians regarding roles, responsibilities and training needs associated with providing supervised exercise programmes for men with CRPC to inform the design and conduct of the feasibility study (COMRADE) (Chapter 4).

Aims:

1) To describe what exercise referral is currently available for men on ADT as provided by the NHS and if a supervised, individually-tailored exercise training package (as per the national NICE guidelines CG175, 1.4.19) is available in usual care for prostate cancer.

2) To explore the opinions of clinicians involved in prostate cancer care regarding the management of men with CRPC with particular emphasis on treatment timing and sequencing since the earlier introduction of chemohormonal therapy and treatment adverse-effects.

3) To explore opinions of clinicians regarding the clinical significance of LBM loss in men with advanced prostate cancer.

4) To explore opinions of clinicians regard to exercise without the use of an anabolic agent as a supportive therapy; to inform the design of a future RCT.

2. Methods: Healthcare professional survey

Clinicians were surveyed regarding the optimum sequencing of therapies and standard care for men with advanced prostate cancer in the care pathway; this also included any established supportive programmes for men with CRPC. In addition, questions regarding LBM loss or "muscle wastage" were asked with the objective to determine how clinically significant muscle wastage was considered, how it might be diagnosed or treated and how clinicians may distinguish muscle wastage from differing aetiologies (e.g. age related sarcopenia and cancer cachexia). Finally, the views and opinions of the exercise as a supportive therapy for men with prostate cancer were sought. This included exploring opinions on the combination of a structured exercise programme with or without anabolic pharmacological agents in with the aim to improve skeletal muscle mass.

2. Methodology

Survey methods are commonly used in health research to evaluate healthcare services. Unlike other qualitative methods such as focus groups and interviews, the predominant benefit of using quantitative survey methods are the number of respondents which can be reached. They are useful to obtain information for a

predetermined group of people and location. Although a relatively small amount of data can be obtained from the population, the geographical spread of data can be used to draw inferences on the wider population to an extent, providing information on a service "*…in a snapshot of time*" (Kelley, Clark et al. 2003). Other methods are often questioned on their representativeness of only nominal group views. Surveys are able to overcome these limitations and obtain such data from HCPs in a short period of time compared to other epidemiological study designs such as observational studies. As a key aim of this study was to determine the provision of exercise referral schemes across the UK in the NHS, it was important to obtain national representation and develop a consensus as to the definition of "usual care" for prostate cancer. In addition, the success of an established exercise referral scheme may be contingent on involving a number of different HCP's therefore it was considered important to have representation from all stakeholders involved in the clinical care of men with prostate cancer. This included primary and secondary care.

The design of the survey and identification of survey respondents was undertaken by the researchers of the STAMINA1 programme (not the author). An independent, health services research consultancy service (Clinvivo) were contracted by the STAMINA programme development grant lead researchers to distribute the questionnaire (http://www.clinvivo.com/). Clinivivo collated the respondent survey responses into a data report, including the data analysis (appendix 1). The interpretation of the data from the questionnaire survey responses was conducted by the author (RG).

2.1 Survey methods

HCPs were identified and invited via professional bodies to take part in a 27-item electronic survey. The survey explored issues around delivering prostate cancer care in NHS practice and specifically to define if exercise referral schemes were available to men with prostate cancer.

2.1.1 Research governance

2.1.1.1 Ethics and research and development approval

This study gained a favourable ethical opinion by NRES Committee South West - Cornwall & Plymouth (15/SW/0260) and in accordance with the Governance Arrangements for Research Ethics Committees and complied fully with the Standard Operating Procedures for Research Ethics Committees in the UK (appendix 2). All

Management permissions were sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

2.1.2 Respondent recruitment

Survey respondents were identified via their professional bodies; British Association of Urological Nurses (BAUN), British Association of Urological Surgeons (BAUS), British Uro-Oncology Group (BUG), Primary Care Urology Society (PCUS); and invited by email or Twitter to participate. The respondents completed the survey through the online tool Clinvivo.

2.1.2.1 Inclusion criteria

Primary and secondary HCPs (e.g. general practitioners (GPs), urologists, oncologists, cancer nurse specialists (CNSs) who are actively involved in prostate cancer treatment

OR Other specialist allied HCPs (i.e. physiotherapists, clinical exercise physiologists).

UK based

2.1.2.2 Exclusion criteria

HCPs not involved in primary or secondary care and not involved in prostate cancer treatment.

OR Not a specialist HCP

Not UK based

2.1.3 Survey items

Full details of the 27 survey items are given in appendix 1.

2.1.3.1 Respondent demographics/characteristics

Questions one to two sought respondent's personal details, such as postcodes and job role.

2.1.3.2 Prostate cancer care pathway

Questions three to seven concern the prostate cancer care pathway. This included questions regarding the delivery and initiation of ADT alongside chemotherapy since the initiation of chemohormonal therapy for hormone sensitive disease.

2.1.3.3 NICE guidelines

Question eight asked respondents if they were aware of the NICE guidelines on prostate cancer (CG175).

Fourteen items explored the respondent's knowledge of exercise programmes/referral schemes, physical activity in their locality and awareness of the current NICE recommendation regarding delivery of supervised exercise to men initiating or undergoing ADT (CG175, 1.4.19) (questions nine to 24 excluding question 20; appendix 1). Question ten asked respondents to subjectively score, their perceived ability to deliver the NICE recommendation on exercise for men on ADT.

Question 20 requested the locality of the training schemes available for staff regarding exercise support for cancer populations if not provided by their own organisation.

Question 25 asked the respondents if they felt charities had the capability to deliver the NICE recommendation 1.4.19 without the support of NHS resources.

2.1.3.4 Further contact for research purposes

Questions 26 and 27 enquired if respondents would be prepared to participate in future interviews and to provide their contact information. Those who consented to have further contact were used as a convenience sample for the proceeding HCP interviews.

2.1.3.5 Item design

Eleven of the questions were designed with "yes", "no" and "unsure" responses. Other items were multiple choice with the option to elaborate i.e. "other (please specify)". These questions related predominantly to HCP and allied HCP roles and regarding the format of exercise programmes (e.g. community/ hospital based programmes). Question ten asked the respondent to rate on a ten point score, scoring one indicating "extremely unlikely" and ten indicating "highly likely". Question five and three asked to provide a response via a slider which ranged from 0-100%.

2.1.4 Procedure

2.1.4.1 Sampling and recruitment

Clinvivo provided details of sampling and respondent recruitment in a written report (appendix 1). To summarise, Clinvivo sent an invitation email to potential respondents, including professional organisations for circulation to their members, and one link to be shared by the investigators to their Twitter followers. Three hundred and ninety-two email invitations were sent on 26th November 2015 and email invitations for members of four professional organisations were sent to their contacts on 1st December 2015. A public Twitter link was shared by the investigators on 11th December 2015. The first

reminder email to invitees were sent on 10th December 2015 and the final reminders on 22nd December 2015.

2.1.4.2 Data Analysis

The results of the survey were summarised using descriptive statistics as provided by Clinvivo, appendix 1 The Clinvivo report. The data was interpreted by the author (RG).

3. Methods: Healthcare professional interviews

There was specific interest in exploring the views of clinicians on embedding a supervised, individually tailored exercise intervention in the prostate cancer care pathway and to determine the feasibility of a full scale trial. It was important to explore the possibility if such programmes for men with castrate resistant disease would be acceptable to HCPs, with or without the use of an anabolic agent to increase or maintain LBM. There was also an exploration of emergent issues resulting from recent changes of the prostate cancer care pathway due to changes in treatment sequencing. One to one in-depth interviews were chosen as the most appropriate research method to explore motivations in decision making, processes, impacts and outcomes with a personal focus on the individual (Pope, Ziebland et al. 2007). Interviews are a more flexible research method where emergent themes can be explored as compared to the structure of a survey whereby the depth of data collated is usually limited (Pope, Ziebland et al. 2007).

3.1 Research governance

3.1.1 Ethics and research and development approval

This study was approved by NRES Committee South West - Cornwall & Plymouth (15/SW/0260) and in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK (appendix 2). All management permissions were sought from the relevant NHS organisations involved in the study in accordance with NHS research governance arrangements.

3.1.2 Informed consent

Full informed consent was obtained from each participant before the commencement of interviews (appendix 3).

3.1.3 Confidentiality

Interview transcripts were anonymised by allocating a participant number (e.g. RGUR0001/ RGONC0001, UR and ONC indicating a urologist and oncologist respectively) to protect the identity of all participants. All data was kept in a password protected drive or encrypted on a password protected USB. No identifiable information was released into the public domain or published. If a participant withdrew consent, their data would have been confidentially destroyed but no participants withdrew in this study.

3.2 Sample and setting

3.2.1 Sampling

A convenience sample was obtained from the survey of HCPs described in section 1. This was used to identify clinicians (urologists, medical oncologists and clinical oncologists) responsible for prostate cancer management and follow-up whom were practicing in the NHS in the UK.

3.2.2 Inclusion criteria

- Urologist, medical oncologist or clinical oncologist responsible for the management and follow-up of prostate cancer.
- Permanently based in an England NHS trust.

3.2.3 Exclusion criteria

- Clinicians not regularly involved in the care, management or follow-up of prostate cancer patients.
- Non-permanently based in England or in the NHS.
- Unable to give or failure to provide full informed consent.
- Previously interviewed as part of the STAMINA[1] programme development grant.

3.3 Recruitment and data collection

3.3.1 Recruitment

The clinicians were identified through data obtained from the survey where they had expressed a willingness for further contact in question 26 and question 27 (appendix 1). The clinicians were initially contacted via email and if expressed an interest were

[1] Sustained exercise TrAining for Men wIth prostate caNcer on Androgen deprivation: the STAMINA programme development grant was a multi-centre investigation of current NHS care involving a web-based survey of NHS prostate cancer care, five focus groups involving 26 men on ADT and 37 semi-structured interviews with clinicians involved in the management of prostate cancer.

subsequently sent an invitation letter, participant information sheet and consent form via post (see appendix 3, 4 and 5). Once consent was returned, dates for interview were confirmed via email or a telephone call at a time convenient for both the clinician and researcher.

3.3.2 Data collection

Interviews were conducted either face to face or by telephone. The preferred method was face to face, however this was limited by geographical location and convenience. Interviews were conducted by one researcher (the author) guided by the interview schedule. As new insights were offered these topics were explored. The interviews were digitally recorded (encrypted Olympus DM-650 Digital Voice Recorder), and then anonymised.

3.4 Interview schedule

The interview schedule was designed based on the relevant literature and theory as well as recent changes in treatment paradigms to prostate cancer care. The schedule was semi-structured with open ended questions and prompts to allow interviewees to express their views and opinions. The interview schedule consisted of 20 questions which covered the STAMPEDE and CHAARTED trial data; the clinician's role and current pathway for men with CRPC, muscle loss and cachexia in CRPC, prostate cancer and exercise interventions and finally novel pharmacological agents in combination with exercise. The interview schedule was designed to be inductive with some deductive reasoning. The detailed interview schedule can be reviewed as appendix 6.

3.5 Data analysis

Digital recordings were transcribed verbatim by an independent transcription service (JHTS audio and transcription service, www.jhts.co.uk) and the data coded via Nvivo10 (Version 1.0, by the author). Familiarisation with the transcripts was first performed and then initial codes were generated (appendix 7). Initial codes were then related to final themes and sub-themes and analysed according to a thematic framework analysis (Gale, Heath et al. 2013). Four transcripts (>20%) were double coded by a second researcher Rebecca Turner (RT) to ensure reliability and rigour of the analysis. Any differences in coding were discussed and a consensus was reached on how the data should be coded. This included either changing the name and context of the code or choosing one of the reviewer's original codes after a consensus was

reached from both researchers. This generated a total of 79 codes in 11 categories. These categories were formed of the superordinate themes and subordinate themes. The data were then charted into the framework matrix of superordinate themes mapped against verbatim quotes from each interviewee grouped via their profession (i.e. Urologist, Medical Oncologist or Clinical Oncologist). An example of an extract from the table is given in appendix 9. The analytical framework was then refined and codes grouped together where they were conceptually related. The framework was then verified by a third party researcher Karen Collins (KC).

3.5.1 Qualitative data analysis options

As the approach to the analysis of the data was deductive, framework analysis was seen as the most appropriate form of analysis because the objectives of the interviews were set in advance rather than emerging from a reflexive research process (Mays and Pope 2000). The overall analytical process however, resonates with the thematic approach, but with the framework approach it is more explicit and informed by *a priori* reasoning (Mays and Pope 2000).

3.5.2 The framework approach

Framework analysis is a systematic analytical approach to qualitative research. It is a matrix based method for ordering and synthesizing qualitative data and was developed by Jane Ritchie and Liz Spencer in the 1980s for large scale policy research (Ritchie and Spencer 2002) but is now widely used in health research (Gale, Heath et al. 2013). In the context of these interviews framework analysis was chosen as it is a pragmatic approach to systematically facilitate rigorous and transparent data management without losing sight of the "raw data" and enabled the classification of the data into key themes and sub themes, judged comprehensively.

3.5.3 The method of the framework approach

The analysis was carried out in a 6 step approach including 1) familiarising with the data; 2) generating initial codes; 3) searching for themes; 4) reviewing themes; 5) devising and naming themes and 6) producing the report (Braun and Clarke 2006).

3.5.3.1 Familiarisation

Before any attempt to sort through the data was made, there was a process of data familiarisation. Transcripts and observational field notes were read and re-read and

recordings were listened to in order to fully immerse oneself with the data in advance of any kind of analytical stage.

3.5.3.2 Generating initial codes and identifying a thematic framework

After initial familiarisation, a process of "open coding" was conducted. This included analysis of a small number of selected transcripts and the coding of data which was felt to have relevance to the research aims and objectives (such as opinions, attitudes, behaviours or views). Each of these initial codes was accompanied with a note to clarify its meaning.

3.5.3.3 Indexing/coding

Coding aims to classify all the data and enable a systematic comparison between the different data sets. Codes are grouped together in categories which are clearly defined to generate themes and subthemes (Gale, Heath et al. 2013). Indexing was conducted electronically using the programme Nvivo which is demonstrated in appendix 8. Indexing indicated which themes in the text were being discussed. Once data had been coded a thematic framework was developed consisting of themes and subthemes. Initial themes were more descriptive rather than analytical or abstract.

3.5.3.4 Charting

Once the main themes and subthemes had been identified, reviewed and finalised, a matrix was created to help delineate the data set. Each column of the matrix was headed with each theme and each row with each participant identifier demonstrated in appendix 9. The relevant sections from each coded transcript were then summarised and entered into the framework matrix so the text can easily be navigated and comparisons can be made between individuals. For each participant summary, selected information was taken from each participant's transcript in order to reflect meaning without losing content. The transcription conventions were:

- *Italics* - Direct quote
- … - Quote has been abridged
- [word] - Where the author has clarified the meaning or phrase from the quotation

3.5.3.5 Mapping and interpretation

Once charting was complete a more refined analysis of the data set was possible with a deeper immersion into the content of the transcripts. Summaries of each theme were

made from identifying relationships between the quotes and links between the data as a whole, providing explanations for the findings and overarching themes (Ritchie and Spencer 2002). This included drawing comparisons between the transcripts highlighting any conflict/consistencies in key terms/ phrases/ descriptions/ views or explanations. Explanations and conclusions were drawn from the analysis, this can be explicit (originating from the participants descriptive statements) or implicit (identified by the analyst). After the final analysis the data were categorised into a priori themes or new themes were constructed as appropriate (Ritchie and Spencer 2002).

3.5.4 Ensuring quality within qualitative research

Quality in qualitative research is multifaceted and includes consideration of the importance of the research question, the rigor of the research methods, the appropriateness and salience of the inferences, and the clarity and completeness of reporting (Smith and McGannon 2018). Although there is much debate about standards for methodological rigor in qualitative research there is widespread agreement about the need for clear and complete reporting. High quality research which is conducted and assessed systematically would enable researchers to synthesise the data, critically appraise the data with greater ease due to transparency and therefore subsequently ensure reproducibility.

To ensure quality, this qualitative research was conducted following the guidelines for standards for reporting, process and methods from the Consolidated criteria for reporting qualitative research (COREQ) criteria (Tong, Sainsbury et al. 2007). The checklist was used to ensure explicit and comprehensive reporting of the final analysis (appendix 10). The NICE public health development guidance and MRC guidance on the development and evaluation of complex health interventions were used to aid the design of the clinician interviews (NICE 2012, Craig, Dieppe et al. 2013). The quality of qualitative research is judged fundamentally differently to that of quantitative methods which predominantly look for internal validity, external validity, reliability and objectivity. This study sought to ensure rigour by the four criteria outlined by Shenton i.e. credibility, transferability, dependability and confirmability (Shenton 2004).

4. Survey results

4.1 Survey respondent characteristics

From the survey, there were 95 postcodes from respondents corresponding to sites across the UK (e.g. hospitals, community centres, local gyms). In total 79 different NHS trusts corresponded to the sites identified, with some sites corresponding to the same trust (appendix 11). The proportions of the mode of invitation of the 95 respondents are described in table 3.1.

Table 3.1 Mode of invitation received by respondents to the survey

Referrer	n	%
British Association of Urological Nurses	13	13.7
British Association of Urological Surgeons	24	25.3
British Uro-Oncology Group	4	4.2
E-mail	42	44.2
Primary Care Urology Society	4	4.2
Twitter (STAMINA twitter account)	8	8.4
Total	95	100

The majority of the respondents were urologists n =35 (36.8%) and second largest proportion were nurses n =20 (21.1%). Respondents professional roles are provided in Table 3.2.

Table 3.2 Professional roles of respondents

Profession	n	%
Allied Health Care Professional	3	3.2
Cancer Care Commissioner	3	3.2
Exercise Physiologist	3	3.2
General Care Commissioner	1	1.1
General Practitioner	7	7.4
Nurse	20	21.1
Oncologist	4	4.2
Physiotherapist	3	3.2
Urologist	35	36.8
Other	16	16.8
Total	95	100

4.2 The prostate cancer care pathway and delivery of care

4.2.1 Proportion of men receiving chemohormonal therapy

In light of STAMPEDE and CHAARTED, respondents indicated that on average 23.3% of men currently commencing long-term ADT were also receiving docetaxel or a similar agent at initiation of ADT. The reasons for not giving chemohormonal therapy is provided in table 3.3.

Table 3.3 Reasons for not giving chemohormonal therapy

Reason	n	%
No funding	17	43.6
Unconvincing evidence	3	7.7
Updating guidelines	8	20.5
Clinician resistance	5	12.8
Patient resistance	5	12.8
Patient unfit	19	48.7
Other	10	25.6
Number of responses (multiple selection allowed)	39	

4.2.2 ADT delivery

Respondents were asked to indicate the proportion of men on long-term ADT receiving treatment in primary care in their area. A total of 64 respondents reported a mean percentage of 84.5%, ranging from zero to 100%. The HCPs involved in delivering ADT are described in table 3.4.

Table 3.4 HCPs involved in initiating ADT.

Profession	n	%
Oncologist	51	77.2
Urologist	62	93.9
Clinical Nurse Specialist	42	63.6
General Practitioner	13	19.7
Outpatient Nurse	0	0.0
Practice nurse	3	4.5
District Nurse	0	0.0
Other	0	0.0
Number of responses (multiple selection allowed)	66	

4.3 The ability to deliver the NICE guidelines (CG175, section 1.4.19)

Of the respondents, n =70 (73.6%) had knowledge of the new NICE guidelines for prostate cancer (CG175). Slightly fewer (61.1%, n =58) were aware of the 1.4.19 recommendations. The respondents were asked to rate on a scale of 10 (1 being extremely unlikely and 10 highly likely) their ability to deliver this recommendation in their locality (the self-rated score), the mean response was 4.87.

N =47 (49.5%) of respondents indicated the existence of local exercise referral/prescription programmes for patients with cancer. Among these respondents, n =38 (80.6%) reported that there were programmes accessible to men with prostate

cancer on ADT with most of the exercise referral schemes being available in the community (n =25, 53.2%), local authority (n =16, 34.0%) and hospital (n =10, 21.3%).

4.3.1 Specialist involvement in exercise programmes

Nurses (n =28, 59.6%), GPs (n =20, 42.6%), physiotherapists (n =18, 38.3%) and hospital consultants (n =16, 34.0%) were the HCPS most commonly reported to be involved in the exercise referral pathways. Other non-clinical specialists involved, included gym instructors (n =21, 44.7%) and personal trainers (n =12, 25.5%). It was the non-clinical professionals, primarily gym instructors, who were reported to be responsible for setting the frequency, intensity and duration of the exercise programme (n =31, 66.0%), and for supervising the delivery of exercise and tailoring and monitoring individuals' programmes (n =32, 68.1%).

Over half of the 47 respondents (n =25, 53.2%) who knew about exercise referral programmes were not aware or were unsure of the existence of training schemes in their organisations for staff on exercise interventions for cancer populations.

4.3.2 Existing programme details

A third of these respondents who knew of an exercise referral programme (n =11, 32%) reported that instead these facilities were based in the community or local authority, n =7 (20.6%) reported that they were available in primary care, secondary care or charities, while most (n =15, 44.1%) reported that these facilities were based in other places. A majority of exercise programmes were offered in group sessions (n =28, 59.6%).

Approximately half of respondents (n =48, 50.3%) did not believe that charity services for lifestyle support without NHS resources would fulfil the NICE guidelines on exercise for men with prostate cancer.

4.3.3 Future contact for an interview

Approximately half of the respondents agreed to take part in a future interview (50.3%, n =48).

5. Healthcare professional interview results

Of the 35 clinicians initially contacted, nineteen expressed an interest being interviewed and of these, 12 were interviewed (63% of sample approached). The demographics of the clinicians interviewed are detailed in table 3.5.

Table 3.5 HCP demographics

	City (UK)	Profession	Sex	NHS Trust
Clinician demographics	**London = 5**	**Medical oncologist = 3**	**Male = 5**	**Teaching hospitals = 11**
	Newcastle = 2	**Clinical oncologist = 6**		
	Sheffield = 3		**Female = 7**	**Non-teaching hospitals = 1**
	Leeds = 1	**Urologist = 3**		
	Kent = 1			

The size of interview samples typically relies on the concept of “saturation” – the point at which no new information or themes are observed in the data (Guest, Bunce et al. 2006). In this case, saturation occurred at 12 interviews.

Four primary themes were identified from the data (table 3.6). Due to the richness of the data "Variability in the cancer care pathway" was discussed as two primary themes "The prostate cancer care pathway" and "Uncertainty with treatment sequencing in CRPC". Verbatim quotes are provided in order to illustrate the findings.

Table 3.6 Primary and secondary themes

	Primary themes	Secondary themes
	Theme 1: Attitudes towards the implementation of an exercise intervention with or without a pharmacological agent for men with CRPC	Assessment of physical fitness for treatment
		Anabolic agents in combination with an exercise intervention
		Exercise and prostate cancer
Variability in the cancer care pathway for men with prostate cancer	**Theme 2: The prostate cancer care pathway**	Cancer care pathway
		Current supportive or palliative programmes
	Theme 3: Uncertainty with treatment sequencing in CRPC	Changes to standard care
		Sequencing of therapies
	Theme 4: Clinicians reporting and management of the adverse effects of standard treatments and advancing disease	CRPC: adverse effects of disease, treatment and impact on QoL
		Treatment decisions
	Theme 5: Clinicians experience of managing muscle wasting comorbidity in men with prostate cancer	Muscle wastage, aetiology, assessment and treatment
		Cancer cachexia
		The clinical significance of muscle wastage

5.1 Theme 1: Attitudes towards the implementation of an exercise intervention with or without an anabolic agent for men with castrate resistant prostate cancer

5.1.1 Assessment of physical fitness for treatment

When asked how physical fitness would be assessed, all clinicians described a subjective assessment. This usually entails basic medical physiology parameters and consideration to comorbidities and medications. Parameters included blood count, BMI, renal and liver function tests as well as a basic physical performance scored using Karnofsky or the Eastern Cooperative Oncology Group (ECOG). This would be taken at baseline, usually on diagnosis, and regularly monitored during treatment.

"…I will ask my patients, you know, how far can you walk on the flat, how do you get on going up a hill…what sort of exercise do you normally do..." **Urologist 2**

General mobility is taken into account and any relevant investigations (CT scanning, bone scanning, examination findings). Two interviewees talked a great deal about the importance of age when considering fitness for treatment, although there was acknowledgement that some older men can be very fit.

"…so it's their performance status…well, we subconsciously do it automatically, ECOG status...Their age is a factor to an extent, but it's not really a factor anymore because the reality is you can get 84-year-olds who are super fit and you can get 60-year-olds who are very unfit, so I think their current quality of life and their performance status is, is really key." **Urologist 2**

As mentioned previously, physical fitness was a crucial factor in decisions on treatment, particularly for chemotherapy.

5.1.2 Anabolic agents in combination with an exercise intervention

5.1.2.1 Perceived benefits and concerns

There was consensus amongst the clinicians for the need of robust data on any anabolic agents, particularly novel agents in the treatment of muscle wastage in men with CRPC. Those discussed in the interviews were novel agents such as SARMS and anabolic steroids. "*What is known in the early pre-clinical data?"* - was a key question that was asked (n =8). Information regarding the side effects and safety profile were considered imperative. The impression given by the majority of the clinicians (n =10) was that there was a lack of knowledge regarding anabolic agents and therefore an inability to make an informed choice. Education and an opportunity to ask questions regarding these agents were considered essential before the clinicians would consider offering it to a patient.

Effects on progression of malignancy associated with the potentially androgenic effects were mentioned by numerous clinicians although some described this as a lesser concern in this advanced stage of disease. For these clinicians, they expressed that as these men are in the terminal phase of the disease, that disease progression and survival were subordinate to potential improvements in QoL.

"At that sort of stage most of the patients are at the terminal event of their life, so I think if you are going to try and gain a quality of life, even though you might arguably speed up the tumour, I don't think I would have that many concerns about

that, as long as we achieved what we wanted to, the quality of life improvement." **Urologist 1**

Contraindications with second line treatment remained one of the biggest concerns, particularly administration whilst on other drugs because of unknown drug interactions.

"…I'm not sure if we would want to be doing that in conjunction with second line treatment. If they'd had all of their treatment then yes, you could give them…the problem that we have is that we think we understand how a lot of things work and what the pathways within the adrenal gland are, etc. but there's probably a lot more crossover and interaction than we realise or we know and I'm not sure how safe, from a disease control point of view, and if these men have other treatment options that can effectively treat their prostate cancer, I'm not sure we should be giving other things that may be detrimental when we don't quite know either way." **Clinical oncologist 4**

Most clinicians were only agreeable to the use of these agents in the context of a trial setting, both tightly controlled and well designed. More specifically, if it was shown to be economically viable, improved QoL, negated muscle wastage, did not compromise other therapeutic agents and weighed up favourably against potential risks and side effects of exercise.

"Yeah, I think if you could prove it convincingly of a positive outcome and not just, you know, not for that short period of time but, you know, longer term positive outcome, then that would be hard to argue against." **Clinical oncologist 1**

5.1.3 Exercise and cancer

5.1.3.1 Knowledge of the current NICE recommendations on exercise

Almost all the clinicians seemed to have knowledge of the NICE recommendations for exercise for men with advanced prostate cancer. However, there was some confusion as to why, given that NICE has made the recommendations, action had not been taken nationally to implement them. One participant suggested it was due to a lack of robust clinical evidence. One participant did admit to not knowing a great deal about the recommendations and another spoke of them exclusively in the context of bone health.

"Well I was surprised to find out that NICE's has actually made recommendations and so usually when NICE makes a recommendation then it eventually happens because it means it's going to be funded…" **Medical oncologist 1**

"Um, not an awful lot except I do know it's recommended in the 2014 update that patients who are embarking on ADT should have a trial of, is it twice weekly supervised exercise programme for 12 weeks to make, to try and minimise the side effects of ADT? And it's interesting that NICE recommend that when there's not any randomised data…to show that and there's some data looking at toxicity profiles, associated radiotherapy and as far as I'm aware there's no difference." **Medical oncologist 2**

5.1.3.2 Barriers to success and implementation of an exercise programme

5.1.3.2.1 Patient barriers: Education and programme specifics

Lack of patient education regarding the rationale for exercise was the most frequently perceived barrier reported by clinicians. It was suggested that there may be a lack of clarity amongst patients regarding what exercise, "physical activity" or "being active" encompasses. Education was considered key to encouragement and motivation for these men to participate in exercise.

The environment in which the exercise is expected to take place seemed to be a crucial factor amongst the clinicians. It was suggested that men are less likely to want to engage in a more public gym setting due to anxiety of being out of their "comfort zone". The location of a programme and ease at which the men can access the facility was thought to encourage adherence. Equally, it was thought a programme where there is a real drive to get these patients recruited and undertaking a specific exercise prescription would be far more effective than simply offering a "walk around the block".

Medical oncologist 3 felt that it was not appropriate to mix men at different stages of disease in a prostate cancer specific exercise programme (e.g. advanced and early stage).

"…they've got other things on, how are they going to get there, what sort of people would go there because if you had people who were in the early stages being mixed with people who were in the later stages, it wouldn't be good for either group.

Because the first group would think oh my God, am I going to end up like that?" **Medical oncologist 3**

5.1.3.2.2 Patient barriers: Age, fitness and comorbidity

There were many comments regarding the recruitment of older men to an exercise programme, who may be frailer, and how they may have much more extensive needs for which proper information and appropriate guidance will be necessary.

"Frail patients won't want to come out and go to a gym or anything like that." **Medical oncologist 2**

One clinician felt that in advanced stages, as the men tend to be older, they are far less likely to express an interest in this type of intervention.

"…well until you try it you don't know but I just see a lot of elderly men being invited to take part in a physical exercise programme regarding the whole thing as grotesque. Yeah, it's just, you know, I'm managing very well as I am, but I may be wrong." **Medical oncologist 1**

There was concern from six of the clinicians regarding an exercise programme for the more advanced men who are disabled by poor health and comorbidity. For some clinicians, there would be no consideration of exercise in men with a poor PS. Chemotherapy was also seen as a factor which may impede the success of the programme. It was thought that whilst on chemotherapy it would be more difficult to assess physical capacity to do exercise but also how appropriate exercise may be (particularly in more public areas such as gyms) whilst these men can have a high risk of infection. Equally, the risk of fracture was a general worry by the clinicians.

"I think doing it, assessing it during chemotherapy can also be quite tricky because you've got so many other things going on with all the side effects of treatment and risks of infection and weakness due to steroids. So there's a lot of other things going on, that it's possibly quite tricky to assess…Sadly probably, again I'm guessing now, 50 or 60% of the men are probably fairly disabled by the symptoms and their other comorbidities and therefore I'm not sure how much they would be able to even exercise at home a great deal." **Clinical oncologist 1**

5.1.3.2.3 Patient barriers: Motivation and behaviour change

Men from lower socioeconomic backgrounds were also perceived as more likely to partake in unhealthy behaviours, such as smoking and drinking. This was seen as more of a cultural barrier, and therefore these men may be harder to confer long- term behaviour change.

"…there's a lot of poverty in the North East and I think a number of our patients are quite happy sitting at home watching the telly, drinking beer and smoking, to be perfectly honest!" **Clinical oncologist 2**

Conversely, a programme would perhaps be very well received by the highly motivated individuals. Men who undertake regular exercise would likely be very interested in such programmes but would not gain the most benefit. Emphasis was made on the need to have an individualised approach to engagement, where some men may not need much incentive others may need encouragement and a reiteration of information.

"…people may not feel like going to the gym and I think the people that are likely to benefit from it most are probably those people who have never really done any exercise all their lives and so suddenly they're just going to be, oh well, I'm 67 and I don't fancy doing a 12-week exercise [programme], so there is going to be that!" **Clinical oncologist 3**

5.1.3.2.4 Finance and clinician capacity

Clinicians were aware that despite of the NICE guidelines (section 1.4.19 in CG175) trusts had not changed practice in accordance and that exercise, as part of prostate cancer care, remained a low priority. However, some trusts had made some general considerations, such as advice and recommendations given in clinic appointments.

Resources and finance were mentioned numerous times by the clinicians and the lack of facilities to carry out a programme on NHS sites. It was thought that for an exercise programme to be realistic the QoL benefit to patients would have to significantly outweigh the cost of implementing the programme.

One oncologist suggested that in order to successfully implement a programme, a business plan would need to be put forward and that designing a very specific programme on a select cohort of patients (i.e. prostate cancer patients) would not be

financially viable and also not logical to exclude the majority of other disease groups who would also benefit. Two of the clinicians would consider such a programme in the NHS more of a luxury than anything else and that if funding was allocated to such a programme it might not entirely be fair when compared to funding needed elsewhere. Lack of current government funding was considered detrimental to the growth and development of overall cancer care, particularly in comparison to other European countries that have superior survival statistics.

"So to try and integrate a new service, we'd have to have a business plan and business case and that might be tricky to show in the void of decent quality [data/research]" **Medical oncologist 2**

"I don't think it would be necessarily right to spend a lot of resource on a specific programme, say for men with localised disease on surveillance. Maybe we'll find that it's really useful, but I sometimes feel there's a quite a sort of unfair allocation of resources to cancer versus other things." **Urologist 3**

The lack of clinician time and capacity was a concern for most of the interviewees. It was felt that they did not have the specialist knowledge to design, facilitate and follow-up a programme tailored to the complex needs of individuals and that this would be better suited to an exercise physiologist or physiotherapist to ensure success. However, it was also a concern that a job role dedicated to the programme in itself would be difficult to fund.

"Well, it's difficult, because you just create more work for ourselves…so to be able to do that for all of our castrate-resistant or all of our metastatic patients who are on long-term hormone therapy, that's a huge pile of work for somebody to do, which nobody has really got capacity to put into their job plan, which means you need another person to do it, which is, you know, not feasible in the current climate." **Clinical oncologist 4**

5.1.3.1 Facilitators to an exercise programme and perceived benefits

5.1.3.1.1 Facilitators to an exercise programme

A good knowledge of the potential benefits to the patients' health and wellbeing aligned to their disease status was seen as integral to facilitating patient engagement in exercise. A dedicated individual, or group of individuals, who have the specialist

knowledge to tailor an exercise intervention to the needs of each man and monitor throughout the process was considered paramount. **Clinical oncologist 6** suggested there should be an MDT approach --*"So I think it, it needs to be individualised and the multidisciplinary team is there to support the patients depending on their individual needs.*"

Almost all of the clinicians (n =11) suggested the need for a physiotherapist, CNS or allied clinician to facilitate an exercise programme and felt this was vital to adherence. There was a consensus for there to be a need for a flexible programme dependant on the patient's circumstances. It was recommended that an experienced physiotherapist should be involved in the programme to ensure the safety, particularly for the more complex patients.

It was thought that a group setting could be very beneficial for some individuals who would benefit from peer to peer support. However, this was not the opinion of all of the interviewees, with some stating that some men would prefer one to one exercise sessions and would be put off by group exercise sessions.

"I think, you know, in terms of methods of supporting doing exercise, I think men benefit from peer to peer support and I think that they benefit from sharing their story with other people and doing things together in a way and they may not think they like that before they get there, but I can guarantee that when they do get there they do enjoy that, because that's been our experience and it's been the experience of other, of other programmes." **Urologist 2**

One clinician also stated that he felt that a diagnosis of cancer was a very "teachable moment" and that these men would be more than willing to improve their potential outcomes. Another clinician felt that it would help some patients to feel they have gained some control over their disease. Urologist 3 also mentioned that treating the exercise programme as a prescription would confer better adherence.

"…if people see it as a prescription from the hospital, like it's a group support, if you say, this is your next appointment, rather than, this is a group…it gets much better uptake, so that's something to consider." **Urologist 3**

5.1.3.1.2 Perceived benefits of an exercise programme

There was consensus amongst clinicians that an exercise intervention would confer the most benefit when initiated as early as possible in the pathway (ideally at hormone sensitive stages) and continued throughout the course of the disease. It was recognised that at this stage men may be at their most active but, as their disease progresses, their needs will change and are likely to require more help from the physiotherapists. Initiation of a programme early on in the cancer care pathway would encourage continued adherence down the line where men are likely to experience more AEs and therefore may gain more benefit. It was felt that an exercise programme would be extremely beneficial and be well received amongst younger patients (i.e. those around 40-50) and those who may be asymptomatic without a great deal of disease burden. It was thought that initiation prior to ADT could help mitigate some of the long-term effects of castration.

The psychological benefits, including beneficial effects to QoL outcomes, from an intervention were considered invaluable and this could gain favourable support from family.

"I'm sure the men would like it. The wives of the men would like it!" **Medical Oncologist 3**

The potential physiological benefits of exercise, mentioned by the clinicians were the maintenance of muscle bulk and bone health which is often compromised on ADT, increased tolerance of treatment and a reduction in complications (surgical or medicinal).

"I think it's, it's beneficial for maintaining muscle strength, quality of life and exercise capacity, which I think is very important for them and it keeps some bone strength, you know, when on their long-term hormones, the more exercise they do the more they can maintain their bone strength, which is going to be a good thing, and it's good psychologically, you know, if they can keep going out and playing golf or doing whatever they do, then I think that's very important for them, so yes, it is." **Clinical oncologist 4**

There was also support for further studies to demonstrate the benefits of exercise training in CRPC from Medical Oncologist 2 who was sceptical of the current available data surrounding exercise for prostate cancer.

"I mean if you, if you can show a treatment works and it's as simple as exercise, it improves energy levels, wellbeing, potentially decreased other side effects with muscle wasting that is, that is what they call a no-brainer" **Medical oncologist 2**

5.2 Variability in the prostate cancer care pathway

5.2.1 Theme 2: The prostate cancer care pathway

5.2.1.1 The Cancer care pathway: continuity of care

It was unanimously accepted amongst all 12 clinicians that the data from the STAMPEDE and CHAARTED trials has changed the prostate cancer pathway, where men with advanced hormone sensitive disease are now being offered chemotherapy alongside initiation of first line ADT (James, Spears et al. 2015, Sweeney, Chen et al. 2015). Two oncologists (one clinical and one medical) stated that as a result they are experiencing an increased number of referrals of men with hormone sensitive disease and therefore the oncologists involvement in the cancer care pathway has increased, where previously they would treat men with CRPC with chemotherapy. This represents a dramatic increase in work load for oncologists and presents potential challenges that may not have been foreseen.

"Before [the] *NHS agreed to fund* [docetaxel for men with metastatic hormone sensitive disease] *in January, we were just doing it based on the American study* [CHAARTED]*, which was the more extensive group* [higher volume metastatic disease]*, and not do the people with minimal disease. And we're trying to still do that, just to keep the numbers down... well I'm in the process of being made to say that we're going to have to have a, a waiting list for these patients…"* **Medical oncologist 3**

Both the urologists and oncologists were clear and explicit when distinguishing their role from each other. The involvement of either clinician is based on an individual's disease stage or treatment. Those who are hormone sensitive are predominantly under the care of their urologists (except where they receive docetaxel from their

oncologist) and only when they progress to castrate resistant stages are they primarily under the care of oncology.

"So, I refer [castrate resistant men] *to oncology!...I don't see that many castrate-resistant men myself…so I may diagnose people, so I diagnose people presenting with metastatic disease just because I'm part of the diagnostics pathway, but usually they're already under the care of the oncologists and I don't really get involved."* **Urologist 3**

However, the referral of care from urology to oncology appeared problematic in some cases. The pathway changes post 2015, and the ensuing change in current practice, appeared to introduce pressures on the cross-over period of a man's care from urology to oncology as it appears earlier in the pathway at hormone sensitive stages. Medical oncologist 3 talked specifically about the time constraints surrounding the simultaneous initiation of chemotherapy and ADT. The current recommendations (based on the trial data) state that docetaxel should be initiated within 90 days.(Specialised Commissioning Team 2016)

"That has caused a problem, at an MDT, yesterday because they referred a patient who was five months out, four or five months out and then the patient got upset that they weren't offered [docetaxel with ADT]*...But then there's no evidence for it, beyond for more than 90 days…surgeons would argue that if there's no evidence you should give [docetaxel]. Whereas oncologists argue that if there's no evidence you shouldn't give [docetaxel]."* **Medical oncologist 3**

5.2.1.2 Current supportive programmes

Professionals were not aware of any supportive programmes specifically targeted to men with CRPC. However, the supportive programmes mentioned which men with CRPC could access, aimed at general cancer populations, were charity funded programmes run by Macmillan and Prostate Cancer UK. This included support groups and wellness programmes offering psychological support for those living with and beyond cancer. No exercise/physical activity programmes embedded in the cancer care pathway were mentioned. Outside of this, palliative care (including hospice care) and alternative therapies, such as acupuncture, were mentioned as was routine support from the patient's cancer nurse specialist.

"So for men in our Trust…they have Macmillan teams available, they have hospice care, we have specialist nurses who support them and we have a survivorship nurse specialist as well…so if a patient comes into hospital in extremis or as a new presentation then there is a palliative care team which is primarily nurse led..." **Urologist 2**

"… they have done things like, auricular acupuncture…they can kind of just direct them to other services." **Clinical Oncologist 6**

5.2.2 Theme 3: Uncertainty with treatment sequencing in castrate resistant prostate cancer

Almost all of the clinicians felt that changes to the pathway had resulted in dilemmas associated with the sequencing of treatment later on when men develop castrate resistant disease. Previous to the STAMINA and CHAARTED data, men with newly diagnosed castrate resistant disease would have been chemo-naïve. Now some men progressing to CRPC will have had a docetaxel regimen and it was understood amongst the clinicians that standard care would likely change.

"So a lot of it [treatment options] *is individual…so* [future treatment] *will change somewhat because the use of chemotherapy may have happened earlier on for hormone sensitive disease…"* **Clinical oncologist 1**

There was a lack of clarity regarding sequencing second line anti-androgens and chemotherapy. Some of the interviewees indicated that men would need a better PS to receive second line ADT (enzalutamide and abiraterone) than to receive second line chemotherapy.

"So you can be fairly unfit to have hormones [ADT]*, but for the chemotherapy we'd only offer that to people who are fit basically, you know, at some level, able to withstand it anyway."* **Urologist 3**

"Having said that, for people who are asymptomatic and haven't got rapidly progressing disease then, you know, something like enzalutamide is relatively straightforward. So obviously if someone isn't physically fit, you're less likely to consider chemotherapy." **Clinical oncologist 1**

"You could give it [enzalutamide or abiraterone] *but you shouldn't but I, I just suspect that some oncologists would give it…But you shouldn't do it…according to*

NICE or NHS, where the data was always in your healthy population. It was never in your poorly population and it shouldn't really be given in the poorly population, but I'm sure some people do…"

"…to get enzalutamide or abiraterone they have to be performance status zero or one. And they have to have, be asymptomatic or minimally symptomatic. So they should be fit enough for chemo when they are fit enough for that." **Medical oncologist 3**

5.3 Theme 4: Clinician's reporting and management of the adverse effects of standard treatments and advancing disease

5.3.1 Castrate resistant prostate cancer: Adverse effects of disease and treatment and the impact on quality of life

Bone metastasis and associated bone pain were considered the most commonly occurring AEs of advancing disease subsequently having the most impact on patient QoL. Clinician's frequently referred to it as the most common AE which was the most difficult to treat. The most common treatment mentioned was radium-223.

"So I think the biggest thing will be if they have, if they've got bone metastases and they've got pain and discomfort and reduced mobility." **Clinical oncologist 6**

"…it tends to be a bony pain depending where their metastatic disease is. Commonly it might be in the back, the rib, the pelvis and typically they do get quite a, a chronic disabling quite painful problem which requires quite considerable quantities of pain relief." **Urologist 1**

Other AEs frequently mentioned were spinal cord compression, fracture, neurological problems and lower urinary tract symptoms (LUTS). It was also noted that for progressing disease, men may not seek to have further systemic treatment until the point they become symptomatic.

PSA progression was the predominant non-symptomatic factor mentioned indicative of advancing disease, and one of the main reasons to initiate second line therapy. Others, but less common, included imaging and biopsy. A pathological fracture might also be one of the ways in which advancing disease presents. **Medical oncologist 2** defined the confirmation of advancing disease:

"…we would like to see…well two things out of three, so radiological change, symptomatic change or biochemical change, so we're waiting for two, two out of those three." **Medical oncologist 2**

Clinician's reported the most common AEs associated with ADT were fatigue, weight gain, hot flashes, muscle weakness/ wastage (particularly worse when compounded with steroids), a decrease in sex drive and breast swelling (gynecomastia). The most commonly mentioned effects of chemotherapy were neutropenia (with a chronic worry of acute death), emesis (vomiting), peripheral neuropathy and fatigue. Sometimes the source of the AE was not always clear.

"…I think it's, it's difficult sometimes to determine which has been the cause and which is the effect, if that makes sense, of the treatments." **Urologist 2**

This was particularly relevant to the symptoms of muscle wasting where it can be difficult to determine the cause of significant muscle loss (see later sections).

Given the impact of AEs on QoL, all clinician's reported that the preservation of patient's QoL was paramount even in this late stage of disease.

"Well, I think the benefits have to be twofold, don't they…there are disease specific benefits and then there's quality of life and they're not necessarily aligned..." **Urologist 2**

"…really quality of life is a, it's a huge issue and there's no point in keeping people alive if we're wrecking their lives." **Clinical oncologist 5**

5.3.2 Treatment decisions

Clinician's perception of the AEs of second generation anti-androgens (Enzalutamide and Abiraterone) was variable reflecting differing patient reported treatment experiences and the clinician's preference for either drug.

"…although my experience of enzalutamide hasn't been as good as my experience of abiraterone, so I am kind of swayed towards [abiraterone] *still as my first line…That's just, my own preference, because I've had, especially in the last few months, all the people I've got on enzalutamide seem to have problems on it"* **Clinical oncologist 4**

"…cognitive state, change in mood, change in energy level, sometimes with enzalutamide in particular, we have this global weakness and sometimes, the associated, neurology, twitching. So that's, that's happening more frequently than we could have anticipated" **Medical oncologist 2**

Whilst some clinicians demonstrated a preference for either abiraterone or enzalutamide due to better tolerance, this was not the case for all. Medical oncologist 3 also mentioned the lack of trial data comparing the two drugs.

Medical oncologist 3 *"The nuisance is that there's no evidence to compare them [Enzalutamide and Abiraterone].*

Interviewer *"Oh OK because from speaking to some oncologists, they've said that they've actually found abiraterone is tolerated a lot better."*

Medical oncologist 3 *"I don't agree with that…I don't because I would probably say most tolerate it pretty well."*

All of the clinicians spoke of the choice of drug dependant on patient PS, comorbidity and therefore risk of complications. Diabetics and those with heart disease are offered enzalutamide, due to the cardiac risk and the need to take prednisolone with abiraterone; epileptics are offered abiraterone, due to the risk of fits associated with enzalutamide. These complications, although affecting treatment decisions, were rarely experienced by the clinicians interviewed.

Chemotherapy was generally considered the treatment which was less well tolerated in comparison to ADT. As a result how a clinician would deem a man clinically suitable for chemotherapy became paramount.

"…they'd have to be PS 0 or 1 for me to give them docetaxel generally, with good renal function, and, you know, just generally a good performance status…with no other significant comorbidities." **Clinical oncologist 4**

Interestingly, aside from fitness to treat and tolerance of therapies, medical oncologist 1 offers a more holistic view and mentions the importance of social support as another factor which is considered, emphasising the need for assistance and support from a partner or family member on "bad days".

"I'm just going, going back thinking, it can be difficult giving chemotherapy to single men…Men who live, men who live alone…They, they're a real worry." **Medical oncologist 1**

Six of the clinicians mentioned patient decision making in their interviews. It was reported that many men are happy as they are or have simply had enough of treatments. Some may only consider further treatment upon the development of symptoms from disease progression. There are also other factors such as pressure from family to pursue further treatment which men may take into account.

"…the patient-related factors, not wanting chemotherapy and some patients would, are keen not to go onto further endocrine therapy so that can cause some delay while we give them a bit of time to, to just confirm that their PSA is rising or their, their imaging is showing progressive disease." **Medical oncologist 2**

Men may prefer to accept alternative therapies such as palliative radiation and analgesia if they choose to avoid second line treatment. Patient treatment decisions are also dependant on their preferences around the monitoring involved with the individual treatments and the impact of such monitoring on day to day living. This in combination with the individual risks carried with treatments.

"…it's difficult…the problem with abiraterone is they have to come fortnightly for bloods and blood pressure, for the first three months. So if you've got one, someone who's active and wants to keep away from hospitals, they'll often say no to that, and also the steroids with the abiraterone puts some patients off, even though you point out that they'll get steroids with the docetaxel, so that sometimes puts them off. If they're a patient who's got, epilepsy or doesn't fancy the chances of a fit they will choose the abiraterone or some patients like to be seen more frequently. They feel as if they're being looked after and they will choose abiraterone…" **Medical Oncologist 3**

5.4 Theme 5: Clinicians experience of managing muscle wasting comorbidity in men with prostate cancer

5.4.1 Muscle wastage aetiology, assessment and treatment

The types of muscle wastage referred to in the interviews were originating from ADT, physical inactivity, steroids (prednisone), sarcopenia (age related muscle wastage) and cachexia.

"…and you've started the drug…and very often people will be saying to you, I was OK and then I started these hormones, …and patients say the same things, they can't get up from squatting position, that sort of thing…" **Clinical oncologist 5**

One example given by clinical oncologist 3 described how ADT was stopped due to extreme muscle wastage in one patient.

"...so I've seen muscle wasting that was quite significant that was stopping somebody from going out and doing their job…they worked in a shop and it was stopping them from doing that. So, although there was data for overall survival benefit in continuing the hormones, I stopped the hormones after discussion, because I felt that we're going to leave him housebound at the end of this and I felt that that was a more, poor prognostic factor in his life…" **Clinical oncologist 3**

Clinicians were unanimous (n =12) that there currently exists no robust diagnostic procedures when distinguishing muscle wastage of different aetiologies. For some, this meant that no official assessment for muscle wastage was made at any stage in the prostate cancer care pathway.

A man who presents as being fairly well but has generalised weakness, ADT related muscle wastage (a common side effect) may be presumed. If however, he presents with proximal muscle wastage following the initiation of steroids, side effects of steroids may potentially be the cause. The interplay between the induced LBM loss associated with treatments and that associated with cachexia resulted in difficulty distinguishing the two. With a lack of clarity and a definitive diagnosis of muscle wastage, accordingly, treatments were the same regardless of aetiology; generally advocating exercise and a healthy diet.

"While I don't have any method in clinic of assessing muscle wastage and I don't, certainly don't have time to sit measuring their muscle bulk...."

"...I probably should weigh them more often, but it depends what I'm going to do about it, I guess." **Clinical oncologist 4**

"…I haven't made a clear distinction between, muscle weakness because of ADT, muscle weakness because of steroids, muscle weakness because of cachexia, um, perhaps we should." **Medical oncologist 2**

" I just advocate a healthy diet but mainly it's the exercise that I think that is the most important…exercise I think is the most important thing to maintain muscle bulk." **Clinical oncologist 5**

5.4.2 Cancer cachexia

Most clinicians felt that recognising cachexia occurred upon the association of progressive disease accompanied with rapid muscle wasting rather than any sort of clinical diagnostic method and is generally identified towards the end of life. Therefore, an accurate patient history which demonstrates the onset of cachexia associated physiological symptoms from the patient's baseline physiological state, was felt to be attributable to the comorbidity. However, the use of long-term steroids, particularly for advanced patients, can also be the origin of muscle wastage. Furthermore, it was not clear how cachexia would be distinguished from muscle wastage associated with ADT. Therefore, the need for a robust diagnostic procedure was highlighted where clinicians can risk the cessation of steroids when the underlying cause is cachexia. Where cessation of steroids is inappropriate, there is a risk to further exacerbate the disease and disease symptoms.

"*The cachexia is usually end stage and it's, you know, and often they're on steroids anyway for their disease control, so if you think its cancer related cachexia then it, it could be steroids."* **Clinical oncologist 6**

As well as nutritional interventions, steroids such as dexamethasone are often used to combat cachexia but this can in turn cause proximal muscle weakness. Cachexia's association with advanced stages of cancer meant exercise was considered inappropriate by one of the clinicians.

"*I don't think it would be appropriate to be telling a patient, you know, who's losing weight because they've got advanced cancer that they should be taking exercise.*" **Clinical oncologist 2**

5.4.3 Clinical significance of muscle wastage

There was significant variation between the clinicians on how they viewed clinical significance of muscle wastage among men with prostate cancer. Whilst for most it was considered of clinical importance, for the urologists it was not seen very regularly or considered a primary concern.

"…but I'd say for the majority of men, although it's objectively there, I'm not sure subjectively it may make a great deal of difference to their quality of life." **Urologist 1**

However, five oncologists however did see muscle wastage as a significant comorbidity, although some alluded to the fact that men may not prioritize it amongst other concerning disease symptoms or survival.

"Yes it's very clinically, very clinically important…the prevalence of the muscle wastage or weakness is… usually is probably quite high." **Medical oncologist 2**

It was also clear that whilst a man may not give the direct complaint of muscle wastage, it may be the loss of mobility or vigour which he notices and this can have profound effect on his QoL. For those men who are more physically active however, they may notice a significant decrease in exercise tolerance and this can have a considerably deleterious effect on his wellbeing.

"…they come and they say, yeah, I feel really tired, I can't play a round of golf anymore, I can't walk as far as I did, so not specific muscle loss, but the consequences are the things that the men complain about." **Clinical oncologist 4**

"…men who say they're not as strong as what they used to be and they can't, you know, do the amount of exercise that they used to do or, you know, find it difficult sort of maintaining their jobs if they're still working." **Clinical oncologist 6**

6. Discussion

6.1 The healthcare professional survey

The 95 respondents represented a range of professions with experience of the prostate cancer pathway based throughout the UK and gave an insight into what could be described as "usual care". This included how exercise programmes which had the potential to meet the NICE guidelines were being delivered nationally.

A clear understanding of the current prostate cancer pathway gives an insight into how changes to the pathway, such as the introduction of exercise as a complementary therapy, are successfully implementable. This is especially the case with prostate cancer where the care pathway is continuously evolving. Establishing a clear picture of key HCP roles within the prostate cancer care pathway in relation to the delivery and

initiation of ADT is paramount. As highlighted in the survey, there are a wide range of HCPs involved in the delivery of ADT but the planning and initiation of these therapies is predominantly the responsibility of urologists and oncologists which was an expected finding.

Despite the survival benefit demonstrated in STAMPEDE and CHAARTED, the current survey revealed an unexpected finding that the average amount of men receiving docetaxel on ADT was as little as 23.3% (James, Sydes et al. 2012, James, Spears et al. 2015, Sweeney, Chen et al. 2015). Furthermore, the responses given ranged between 0-87% indicating that the low average may represent differences in care between trusts rather than a national picture of men receiving docetaxel.

The most common barrier to chemohormonal therapy was "patient unfit" indicated by just under half of the respondents. This suggests that in order for patients to have the best possible chance of receiving the highest standard of care, fitness is at the core to accessing treatments. Patient fitness is a contentious issue, where it is very much subjective how a clinician may determine a patient as physically fit and whether such subjective assessments are adequate (Greasley, Turner et al. 2018).

Previously it has been reported that HCPs experience significant barriers preventing the discussion of physical activity with their patients, including how it is not deemed to be a part of their role (Jones, Courneya et al. 2005, Karvinen, McGourty et al. 2012, Spellman, Craike et al. 2014). It was key to establish how supervised exercise programmes may or may not be embedded in the NHS despite the NICE recommendations. A large proportion of respondents (74%) indicated having knowledge of the NICE recommendations (CG175, 1.14.19). However, the average score for ability to deliver on these recommendations was only 4.87, indicating that despite knowledge of these recommendations, there remain barriers to implementation.

The findings show that across the UK there is either very little to nothing being offered in the form of an exercise referral programme (for more than half the population) or some level of accessible exercise programme available for these men. This indicates a potential disparity between UK trusts, where some are failing to deliver NICE recommendations by simply not having any available programmes for men to access.

It is clear that there is huge variability nationally in what is being delivered to meet the NICE guidelines. Where trusts have attempted to put in place exercise programmes for cancer patients, there remains further variation. Although the majority indicated that these programmes would be accessible to prostate cancer patients on ADT and that the programmes predominantly run in a community setting, 20% of the respondents indicated that these programmes would not be available for these men, potentially indicating that the programmes are designed for other cancer types, such as breast/colorectal, although this was not clear.

However, a positive finding was that of the programmes that exist the predominant HCPs involved are nurses and GPs indicating primary care and secondary care involvement in exercise referral in some trusts. In addition, gym instructors were primarily responsible for setting the frequency, intensity, and duration of exercise. However, a disappointing 53% of respondents reporting an exercise referral programme indicated that no staff training was provided for exercise programmes in cancer populations, or that they were unsure if such training existed. Without proper training for HCPs in the benefits of exercise programmes it is doubtful that conversations regarding exercise or physical activity in clinic with cancer patients will arise especially where time is often limited during appointments (Clark, McArthur et al. 2017). In addition, without proper education, fears regarding advising physical activity due to issues of safety could prove a significant barrier (Tsiouris, Ungar et al. 2018). A training programme could help create clinician "buy in" to endorse exercise as a supportive therapy.

Furthermore, issues regarding the cost of implementing physical activity guidelines and exercise programmes have been an established barrier (Nwosu, Bayly et al. 2012, Clark, McArthur et al. 2017). With half the respondents indicating the need for charity financial support to ensure the implementation of programmes which meet NICE guidelines for these men. CRUK has recognised that health inequalities in cancer care span from information, support and cancer services all the way from provision to palliative care (CRUK 2006). The three factors presented in the survey (fitness, funding and updating guidelines) denoting substandard care can be summarised by what has been suggested as root causes in cancer care inequality nationally (Macmillan 2014). Profound changes in cancer care increases the risk of health inequalities where some services lack the capability to adapt successfully, there needs

to be a recognition that the support needs for trusts to undertake a rapid change in care to ensure the best outcomes of their patients likely differ for those trusts that lack the necessary resources and therefore are significantly challenged to adapt. Equally, as the aspects of care change and become more complex, some patients may lack the ability to confidentially act on the information regarding his care. Conversely those patients most capable of sharing decisions and self-manging are able to get the most out of their care. As cancer care pathways evolve and become more complex, services must act to prevent a variation in care quality. As Macmillan outlines in "The Dividing Line in Cancer Care for 2030"

"*…transfer power to the people who use services, enabling them to take greater control of their cancer team and their cancer journey…*" and with that enlisting patients in their own care (Macmillan 2014).

Self-care is a critical dimension of healthcare and exercise programmes are a powerful self-care approach that have been demonstrated to be effective at managing side-effects of disease and treatment. Despite the NICE recommendations, the variability in what is being delivered nationally demonstrates the need for a structured exercise referral pathway embedded into the care pathway. This would also require HCPs as key stakeholders for these men to champion this self-care approach and create an effective programme.

6.2 The healthcare professional interviews

6.2.1 Attitudes towards the implementation of an exercise intervention with a pharmacological agent for men with castrate resistant prostate cancer

Views on the use of anabolic agents in men with CRPC alongside an exercise programme were varied. Clinicians were questioned about the use of widely available anabolic steroids as well as the more novel anabolic agents in combination with an exercise programme to enhance the effects. Although there was a positive feel towards the use of anabolic agents in a clinical trial there was some concern over the safety of such drugs. Few of the clinicians demonstrated a complete lack of support for the use of these drugs, for these clinician's the androgenic effects on the prostate were the primary concern and outweighed any potential benefits. Most of the clinicians stressed the need to see the preclinical research and be educated about the use of

such drugs in order to make an informed decision regarding their use in the context of a clinical trial.

Medical oncologist 2 stated a lack of randomised data surrounding exercise as a therapeutic for men with prostate cancer. This was particularly interesting as to date there is level one evidence demonstrating improved outcomes in men with prostate cancer with exercise interventions in multiple reviews, systematic reviews and meta-analysis of RCTs. These are highlighted in chapter 2. Importantly, Medical oncologist 2 was recruited into this qualitative study via the recommendation of another participant and did not demonstrate a research interest in exercise for men with prostate cancer. It could be argued that medical oncologist 2's view was representative of some clinicians who have a lack of belief in exercise as a therapy; views which may have otherwise not have explored in this cohort.

In qualitative research, a self-selection or non-response bias can result from participants declining to participate due to a lack of interest in the interview subject matter. As a result, the non-representative sample fails to capture some views and opinions. For this reason, medical oncologist 2 gave vital information for us to understand why exercise programmes may not be supported by clinicians. Medical oncologist 2 has demonstrated that this could be due to a lack of knowledge of the most current data supporting exercise interventions.

However, largely there was support for the NICE guidelines recommending exercise for men with prostate cancer initiating ADT. Thus it could be argued that a combination of a lack of advocacy for such interventions by some clinicians and insufficient NHS funding are the reasons for why the guidelines have not been successfully implemented. Funding in the NHS, and lack thereof, was mentioned on several occasions in the interviews as a barrier to exercise programmes and cancer care in general. As well as this clinician capacity including time and specialist knowledge meant that programmes would likely be best placed to be facilitated by exercise specialists/physiotherapists with a good knowledge of the relevant individual medical conditions. This has previously been shown in other qualitative studies examining clinicians views on exercise referral schemes and for other chronic conditions (Din, Moore et al. 2015, Learmonth, Adamson et al. 2017). However, as demonstrated in the present study, clinicians are a patient's first point of contact regarding their health

and wellbeing and key drivers in patient based decision making (Bridges, Hughes et al. 2015) it is therefore key that they are campaigners for exercise as a fundamental aspect in cancer care. Currently, the data for the cost effectiveness of exercise programmes for advanced cancer populations undergoing palliative treatment is lacking (Santa Mina, Alibhai et al. 2012). However, these patients stand to gain a great deal of specific benefits relevant to their condition (Eyigor and Akdeniz 2014). Although expensive to implement initially, promoting habitual exercise in some cancer populations has been shown in to improve cost per QUALY, suggesting long-term financial benefits for the NHS (Haas and Kimmel 2011, May, Bosch et al. 2017).

Lack of patient education and physical fitness were perceived by HCPs as significant barriers to exercise. In particular, men at advanced stages with potential multiple comorbidities, may be put off from exercise if they are not feeling well or physically capable. Similar findings have been demonstrated in clinician interviews regarding physical activity for lung cancer patients, stating the difficulty of "selling" physical activity at stages where there are symptoms and treatment side effects (Granger, Denehy et al. 2016). Educating patients and an individualised approach to the exercise programme was seen as paramount for successful engagement. Education would hopefully encourage the participation of those who are amongst the hardest to recruit, i.e. those who are from a lower socio-economic status and/or are older. Such an approach could help overcome some patient perceived barriers and fears regarding exercise.

The timing of an exercise intervention was an essential consideration. The clinicians regarded a programme started as early as possible in the cancer care pathway would confer the most benefit i.e. at hormone sensitive stages where men are much "fitter". They did however feel that an opportunity to participate should be available at all stages in the cancer care pathway. An intervention at earlier staged was felt to potentially confer long-term behaviour change and maintain levels of fitness. Rate of change of new therapeutics also means there potentiates a change in the history of disease. It is not clear how initiation of such treatments like docetaxel earlier in the pathway may affect a man's physical fitness and therefore perceived ability and motivations to undertaking exercise training. A previous qualitative study of HCPs has identified the perceived benefits of exercise interventions as early as possible, potentially mitigating the side effects of treatment and/or disease (Granger, Denehy et

al. 2016). Furthermore, initiating an exercise intervention as early as possible in the treatment pathway has been suggested to help mitigate muscle loss associated with cachexia (Bayly, Wilcock et al. 2017). At later stages it was felt that barriers such as advancing disease and comorbidity would present an issue. It was felt this could present some issues of safety. This was particularly the case during chemotherapy treatment and those who have advanced disease, and have remained on treatment for a number of years and therefore are likely to experience a number of side effects (Shapiro and Tareen 2012, Sountoulides and Rountos 2013). For example, the risk of infection in neutropenic patients, which can be fatal, due to chemotherapy in a gym environment was a primary concern. Concerns of exercise outside of cycles of chemotherapy or during ADT were not expressed by the HCPs. However, long-term effects of ADT were a consideration including patients experiencing a decline in bone health who potentially have osteoporosis or significant bone pain. They may be at significant risk of fracture, where fractures can result in significant morbidity and increased all-cause mortality (Van Hemelrijck, Garmo et al. 2013). Despite these concerns the clinicians still felt that an exercise programme would be accessible by the "fitter" patients with CRPC.

It was therefore considered paramount that an exercise programme would be adaptable and flexible dependant on the individual and their stage of treatment and disease, both from a safety perspective and also from the perspective of patient engagement. This would likely be driven by the individual, giving them an option to "opt out" of a session where necessary and an understanding that these men will have "good weeks and bad weeks" was considered fundamental to better exercise compliance.

It was also suggested that treating an exercise programme as a prescription would support better adherence. It was mentioned that men would likely prefer a programme where they did not mix with other men at other stages of the disease or where it is not necessarily within the community in a "typical" gym setting. But the clinicians in this study did not refer to exercise as a stand-alone treatment. In general, the clinicians spoke of exercise more as an adjunct to existing therapeutics, valuing it as a supportive therapy to help physical and psychological wellbeing. Overall, the clinicians were happy to advocate exercise and would support a trial for men with CRPC.

Exercise was seen as a valuable method for psychological benefit, including beneficial effects to QoL outcomes, the maintenance of muscle bulk and bone health, increased tolerance of treatment and a reduction in complications (surgical or medicinal). Although it was not recommended that exercise be used for those with advanced cachexia due to extremely poor PS', the use of exercise for LBM loss at earlier stages, such as pre-cachexia described in chapter 1, could be feasible. The potential for exercise to promote better tolerance to treatment is of particular value considering the importance of fitness for treatment and best treatment outcomes described in section 6.2.2 and 6.2.3. All of the HCPs supported the use of a trial of resistance exercise as a supportive intervention for men with CRPC with an aim to LBM loss with long-term ADT, and the majority also supported it in combination with an anabolic agent.

Overall, the HCPs showed support for an exercise intervention for men with CRPC, however the described barriers brought questions regarding its feasibility. Given the described issues regarding funding, comorbidities and patient pathway there would be challenges to an exercise programme for men with CRPC in the prostate cancer care pathway and the NHS. Logistical barriers include the lack of resource, the lack of clinician time and an ever evolving prostate cancer care pathway, including the changes in treatment sequencing. This could bring about barriers in terms of the optimal timing of an intervention. Despite the support for an exercise intervention for men with CRPC, most of the HCPs felt that the best time to introduce a man to an exercise intervention would be as early as possible, whilst maintaining the ability to be referred throughout his entire treatment pathway. This in part was due to concerns regarding the physical barriers which include progressive decline in health with ongoing long-term treatments and their side effects. Despite this, the HCPs were supportive of an exercise intervention for men with CRPC.

Furthermore, an exercise intervention was viewed more as an addition, a supportive therapy, to standard treatment for men with prostate cancer rather than a stand-alone treatment. Physical fitness was described as a barrier to accessing treatments in both the survey and in the interviews, with the HCPs interviewed demonstrating its effect in treatment decision making. Given that physical fitness is a pivotal issue when prescribing therapeutics, exercise could be seen as a welcomed supportive therapy, improving or maintaining physical fitness and therefore granting access to treatments. This can be pivotal at later stages of disease where men have remained on treatments

for long periods of time. Exercise may be able to mitigate some of the functional decline experienced in these men. Furthermore, given that drugs such as enzalutamide and abiraterone have greater efficacy in men with a good performance status, these men may tolerate treatments better and get better outcomes. The difficultly would undoubtedly lie in determining who is fit enough to exercise but perhaps not fit enough for treatment, and potentially bringing those men to a fitness level good enough to receive further treatment should they want or require it. This area is yet to be explored in research.

6.2.2 The prostate cancer care pathway: continuity of care

Docetaxel is a widely used drug and a common therapy for CRPC. Its use has moved earlier in the prostate cancer pathway for suitable men upon the initiation of long-term ADT. It has been recognised that whilst the implementation of docetaxel earlier in the pathway is both recommended and feasible, there would be potentially adverse implications on the clinical pathway and resources (South, Burdett et al. 2015). The changes to the pathway have increased demand on oncology units and subsequently an additional workload to oncologists. Previous to such changes, oncologists would predominantly see men with CRPC, not hormone sensitive disease, when they are offered cytotoxic agents. As a result, any disjoint between urology and oncology may risk a delayed referral from one to the other. Ergo, if this falls outside of the 90 day window, a docetaxel regimen which can be offered to an eligible man is compromised. The findings of the present study suggest that for one oncologist, this has arguably risked sub-optimal patient care where the trust was challenged to accommodate the changes to the care-pathway by restricting the numbers of men referred for chemotherapy.

The oncology team's involvement earlier in the pathway highlights the importance of a flexible integrated pathway of care between oncology and urology teams. Whether this is at the point where a man enters castrate resistant disease or where he is able to initiate docetaxel alongside ADT in hormone sensitive stages, a fractured pathway risks substandard care. An efficient and effective service would operationalise and adapt to changes in standard care to facilitate the best health outcomes for its users. Where the pathway lacks continuity, it is unlikely that trusts are able to implement additional supportive programmes for men across all stages of disease with prostate cancer. This may provide some evidence as to what was observed in the survey,

where there was significant variability across trusts in the implementation of exercise programmes for men with prostate cancer due to the NICE recommendations.

It was clear that there was a distinct lack of embedded supportive programmes designed for the complex needs of men with CRPC. A 2013 survey suggested that 81% of men with prostate cancer had some unmet supportive care need(s) (Cockle-Hearne, Charnay-Sonnek et al. 2013). The clinicians mentioned that these men could access general psychological support programmes and palliative care programmes, both charity based and trust run; but whilst these men remain a part of the cancer pathway for a number of years, their needs differ significantly to those who may be at earlier stages of disease or those with other types of advanced cancer. So it is indeed surprising that there seemed to be a lack of guidance on how to specifically support these men through the terminal phase of their disease. These men are often signposted to generic "palliative" programmes as opposed to a programme which promotes more of a "self-care" approach. Such an approach is considered imperative to managing symptoms/AEs and promoting positive health outcomes (Cockle-Hearne and Faithfull 2010). Lifestyle changes, such as diet and exercise, have been demonstrated as an important, valued aspect of self-care in men with CRPC, promoting empowerment and a sense of control (Dodd and Miaskowski 2000, Miaskowski, Dodd et al. 2004, Street Jr, Makoul et al. 2009, O'shaughnessy, Laws et al. 2013).

6.2.3 Treatment sequencing

In addition to the immediate pressure of additional referrals to oncology units brought on by the change in the prostate cancer clinical pathway, it is important to consider how the introduction of docetaxel earlier will affect subsequent treatment sequencing. Some of the clinicians commented that second generation anti-androgens, abiraterone and enzalutamide, would be offered in the place of chemotherapy were it is felt men may not tolerate docetaxel due to a poorer PS. There was also a lack of clarity amongst clinician's in this study in how docetaxel and second generation anti-androgens may be sequenced for men in the post-2015 pathway changes.

The trials to date which have assessed the use of abiraterone and enzalutamide for men with CRPC were predominantly in men with no or mild symptoms (ECOG 0-1) (Danila, Morris et al. 2010, Scher , Fizazi et al. 2012, Scher, Fizazi et al. 2012, Loriot,

Bianchini et al. 2013, Beer , Armstrong et al. 2014). For the minority of men in these trials whom did have a poorer PS (ECOG ≥2) no significant OS benefit was demonstrated for either abiraterone or enzalutamide. Contraindications to docetaxel use are a poor PS (ECOG 3-4, caution for those with 2). This gives such men with a poorer PS few if not no treatment options. With these limitations we can conclude that fitness for treatment (and improved PS) can be the crux in treatment decision making by HCPs.

Furthermore, the findings indicate some clinicians are treating men with abiraterone with poorer PSs' preferentially over chemotherapy whilst there is a lack of data to support whether it may actually improve survival. The nature of high quality RCTs address the need for internal validity, but this may confound the "reach" within populations of patients recruited into these trials (Elting, Cooksley et al. 2006). Consequentially a selection bias exists in preference of men with better PSs (Elting, Cooksley et al. 2006, Geyer 2018, Gillessen, Attard et al. 2018). Equally, recruiting such patients with poor PS whom have a significantly shorter survival time may lack relevancy in the "real world" when the approval of such drugs by NICE ultimately comes down to cost per quality adjusted life years (QUALY) (Elting, Cooksley et al. 2006, Gillessen, Attard et al. 2018). With this exists a therapeutic quagmire with researchers and commissioners having to balance the need for data with clinical relevancy and economic viability.

With a lack of trial data, clinical guidance and clarity within the cancer care pathway treating physicians face a major dilemma. They may have to make a treatment evaluation on a patient and potentially offer unsuitable treatments based on the premise that there is no suitable alternative. Furthermore, the optimum pre- or post-docetaxel therapy is heavily debatable in CRPC given that there is no suitable comparison data, forcing physicians to make decisions based on assumptions and clinical experience rather than true "level one" data (Fitzpatrick and de Wit , van Soest, van Royen et al. , Sade, Baez et al. 2018).

Therefore, if at present the available data for these treatments lack evidence for their efficacy in less fit populations with a poorer PS, interventions with an aim to improve and maintain of PSs and physical fitness in men with prostate cancer, introduced as

early as possible, would enable the best possible outcomes. Something which too was reflected in the opinions of the clinicians interviewed.

6.2.4 Variability in the cancer care pathway and exercise implementation

The variability in the care pathway and the problems faced with treatment sequencing can present significant barriers to the implementation of exercise programmes in the UK. This is further reflected in the findings of the survey, where less than half of UK trusts represented in the survey were able to offer an exercise programme to meet the NICE guidelines (section 1.4.19 in CG175).

The lack of continuity between trusts in the cancer care pathway presents a structural barrier to the implementation of exercise interventions or programmes. Each trust is likely to have its own individual barriers which must be addressed, finance may be a problem for one, or the demographic of patients between trusts can be different and therefore differing social barriers may exist. Furthermore the lack of clinician time and capacity can differ between departments within the care pathway, as demonstrated in the oncologists interviews. Similar findings have been shown in other qualitative interview studies of healthcare professionals (Din, Moore et al. 2015, Granger, Denehy et al. 2016, Clark, McArthur et al. 2017). The difference in clinicians time and capacity will likely cause problems as to who is expected to facilitate conversations of exercise with the patient, and as demonstrated in the interviews, often it was felt to be the responsibility of the physiotherapist, CNS or allied clinician. However, it is recommended that for implementation of exercise requires a team approach at all points of contact a patient experiences in the cancer care pathway (Mina, Sabiston et al. 2018).

Furthermore, issues surrounding the funding of such a programme were a primary concern. If there is no funding for a programme then despite the best intentions of a clinician, they are unable to refer these patients to the support which may help promote exercise behaviour. Furthermore, facilitating HCP and allied HCP training to increase "buy in" and create clinical champions for exercise as a part of clinical care to promote discussion physical activity and exercise with their patients will incur further cost. Referral schemes and supervised exercise have continually been demonstrated to promote exercise behaviour compared to home-based independent exercise. Therefore an established referral pathway is therefore considered the best evidence

based approach to encouraging exercise in cancer patients (Gaskin, Craike et al. 2017, Yang, Hausien et al. 2017). However, given there are barriers to appropriate treatment to established cancer therapies described in the survey, and the findings in the present study demonstrating that some clinicians felt that an exercise programme would be considered more of "a luxury", the likelihood of increased specific funding for a programme could be problematic. Therefore there is a need for robust cost-effective data for implementation of exercise programmes in the NHS and, as one clinician had described, to generate a viable "business plan".

6.2.5 Experience of the adverse effects of standard treatments and advancing disease

Determining the root cause of an AE can have a profound impact on maintaining a patient's QoL whilst succeeding with the best possible treatment regimen to control disease. Dropping the dose, treatment breaks or switching to an alternate therapy can be an option, and so if a man's experience is such that the clinician regards this to be necessary then he/she must be sure of where the AE stems from to not compromise treatment. Dependant on the reaction to the previous treatments will also determine how the following treatment is offered. For example, if they have not tolerated first line ADT well, then new considerations need to be made for 2nd line ADT; and now considerations must be made for previous adjuvant chemo as the landscape has changed post STAMPEDE and CHAARTED.

The interviews highlighted the importance of shared decision making for treatments between clinicians and patients. Shared decision making is preferred by a majority of patients and crucial in ensuring they feel fully informed and satisfied with their care (Blanchard, Labrecque et al. 1988, Joosten, DeFuentes-Merillas et al. 2008). Although it was highlighted that clinicians professional opinion on therapies are governed by a number of factors; such as the preference for a particular drug, comorbidity or contraindications and fitness for treatment; the maintenance of a man's QoL was always the primary concern. This would be guided by the patient's (and the patients family's) own preference a known key factor in decision making (Hobbs, Landrum et al. 2015, Al-Bahri, Al-Moundhri et al. 2017).

6.2.6 Experience of muscle wasting comorbidity in men with prostate cancer

Fitness for treatment is a predominant factor in a clinicians treatment based decision making (Kelly and Shahrokni 2016). Treatment evaluation of a patient with CRPC

remains a significant issue given the predominance of muscle wasting and deterioration in bone health (Perlmutter and Lepor 2007). Further, retrospective data has associated better OS in men with metastatic prostate cancer receiving docetaxel with increased LBM (Wu, Liu et al. 2015). The overwhelming consensus amongst the clinicians was that both recognition and treatment or prevention of muscle wasting is a clinically unmet need but not necessarily one they feel they can address in practice.

The findings highlight a lack of clarity over the origin of the muscle wastage and how these are to be subsequently assessed and treated. This is likely to reflect populations at different stages of disease but equally the complex nature of muscle wastage means there is greater difficulty in determining the aetiology. Given that the clinicians described a non-specific assessment for the diagnosis of cachexia; including a general functional decline of the patient, knowledge of their current treatments and disease stage and weight loss; very little preventative measures are put in place.

There was an overwhelming view amongst clinicians that currently, very little is offered in the way of treatment to address muscle wastage. Generally, advocating a healthy diet and exercise was encouraged to treat the majority of muscle wastage seen in the clinic with the exception of cancer cachexia. Success from this approach was viewed as variable. This may be in part due to a lack of consistency from clinician to clinician in the subjective nature of general "exercise and diet advice". However, equally the "one size fits all" approach to tackling muscle wastage of differing aetiologies is unlikely to be efficacious. Compromising treatment was also mentioned by some of the clinicians resulting in the cessation of ADT or restricting the use of steroids for men whom muscle wastage becomes a problem. Muscle wastage is particularly complex in its aetiology and therefore notoriously difficult to mitigate or treat. A huge challenge faced by clinicians is the lack of available therapeutic options for men where muscle wastage becomes a significant detriment to QoL, in some cases compromising treatment at the potential cost of a survival benefit (Andreyev, Norman et al. 1998, O'Gorman, McMillan et al. 1998). Equally, the effects of muscle wastage appear to have significant implications on the fitness and PS of a man, and therefore not only impacting his current therapy but also likely to affect future treatments he is offered as his disease progresses.

7. Study limitations

It is important to acknowledge the limitations to these studies. The primary limitation of the survey was the number of respondents and the limit to the information gained. With surveys it is not possible to get in-depth detailed answers as is the case with interviews. Although interviews were subsequently conducted, this included only the limited professionals, i.e. medical and clinical oncologists and urologists. The views of other professionals which were identified in the survey such as CNSs, physiotherapists and gym instructors were not gained. Therefore the findings of these professionals were limited to the data in the survey.

Furthermore, the HCP interviews did not include the views of men with CRPC. They were an insight into the views and opinions of 12 clinicians and for this reason is limited in its generalisability. The interviews included the opinions of three urologists, three medical oncologists and six clinical oncologists. As the majority of interviewees were clinical oncologists the data may be more biased to the perspectives of this particular group of professionals. Due to the nature of how these participants were recruited into the study, it is acknowledged that a self-selection bias may also exist. Of the 35 clinicians contacted 54% (n =19) expressed an interest in the research themes (12 subsequently interviewed); the sampling of the participants in this study failed to address the views of those who did not express an interest. Some of these invited HCPs also expressed that they could not participate due to time-constraints, which indeed is a finding of the present study. The thematic framework approach to analysing the data was used, although commonly used in healthcare research; this form of analysis is more deductive and therefore stays strongly informed by a priori reasoning (Mays and Pope 2000).

Finally, it is important to recognise that this work was the first qualitative work undertaken by the author (RG). Therefore, it should be noted that whilst the interviews provided some insights into the HCPs views and opinions, there was a limitation in the lack of experience of the author. Given that these HCPs were senior clinicians, the authors experience of the interviews was very different, in terms of both content, rapport and power dynamic than that of the focus groups described in chapter 5.

8. Conclusion

The provision of exercise nationally was widely variable between trusts represented in this survey. Irrespective of the 2014 NICE recommendation (section 1.4.19 in CG175) there are inconsistencies in the NHS in how men initiating or undergoing ADT are offered supervised resistance and aerobic exercise. These inconsistencies were not only amongst all 79 trusts identified in the present study but also amongst the 47 sites determined by us as having an exercise programme or exercise referral scheme which had potential to meet the NICE recommendations. There is a need to standardise exercise programmes which can be fully integrated into the cancer care pathway and therefore consistently be available for all men initiating or undergoing ADT.

Fitness for treatment in advanced prostate cancer remains a significant barrier for access to the available therapies in those with a poor PS. This has become even more pressing since changes in the current pathway. Given that men will have already received a docetaxel chemotherapy regimen, it is less clear how this may affect future treatment options and their physical fitness due to long-term effects of chemotherapy. In addition, muscle wastage is too of significant clinical impact, affecting fitness for treatment and in some cases compromising current therapy. There appears to be a significant unmet need for effective treatments to tackle muscle wastage and current practice is an imprecise approach; however the use of anabolic agents in combination with an exercise intervention to tackle muscle wastage was received relatively well in the context of a clinical trial.

These clinician interviews have demonstrated support for a cost effective, individualised and adaptable exercise programme for men with CRPC which could improve fitness and mitigate some of the long-term effects of their cancer/cancer therapy. However, there exists potential and significant barriers to successful implementation in the NHS, which may result in this service falling outside of NHS provision. However, supportive programmes which promote "self-care" are lacking significantly in the current prostate cancer care pathway for men with CRPC; there is a significant gap for such programs tailored to the complex needs of this group. Where there is a lack of continuity in the pathway, their successful implementation is less likely. In order for such a programme to be successful, there must also be a recruitment strategy which educates both the patient and the clinicians involved in the care of these men. Furthermore, it was expressed by the HCPs that there would need

to be consideration to the timing of the intervention, particularly when faced with treatments and disease related barriers.

The described barriers and facilitators to implementing exercise interventions were taken into account when conducting the feasibility RCT (COMRADE). The following study (chapter 4) will explore the feasibility of a uniquely tailored and adaptable exercise programme with dietary supplementation for this group of men which will aim to improve outcomes including changes in LBM, bone health QoL and physical function.

Chapter 4 The feasibility and safety of a lifestyle intervention in men with castrate resistant prostate cancer: a randomised controlled trial

1. Introduction

In consideration of the evidence provided in the previous chapters, the following study was designed to determine the feasibility of a lifestyle intervention of resistance exercise, dietary supplementation and dietary guidance for men with CRPC in order to improve outcomes in these men. In the current study, an adaptive programme of resistance exercise was designed to promote beneficial effects in physiological and psychological outcomes for men with CRPC. In addition, whey protein and creatine monohydrate supplementation were consumed to promote anabolic effects including improved LBM. Dietary advice to promote healthy eating behaviours was also provided. The target population were men who were inactive and mostly sedentary and therefore not already meeting the NICE guidelines (section 1.4.19 in CG175).

This study aimed to be the first to explore the feasibility of such a lifestyle intervention, examining the use of exercise and dietary intervention specifically tailored to the needs of men with CRPC. The research question for the present COMRADE (A **Com**bined Prog**ra**mme of Exercise and **D**ietary Advice in M**e**n with Castrate Resistant Prostate Cancer) Feasibility RCT was:

Is a RCT of a lifestyle intervention, including supervised resistance exercise training, whey protein and creatine supplementation, and dietary advice feasible in men with CRPC?

2. Methods

2.1 Research design

A phase II feasibility RCT was used as an exploratory research method to assess exercise in improving outcomes for men with CRPC. Phase II trials "…*describe the constant and variable components of a replicable intervention and feasibility of the protocol for comparing the intervention with an appropriate alternative*" (Gorard and Taylor 2004). The advantages of the RCT design mean that systematic differences between the groups in the study do not occur due to randomisation and an unbiased estimation of the average effect can be gained compared to non-randomised intervention trial design (Gorard and Taylor 2004). Such trials are also conducted in preparation of a definitive larger scale RCT and therefore aim to assess the clinical and economic viability of an intervention.

Feasibility studies are recommended by the MRC to identify problems which may occur or address uncertainties in a larger scale RCT (Craig, Dieppe et al. 2013). The MRC suggests the aims of such studies should include the testing of procedures for their acceptability, estimating rates of recruitment and retention, and the determination of sample sizes (Craig, Dieppe et al. 2013). The current study aimed to assess these outcomes of feasibility for comparing the intervention to the alternative or standard NHS care (control). Although an RCT used alone poses its limitations in real world implementation, in combination with the methods used previously it could provide robust evidence for the feasibility of a RCT of a lifestyle intervention providing a potential supportive therapy for these men to combat some of the effects associated with treatment and disease.

2.1.1 Aim

To determine the feasibility of a 16-week lifestyle intervention of resistance exercise, whey protein and creatine supplementation and dietary guidance in men with CRPC.

2.1.2 Primary outcomes

1. Determine the rate of recruitment.
2. Determine the eligibility of men among those screened to take part in the trial.
3. Measure intervention adherence.

4. Measure study completion rate over 16-weeks (attrition rate).

5. Measure adverse events (safety).

6. Assess objectives 1-5 using standard methods for rates and proportions.

2.1.3 Secondary outcomes

1. To measure changes in physical function and fitness.

2. To measure changes in muscle hypertrophy, lean body mass (LBM), fat mass (FM) and bone mineral density (BMD) assessed by dual energy x-ray absorptiometry (DXA) scanning and anthropometric measurements.

3. To measure changes in prostate specific QoL and fatigue perception.

4. To measure changes in serum biomarkers, including sex hormone binding globulin (SHBG), testosterone, PSA and lactate dehydrogenase.

5. To measure changes in the dietary and nutritional status using 3-day diet diaries.

2.1.4 Participants

2.1.4.1 Inclusion criteria

Men with CRPC, defined as men with histologically confirmed prostate cancer on long-term ADT with either:

- PSA>2ng/ml above nadir and a PSA level that has risen serially on at least two occasions (each at least 4 weeks apart) in the presence of castrate levels of testosterone or;

- Evidence of symptomatic disease progression whilst undergoing first line androgen deprivation therapy (ADT) in the presence of castrate levels of testosterone or;

- Radiographic disease progression whilst undergoing first line ADT in the presence of castrate levels of testosterone.

2.1.4.2 Exclusion criteria

- Participation in other trials which might bias the evaluation of the primary outcomes of the present study.

- Current participation in regular physical activity. This was defined as purposeful physical activity of a moderate intensity for 90 minutes per week for at least six months.
- Unstable angina, uncontrolled hypertension, recent myocardial infarction, fitted with a pacemaker.
- Uncontrolled painful or unstable bony metastatic lesions.
- Within two months of invasive surgical treatment (transurethral surgery allowed).
- Any physical, neurological or psychiatric impairment, disease or other condition, or non-English speakers/readers that would limit the ability to understand and complete the study assessments and complete the required questionnaires, recall and record of dietary information would be excluded.

2.1.5 Sample size

As this study was a feasibility RCT, a power calculation was not conducted to determine sample size. A target recruitment figure of 50 patients was set empirically to promote estimates for this feasibility study. Fifty participants can provide estimates of feasibility measures and of variability in secondary outcomes for use in power calculations with reference to the design of a subsequent larger-scale RCT (Lancaster, Dodd et al. 2004, Bourke, Doll et al. 2011).

2.1.6 Study design

Participants were randomly allocated to receive either 16 weeks of resistance exercise training, dietary supplementation and dietary advice, or 16 weeks of usual care. Repeat assessments were performed after 8 weeks (mid-point assessment) and 16 weeks of the intervention (end-point assessment). There was also an option to partake in a post-study completion focus group (chapter 5). The patient pathway through the study is shown in the study schematic Figure 4.1.

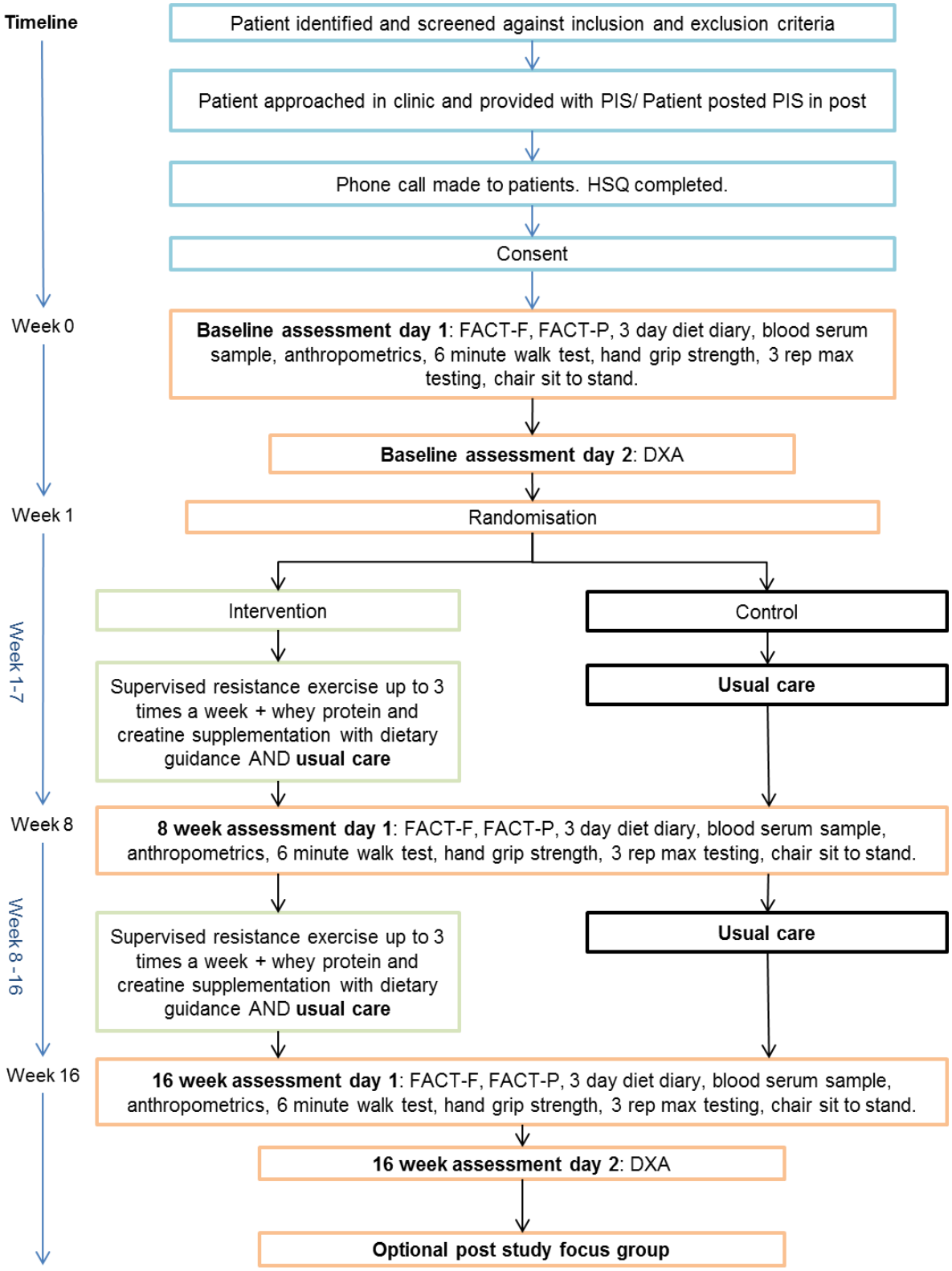

Figure 4.1 A schematic of the COMRADE trial recruitment and assessment schedule

2.1.7 Ethics approval

This study was approved by North East - Newcastle & North Tyneside 2 Research Ethics committee (15/SW/0260) and in accordance with the Governance

Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK. All Management permissions were sought from the relevant NHS organisations involved in the study in accordance with NHS research governance arrangements (appendix 12). ClinicalTrials.gov Identifier: NCT03017417. All participants gave their informed consent before participation in this study.

2.1.8 Recruitment methods

Patients were identified from treatment lists and clinic lists from urology (by a study research nurse or the author) and oncology outpatient clinics (by the author) in Weston Park Hospital and The Royal Hallamshire Hospitals in Sheffield, UK. The clinics consisted of clinician or nurse led follow-up clinics and treatment clinics. Patients were screened (by the author or study research nurse) against the inclusion and exclusion criteria via the electronic notes on the electronic document management system (EDMS) or Lorenzo prior to attending clinic or via paper notes in the clinic where electronic notes were unavailable. LORENZO and EDMS are patient health record systems which allow access to patient details (date of birth, address, phone numbers etc.), dictated clinic letters as well as the results of any clinical investigations. Those identified as potentially eligible were approached in person in clinic by a member of the research team (the author or the study research nurse) and given a recruitment pack, consisting of a patient information sheet (PIS) and invitation letter (appendix 13).

Patients were then given a minimum of 24 hours to read the PIS before a follow up phone call was made (by the author). Alternatively, a recruitment pack was posted and a follow up phone call followed between 3-7 days from posting (by the author). For transparency the data for the recruitment of men with CRPC is displayed in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 5.2). Recruitment posters were displayed in clinic waiting areas where prospective participants were given the trial contact information (appendix 14).

2.1.9 Invitation follow-up phone call and post screening health screening questionnaire

Participants were contacted by phone after a minimum of 24 hours from receiving the PIS. Participants who expressed an interest in the study were requested to complete a health screening questionnaire (HSQ) over the phone (appendix 15). Patients were re-screened against exclusion criteria. During this phone call the participants were given

a chance to ask any questions and address any concerns with the member of the research team. The trial assessments, randomisation, intervention protocol, time commitment and general practicalities of the study (parking, location of rooms etc.) were reiterated and discussed to ensure sufficient understanding of the commitment required for the study. If participants still wanted to be included in the study they were invited to provide informed consent (appendix 16) and undergo a baseline assessment at Sheffield Hallam University (SHU).

2.2 Baseline assessment and randomisation

Prior to baseline assessment, participants completed written and verbal informed consent procedures on site at SHU. See figure 4.1 for the recruitment and assessment schedule. Assessment visit one was undertaken at baseline and repeated at 8 and 16 weeks. Assessment visit two was undertaken at baseline and repeated at 16 weeks only.

Assessment visit 1: Sheffield Hallam University

At visit 1 the participant underwent a series of physical functioning assessments and muscle strength tests (conducted by the author or a research technician). In addition, whilst on site, a blood serum sample was taken (by RG), two questionnaires and a diet diary was provided for completion. In this session participants had their second assessment visit confirmed with the member of the research team. Outcome measures are described in detail in section 2.4.

Assessment visit 2: The Clinical Research Facility, The Northern General Hospital

During visit 2, participants underwent whole body DXA scan (conducted by researchers at The Clinical Research Facility) details of which are described in section 2.4.

Randomisation procedures

Once castrate levels of testosterone (from blood serum analysis conducted by labs at STH) were confirmed, patients were randomised at an allocation ratio of 1:1 to either to the resistance exercise and dietary intervention arm plus usual care (intervention arm) or the exercise guidance plus usual care (control arm). Men randomised to the control arm were provided with Macmillan independent exercise advice guidelines for

cancer patients (Macmillan Move More Pack). The randomisation was completed by an independent researcher via a computer generated algorithm randomisation tool:

(https://www.random.org/sequences/?mode=advanced).

The sequence generation was undertaken by an academic blind to allocation who then kept the sequence blind to the research team. Once successfully randomised, the participants GP was sent two letters to notify the participants recruitment into the trial and to notify that the participant was required to undergo two DXA scans (appendix 17).

2.2.1 Intervention habituation sessions (week 1)

Participants randomised to the intervention undertook a familiarisation week during week one, consisting of two separate sessions. On day one, the participants were introduced to the 16-week resistance exercise programme plan with an explanation of the design of the programme (including a whole body approach, reasons for warm-ups/cool-downs etc.). On this day, participants were also inducted to the exercises (day one, phase one) of the trial. This included the correct use of the exercise equipment; how to perform exercises using appropriate technique and correct form throughout an optimal range of movement. It was explained that this was to ensure exercises were undertaken safely and to reduce the risk of injury. Men were also requested to bring their own towel, for hygiene purposes, and water was provided *ad libitum* in each session. Advice was provided on speed of concentric and eccentric phases of the exercises and breathing techniques. This included a 1:2/1:3 ratio in the velocity of concentric to eccentric phase of the exercise whilst exhaling on the concentric phase and in on the eccentric phase. The exercise specialist (by RG or research technician) also took this time to assess the individual's ability to safely perform exercises and adapt exercises, where necessary, with regressions or progressions. Participants were provided with the dietary guidance booklet which includes recommendations and dietary advice based on the NHS healthy eating guidelines (appendix 18).

In the second session (day two, phase one), participants were again inducted to the exercises. Participants were also given the whey protein, creatine supplements, and a protein shaker (see section 2.3.3 supplementation). The protein and creatine supplementation, including reasons for taking the supplements and how to take the

supplements, was also discussed with participants in person at the session (appendix 19, SOP).

2.3 Lifestyle intervention

2.3.1 Exercise sessions

The exercise sessions took place in the exercise facilities in A205 Collegiate Hall on Collegiate Crescent at SHU. All sessions were supervised by an exercise specialist (with CQC Level 3 exercise referral qualification, the author (RG) or physiotherapist) to ensure safety and correct form during exercises. Sessions took approximately 45 to 60 minutes dependant on the time taken to complete all exercises. The sessions consisted of a 7 to 10 minute warm up on a piece of cardiovascular equipment (treadmill, cross-trainer, bike or rower based on personal preference) and 6 resistance exercises. The cool down lasted approximately 5 to 10 minutes, which was also undertaken on a piece of cardiovascular equipment. Each resistance exercise was performed for 2-3 sets of 6-12 repetitions with a 30-90 second rest period between sets.

The exercises sessions were split into three phases, each phase consisting of 5-6 weeks and included two alternating days of exercises. The full exercise programme is available in appendix 20. Phase one consisted of body weight squat, seated cable row, bench press, body weight lunge, lateral raise, dumbbell side bends, push ups, glute bridge hold, single arm bent over row, farmer carries and 1-arm kneeling lateral pulldown. Phase two consisted of body weight sumo squat, dumbbell deadlift, leg raise, upright row, dumbbell shoulder press, tall plank, knee extension, back extension, standing bicep curl, leg press, standing tricep pulldown and sit-ups. Phase three consisted of body weight squat, leg press, cable row, bicep curl, cable tricep pulldown, tall plank, bench press, deadlift, hip abductor, lateral cable hold, kick-backs and dead bug. Each phase was sequential, in which phase one was weeks 1-5, phase two was weeks 6-10 and phase three was weeks 11-16. The exercises targeted all major muscle groups and the phase approach was chosen to ensure variety in the exercise session to encourage adherence and reduce monotony. In addition, such an approach helped to sedentary participants to progress (both in physical ability and in confidence) to more complex exercises, increasing in intensity, which recruit an increased number of major muscle groups or required more balance.

The exercise volume, frequency and intensity were based on the number of sets, repetitions and weight (kg) lifted. The programme was designed to increase exercise volume, frequency and intensity progressively, with no more than 2 reps/1 set/ 15%-40% increase in weight (kg) if the exercise was progressed. At the beginning of a new phase, the initial weight, number of sets and number of repetitions was determined during familiarisation sessions. The familiarisation sessions also determined the positioning on the exercise equipment, for example if a man could not lie flat during a bench press, the angle of the bench where he could perform the exercise safety and comfortably was recorded. In this case, a further aim would be to progress to the proper exercise form as well as in weight, sets and repetitions. A progression would be made based on the ease of the last set completed, this included whether the participant felt they could do more than 2 additional repetitions in their last performed set.

However, when necessary the exercise volume, intensity or frequency would either not progress or be regressed (e.g. the type of exercise or the weight reduced from the last recorded weight in a completed set). An example of where such regressions would be made included either when a man arrived at the sessions with worsened symptoms of disease and/or treatment or when he had some absence (due to illness for example). At the beginning of each session, each man was asked how he felt to ensure any regressions were adopted if necessary.

In addition, participants were given a 16-week independent exercise diary in which they were asked to log at least one form of moderate- high intensity aerobic activity lasting 30 minutes or more a week (appendix 21). They were asked to undertake aerobic activity which was most convenient for them such as walking or cycling. The diary allowed participants to record the activity undertaken, the duration of the activity and the rate of perceived exertion (RPE) using the BORG scale and ask to undertake activity which was 12 or higher (Borg 1982).

2.3.2 Dietary guidance

Participants randomised to the intervention arm were offered a dietary guidance document with recipes (appendix 18). The 28 page dietary guidance document gave dietary advice based on the widely available national guidelines for healthy eating (Eat Well.NHS 2016). The dietary guidance also contained nutritionally balanced recipes

which were independently reviewed by two registered nutritionists from SHU (both with Doctorates of Professional Studies related to sports nutrition; Dr Dave Rogerson and Dr Trevor Simper). Dietary advice encouraged participants to adopt a diet rich in nutrient dense whole foods, fruit and vegetables and discouraged processed foods and those high in refined carbohydrates and saturated fats. Participants were asked to drink 6-8 glasses of fluid a day, preferably water, but inclusive of tea, coffee and sugar free/low sugar drinks (more when exercising) and to limit alcohol intake. The recipes provided encouraged a high protein, moderate fat, high fibre and low carbohydrate meals.

2.3.3 Supplementation

Whey protein: To promote muscle protein synthesis, participants were required to increase protein consumption via whey protein supplementation provided. Whey protein is rapidly digested and has a high leucine content which appears more efficient at muscle protein synthesis than other protein alternatives (e.g. soya protein) post-resistance exercise (Wilkinson, Tarnopolsky et al. 2007, Villanueva, He et al. 2014). Participants were provided with whey protein to consume with 300-500ml of fat-free milk or water (Hartman, Tang et al. 2007). The recommended dosage of protein was 1.2 g/day per kg^{-1} of bodyweight as previously described (Burke, Chilibeck et al. 2001).

Creatine: The intervention group were asked to take 0.25 $g \cdot kg^{-1}$ of LBM per day of creatine during the acute loading phase (the first 5 days of creatine supplementation) and thereafter a maintenance dose of 5 grams per day. This dosage has been previously described in research (Burke, Chilibeck et al. 2001, Naderi, de Oliveira et al. 2016).

2.4 Outcome Measures

Outcome measures were obtained during the assessment visits at baseline, 8 weeks (mid-point) and 16 weeks (end-point) for all participants. All assessments were undertaken by assessors blind to group allocation. Questionnaires and three day diet diaries were given to the participant at the assessment visits and asked to return them via post in a prepaid envelope.

2.4.1 Eastern Cooperative Oncology Group and Karnofsky

PS was assessed by the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status (KPS) assessment tools (Yates, Chalmer et al. 1980,

Oken, Creech et al. 1982). The breakdown of the ECOG and KPS scoring is given in appendix 22.

2.4.2 Functional Assessment of Cancer Therapy - fatigue

The Functional Assessment of Cancer Therapy - fatigue (FACT-F) scale is a 13-item questionnaire assessing fatigue/tiredness in cancer patients and its impact on activities of daily living. Question items are scored from 0-4, where a higher total score is indicative of lower levels of fatigue (Yellen, Cella et al. 1997). The Fatigue Subscale is a validated brief and reliable measure of fatigue in cancer patients (Yellen, Cella et al. 1997). FACT-F is presented in appendix 23.

2.4.3 Functional Assessment of Cancer Therapy - prostate

The FACT-P scale is a 39 item questionnaire assessing the health related quality of life of prostate cancer patients. The FACT-P is a widely used validated tool and comprises of four subscales of health related quality of life (physical well-being, social/family well-being, emotional well-being, and functional well-being) as well as the prostate cancer subscale (PCS) (Esper, Mo et al. 1997). The FACT-P questionnaire items are scored from 0-4 and a higher overall score is indicative of a better quality of life. FACT-P is available in appendix 24.

2.4.4 Three day diet diaries

Three day diet diaries were used to assess dietary intake over three consecutive days where participants would be eating a "typical" diet for themselves. Participants were asked to complete the diet diaries during periods were they would be eating and drinking as considered 'normal'. For example, a participant would be advised to avoid recording in the diary on days he was on holiday and would be frequently eating out. Open-ended food records, including the three day diet diary, have been demonstrated as a reliable and validated tool for dietary assessment and when compared to other tools such as 24-hour food recall or food frequency questionnaires are better at correctly placing an individual's distribution of habitual diet (Bingham, Gill et al. 1994, Day, McKeown et al. 2001). The three day diet diary is presented in appendix 25. Diet diaries were analysed using the dietary analysis software Nutritics Education (v4.315) by a paid student researcher experienced in using the software and in dietary analysis to assess the participants macro/micronutrients based on the diet data.

2.4.5 Dual-energy X-ray absorptiometry (DXA) Scan

At baseline and 16 weeks, a full body DXA scan was performed to determine post-cranial appendicular LBM and FM. DXA also allows bone health to be assessed by examining BMD at the lumbar spine, total hip and whole body. DXA scans were the chosen method to provide information on body composition as they are fast, precise and one of the only available measures to provide data on fat, lean and bone mass (Andreoli, Garaci et al. 2016). DXA scanning has become one of the most widely used and clinically relevant methods for determining body composition and has been validated in numerous studies (Ellis 2000, Norcross and Van Loan 2004, Rothney, Brychta et al. 2009). It is deemed a safe method since the effective radiation dose from DXA scans is 32μSV less than one year's radiation dose and considered "low risk". Public Health England describes a radiation exposure equivalent to a few years average natural background radiation as 'Low Risk', with between 1:10,000 and 1:1,000 lifetime additional risk of cancer.

Areas of previous fracture or where known bone metastasis exist were excluded from the region of interest to calculate BMD. Scans were performed using the Hologic densitometer, at The Clinical Research Facility, Northern General Hospital and analysed by the scan technician using standard DXA software. Participants were asked to lie flat in the centre of the scan table and remain still for the duration of the scan.

2.4.6 Three Repetition max testing

Three-repetition maximum (3RM) strength tests were carried out on the leg press and chest press at baseline, 8 weeks and 16 weeks using resistance machines in physiology testing suites at SHU. These exercises were chosen as measures of both upper and lower body strength in major muscle groups. The 3RM test was defined as the maximal load that could be moved through the full range of motion with proper form for three repetitions (Delmonico, Kostek et al. 2005, Hanson, Sheaff et al. 2013). Participants underwent at least one familiarisation session before to the testing session in which they completed the exercise with little or no resistance and instructed on proper warm-up, stretching, and exercise techniques to help prevent injuries and reduce muscle soreness after the strength testing assessment. An investigator was present conducting the strength tests with consistency of seat adjustment, body position, and level of verbal encouragement. The 3RM was achieved by gradually

increasing the resistance from an estimated submaximal load after each successful exercise repetition until the maximal load was obtained. The chest press was conducted on a flat or inclined bench with free-weight dumbbells and the leg press conducted using the leg press resistance machine (Life fitness, Insignia Series Seated Leg Press) present in A205 physiology suite. 3RM testing was deemed safer than one-repetition max testing for older deconditioned adults. Sub-maximal testing is a widely used, inexpensive and practical test of muscle strength (Brzycki 1993, Verdijk, van Loon et al. 2009).

2.4.7 Six minute walk test

Participants walked along a marked ten meter course at their normal pace with the number of steps and distance recorded to the nearest second for six minutes. Steps were measured using a validated pedometer (Omron, Walking Style One 2.1 Pedometer) attached to the waistband or pocket of the participant and distance was recorded using a tape measure (Holbrook, Barreira et al. 2009). The test was repeated three times, with other physical function tests performed in-between to allow for recovery time, and the average time and best time recorded. Data has demonstrated that walking distance tends to increase with repeated test administration due to familiarisation effects. Because the distance walked tends to plateau after 3 walks, 1 to 2 initial walks have been performed before determining an individual's functional capacity (Wu, Sanderson et al. 2003). Walk tests are a simple and inexpensive test of physical function. It has been demonstrated that the inability to perform a six minute walk test is a reliable indicator of disability and high dependency (De Feo, Tramarin et al. 2011, Kim, Yabushita et al. 2012).

2.4.8 Hand grip strength

Measurements were made using a digital hand held dynamometer (Camry Scale, USA). The hand dynamometer was individually adjusted to fit the hand of the participant. Participants were asked, whilst standing with their hands by their side, to grip the dynamometer for five seconds as hard as possible. The results were recorded, repeated on each hand alternatively three times. The best attempt was represented as maximal grip strength as it has been demonstrated as a reliable surrogate measurement for overall muscle strength and predictive of short and long-term mortality and morbidity (Ling, Taekema et al. 2010, Norman, Stobäus et al. 2011).

2.4.9 Chair sit-to-stand

Participants were seated in a hard-backed chair, arms folded across their chest, and instructed to rise as fast as possible to a full standing position and then return to a full sitting position as many times as they could for 30 seconds. The same chair and seating position was used at each assessment. The number of repetitions was recorded. The chair sit to stand test is a valid and inexpensive measure of lower body muscle strength (Jones, Rikli et al. 1999). The inability to stand from a sitting position is associated with disability and a poor functional status (Bohannon 1995, Jones, Rikli et al. 1999, Janssen, Bussmann et al. 2002).

2.4.10 Anthropometrics

Height (m), body mass (kg), body mass index (BMI, $m.kg^{-2}$, calculated as the weight (kg) divided by height (m)) and mid-arm circumference were also recorded at baseline, 8 weeks and 16 weeks. Mid-arm circumference was determined using a tape measure. Weight and height were determined using the same stadiometer and scales in each assessment period. BMI is a widely used tool which can be indicative of total body fat (Deurenberg, Weststrate et al. 2007). Mid-arm circumference is widely used as reliable and validated method predictive of nutritional status and muscle mass depletion (Soler-Cataluña, Sánchez-Sánchez et al. , McWhirter and Pennington 1994).

2.4.11 Blood analysis

At baseline, 8 and 16 weeks blood samples, for the assessment of LDH, SHBG, testosterone and PSA, were collected by the author, unless there was significant difficulty obtaining blood samples. If this was the case, the participant would be accompanied to the phlebotomy department for blood draws to be made from an experienced phlebotomist whilst chaperoned by the study research nurse. Approximately 20ml of venous blood was drawn. Serum samples were analysed according to STH laboratory standard operating procedures and reported on ICE (Integrated Clinical Environment, Sunquest). Blood serum LDH is a regulatory enzyme involved in anaerobic glycolysis activity and is correlated to muscle fatigue and tissue damage (Machado, Koch et al. 2011, Washington, Healey et al. 2014) as well as prostate cancer progression in advanced disease (Naruse, Yamada et al. 2007).

SHBG is a glycoprotein with a high affinity binding for hormones such as testosterone and oestradiol and its use in combination with total testosterone provides information regarding the proportion of protein bound and free testosterone (Selby 1990). PSA is a

protein secreted by the epithelial cells of the prostate gland and was monitored as a surrogate biomarker for disease changes. Blood samples were sent to STH central laboratories for analysis. The anonymised blood results were made available for research staff by central laboratories according to local policy.

2.5 Analysis and interpretation

Outcomes including feasibility measures were assessed using descriptive statistics including standard methods for rates and proportions (Eldridge, Chan et al. 2016). Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows (version 24, IBM incorporated, New York, USA).

Adherence data is provided for those who completed the 16-week intervention. Data on adherence were quantified in terms of number of prescribed exercise sessions attended as a proportion of those prescribed, which has previously been used to describe exercise adherence (Bourke, Homer et al. 2013). For adherence data, each participant's attendance was calculated based on the number of agreed sessions per week, i.e. 3, 2 or 1 sessions, over the 16-week intervention period. The maximum amount of sessions which could be attended were 48, 32 or 16 sessions for those who agreed to attend 3, 2 or 1 sessions of exercise sessions per week, respectively. The adherence was calculated as a percentage:

$$\text{Adherence (\%)} = \frac{\text{(Number of sessions actually attended during the intervention}}{\text{Maximum number of sessions agreed to attend)}} \times 100$$

The average attendance was then calculated for the participants who agreed to attend the same number of sessions e.g. all participants who agreed to 2 sessions per week.

$$\text{Average (}\mu\text{) adherence per number of sessions agreed (\%)} = \frac{\text{(}\Sigma\text{ Attendance of participants per number of sessions agreed}}{\Sigma\text{ Number of participants per number of sessions agreed)}} \times 100$$

Finally total adherence was calculated:

$$\text{Total average (}\mu\text{) adherence (\%)} =$$

$$\frac{\text{(Average when 3 sessions agreed (\%) + Average when 2 sessions agreed (\%) + Average when 1 session agreed (\%))}}{3} \times 100$$

For the independent exercise, by totalling the minutes of moderate-high intensity exercise during the 16 weeks it was determined if they had reached the prescribed 30 minutes of independent exercise per week (total 480 minutes across 16 weeks). If 480 minutes or more were recorded in the diary 100% adherence was given, any less was presented as a percentage of the 480 minute target. This data was only available for those who had completed the independent exercise diaries.

Average (μ) independent exercise adherence =

$$\frac{\Sigma \text{ (Independent exercise adherence from participants with data)}}{\Sigma \text{ (Participants with independent exercise data)}} \times 100$$

Adherence to supplementation (whey protein and creatine) was reported as a percentage of the total dose initially prescribed. For example, adherence to whey protein would be 50% for someone who consumed half of their prescribed dose over the 16-week intervention period.

Average (μ) adherence to supplementation =

$$\frac{\Sigma \text{ (Participant adherence to supplementation)}}{\Sigma \text{ (Participants with supplement data)}}$$

Rates of recruitment and attrition were calculated as a percentage:

$$\text{Rate of recruitment} = \frac{\Sigma \text{ participants recruited}}{\Sigma \text{ of patients approached}} \times 100$$

$$\text{Attrition} = \frac{\Sigma \text{ those randomized who dropped out from the study}}{\Sigma \text{ participants recruited}} \times 100$$

For baseline demographic data, descriptive statistics including means and standard deviations were used to describe both the intervention and control groups. After checking for normal distribution using the Shapiro-Wilk test, differences between groups at baseline were assessed using independent t-tests or the non-parametric equivalent (Mann Whitney-U) with all tests performed two-sided. Statistical significance was set as $p < 0.05$. Variation in frequency distribution for demographic data was examined using Pearson's Chi squared test.

For outcome data, effect sizes (*d*) were calculated for variation between groups for the difference from baseline measures using Cohens *d*. An effect size expresses a difference between groups or change within groups as a fraction of the variability between participants, therefore it is possible to estimate the impact and clinical relevance of the intervention on the chosen outcome (Winter, Abt et al. 2014). As this study was not aimed or powered to determine significant changes in secondary outcomes, effect size calculation was chosen to reflect differences between groups (Winter, Abt et al. 2014). Thresholds were set at 0.0-0.19 for a trivial effect, 0.2-0.49 for a small effect, 0.5-0.79 for a medium effect and 0.8 and above for a large effect (Cohen 1992, Sullivan and Feinn 2012).

The change (Δ) within groups observed between baseline and 16-week time-points were reported for participants with complete data for each outcome (i.e. no missing data at baseline or 16 weeks). A positive score indicated an increased change from baseline and a negative score indicated decrease change from baseline. Data are presented as mean ± standard deviation (SD) unless stated. The mean (μ) change (Δ) and the SD for each group was then calculated and used to determine the effect size (*d*).

$$\mu\Delta = \frac{\Sigma\ [\text{16-week value - Baseline value}]}{\text{Number of participants with baseline and 16-week data}}$$

$$d = \frac{[\mu\Delta \text{ experimental group}] - [\mu\Delta \text{ control group}]}{SD_{pooled}}$$

Microsoft Excel (version14, Microsoft Office Professional Plus, 2010) was used to graphically represent the means within the groups for participants with complete baseline, 8-week and 16-week data at a given time point. Graphs were used to compare changes in the control and intervention groups over the three assessment points for the physical function measures.

3. Results

Of the 280 men identified as potentially eligible for the trial, where possible men were approached in clinic or contacted via letter. It was not possible to contact 54 men due to missing, incorrect or incomplete contact details. In total 39 men expressed an interest in the study. Of these men, 35 were successfully screened via the health screening questionnaire, three men once screened were deemed ineligible due to being too physically active (n =2) or it was determined that travel was a problem (n =1). In total 32 men underwent baseline assessment, one man then changed his mind about participation pre-randomisation. In total, 31 were successfully randomised into the trial. The mean ages of those randomised were 70 (SD:5.49) and 73 (SD:6.56), for control and intervention respectively.

3.1 Baseline demographics

Baseline demographics are summarised in table 4.1 Groups were well matched at baseline and there were no statistically significant differences between the group demographics. Table 4.2 details the baseline blood serum data for both groups. All participants were confirmed castrated with serum testosterone levels of less than 50 ng/dL (1.735 nmol/L) at baseline, 8 weeks and 16 weeks (Gomella 2009).

Table 4.1 Baseline demographics

	Control (n =13)	Intervention (n =18)
	μ (SD)	**μ (SD)**
Age (years)	70.00 (5.49)	73.00 (6.56)
White British	13.00 (0.00)	18.00 (0.00)
Body mass (kg)	90.00 (13.45)	97.10 (16.17)
Height (cm^2)	173.70 (5.84)	174.06 (6.55)
BMI (kg/m^2)	29.84 (4.24)	31.95 (4.35)
Disease stage	**n (%)**	**n (%)**
Node positive	10 (78)	11 (61)
Metastatic	11 (85)	10 (56)
Treatment history		
ADT	**μ (SD)**	**μ (SD)**
No. of years on ADT	6.69 (4.84)	7.79 (3.95)
No. of years castrate resistant	3.85 (3.18)	4.56 (3.21)
	n (%)	**n (%)**
CAB/MAB	10 (78)	13 (72)
Enzalutamide	4 (31)	10 (56)
Abiraterone	5 (38)	2 (32)
Chemotherapy	**μ (SD)**	**μ (SD)**
No. of years since initiation of first chemotherapy regimen	1.20 (0.72)	1.38 (0.5)
No. of chemotherapy cycles	6.67 (1.15)	8.33 (3.21)
	n (%)	**n (%)**
Docetaxel	3 (23)	3(17)
Carbazitaxel	1 (8)	2 (11)
Other treatments		
Dexamethasone	3 (23)	6 (33)
Palliative RTx	3 (23)	2 (11)
Standard RTx	3 (23)	7 (39)
Radical prostatectomy	3 (23)	7 (39)
Health history	**n (%)**	**n (%)**
CVD	9 (69)	11 (61)
Family history of cancer	4 (31)	9 (50)
Family history of CVD	10 (78)	13 (72)
MSK comorbidity	7 (52)	9 (50)
Metabolic comorbidity	1 (8)	2 (11)
Registered disabled	2 (15)	6 (33)
Lifestyle	**n (%)**	**n (%)**
Working	1 (8)	4 (22)
Smoker	0 (0)	1 (6)
Previous smoker	8 (62)	9 (50)
Drinks alcohol	9 (69)	14 (78)

BMI - Body mass index; CAB/MAB - Complete/Maximum androgen blockade; RTx - Radiotherapy; CVD - Cardiovascular disease, MSK - musculoskeletal.

Table 4.2 Baseline blood serum data

	Control (n =13)		Intervention (n =18)	
	μ	SD	μ	SD
LDH (IU/L)	425.77	130.14	397.39	81.53
SHBG (nmol/L)	71.32	36.85	73.00	47.14
Testosterone (nmol/L)	0.48	0.20	0.54	0.22
PSA(ug/L)	100.91	195.95	29.91	72.28

LDH - Lactase dehydrogenase; SHBG - sex hormone binding globulin; PSA - prostate specific antigen.

3.2 Feasibility outcomes

3.2.1 Eligibility and recruitment

A total of 3607 patients were screened for eligibility, of 280 deemed potentially eligible, 229 were approached. The rate of recruitment was 13.5% from men approached to those who were successfully randomised (n =31). Among those screened those found to be potentially eligible were 6% (see figure 4.2 CONSORT diagram for further detail).

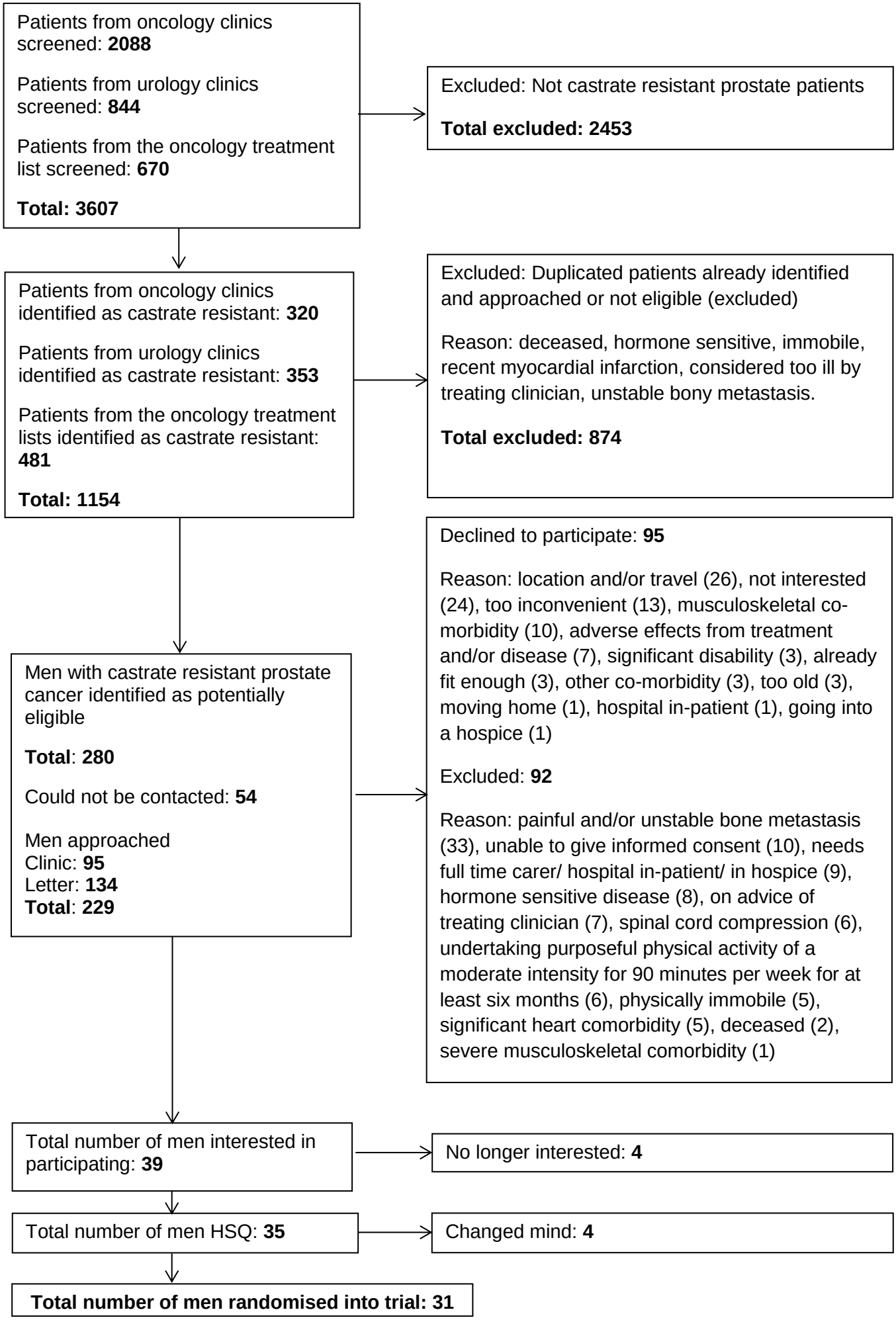

Figure 4.2 CONSORT diagram detailing the recruitment of men with CRPC.

3.2.2 Adherence and attrition

31 men with CRPC were recruited into the trial and were successfully randomised to the lifestyle intervention (n =18) or control group (n =13). During the intervention period a total of four men dropped out from the intervention group (all within 4 weeks of randomisation) and one man died in the control group (due to disease progression). This data is summarised in figure 4.3. Therefore, the attrition rate was 22.2% and 7.7% in the intervention group and the control group respectively.

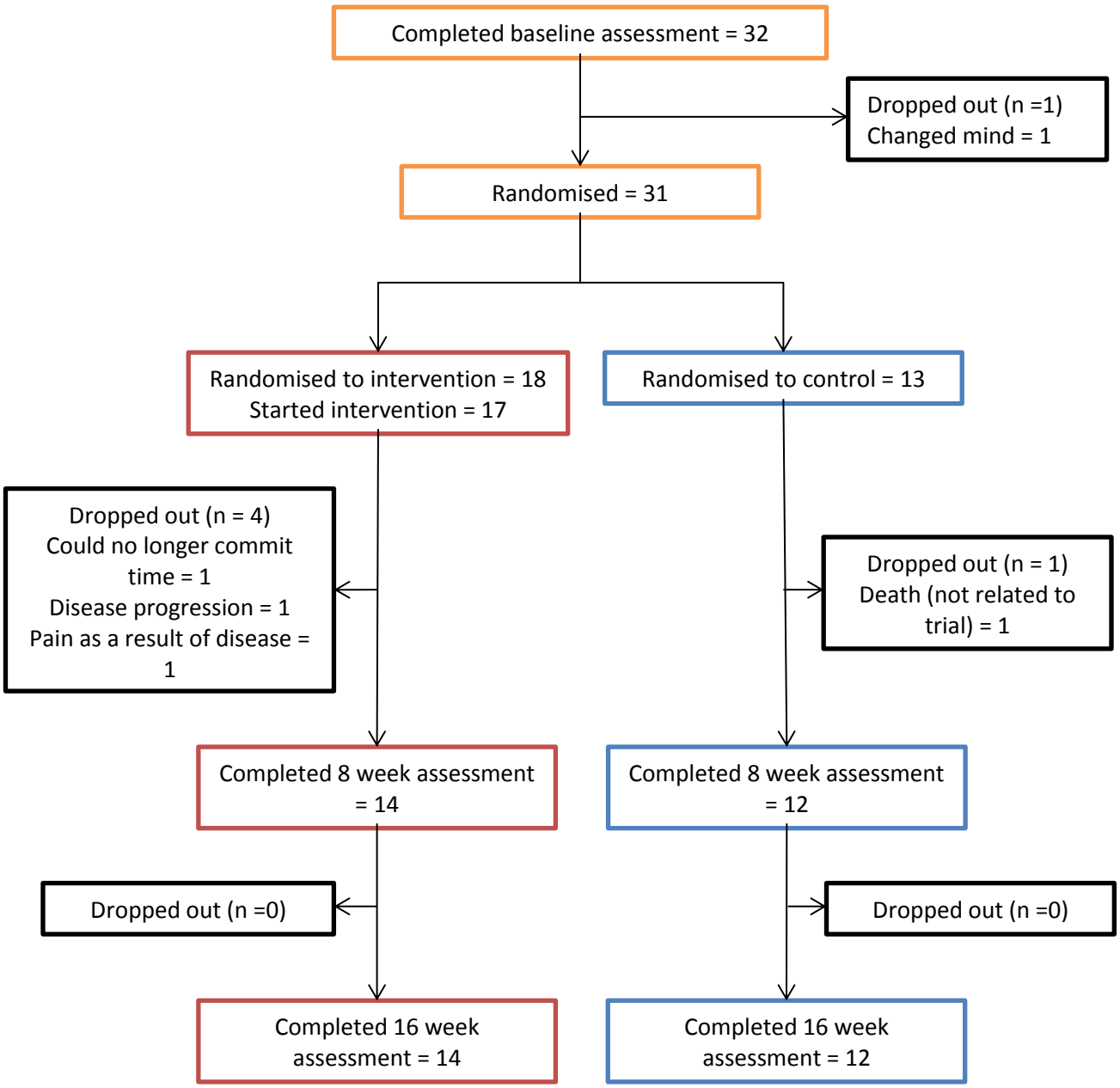

Figure 4.3 COMRADE trial recruitment diagram

Men randomised into the intervention group were given the choice of attending the university up to 3 sessions of supervised exercise a week. In total, adherence to the exercise sessions was 69% when combining the adherence data. A breakdown of the adherence at supervised exercise sessions based on number of days chosen to attend per week is given in table 4.3. Adherence to the exercise allocated in the exercise session was 100% as exercise was always adapted to the individual as described in section 2.3.1. Adherence to the whey protein supplementation was 68% (0-100%) and creatine supplementation 71% (0-100%).

Table 4.3 Sub-group adherence to exercise in days per week training

Number of agreed days per week exercise training (max 3)	n	Adherence (%)
1	3	51.1
2	6	63.3
3	5	78.8

The adherence to the independent exercise was 78% (i.e. patients reporting at least 30 min of aerobic exercise in their log books). With an average 117.42 minutes of moderate intensity exercise reported (BORG 11-14) and 42 minutes of high intensity exercise reported (BORG >14). Two participants failed to return their independent exercise diaries.

3.2.3 Safety

In total nine AEs were reported and six SAEs were recorded. Of the AEs, there were three instances of gastrointestinal discomfort associated with the supplementation and one instance of positional vertigo during a DXA scan. No other AEs were thought to be related to trial procedures. Of the SAEs there were no instances attributed to trial procedures. Breakdowns of the reported events are provided below. Table 4.4 presents the AEs and Table 4.5 the SAEs

Table 4.4 AEs reported in the COMRADE trial

Participant number	Date	Detail
COMRAD0010	13/05/17	GI discomfort from intervention supplements. Participant stopped taking supplements.
COMRAD0006	27/07/17	Ankle pain.
COMRAD0004	02/08/17	Positional vertigo during a DXA scan
COMRAD0017	13/09/17	Involved in road traffic accident. Fractured sternum. Not admitted to hospital.
COMRAD0017	19/09/17	Faint in bathroom. Received cardiology review and given all clear.
COMRAD0018	03/10/17	GI discomfort from supplements. Supplements stopped.
COMRAD0014	04/10/17	GI discomfort from supplements.
COMRAD0019	07/10/17	Fall in garden at home. Pain in left side.
COMRAD0013	13/11/17	Skin rash

Table 4.5 SAEs reported in the COMRADE trial

Participant number	Date	SAE details	Conclusion
COMRAD0015	18/09/17	Participant admitted to hospital with neutropenic sepsis (resulting from chemotherapy).	SAE not related to trial.
COMRAD0018	21/10/17	Initially reported as a UTI (and recorded as an AE, not SAE due to detail provided by participant), after obtaining detail from care team, the participant suffered haematuria and was admitted to hospital.	SAE not related to trial.
COMRAD0019	08/01/18	Participant reported to A&E with a flu-like illness. Admitted to hospital with pneumonia.	SAE not related to trial.
COMRAD0021	09/01/18	Participant reported to A&E with a flu-like illness. Admitted to hospital with a respiratory infection.	SAE not related to trial.
COMRAD0016	18/01/18	Participant died due to prostate cancer progression (control arm participant)	SAE not related to trial.
COMRAD0018	19/01/18	A second instance of haematuria for this participant. Admitted to hospital for treatment.	SAE not related to trial.

3.3 Secondary outcome measures

During assessments, some men were either unable to attend or undertake physical assessments, for example due to dropping out of the study, ill health or fatigue. As a result the number (n) of complete data for outcomes is indicated in the tables below.

3.3.1 Fatigue and prostate cancer specific quality of life questionnaires

Data for the FACT-F (Fatigue) and FACT-P (QoL) outcome measures are provided in table 4.6. Groups were well matched with no significant differences at baseline for FACT-P and FACT-F. There were 11 (85%) control and 13 (72%) intervention participants with complete data sets.

3.3.1.1 Effect size

There was a medium effect size for the increase in physical wellbeing domain of the FACT P (QoL) favouring the intervention group after 16 weeks (*d* = 0.602). There were no other notable effect sizes for all other outcome measures (*d* < 0.49).

Table 4.6 The change in fatigue and prostate cancer specific QoL outcomes from baseline to 16 weeks

Questionnaire	Control				Intervention				
	n	0 wk μ (SD)	16 wk μ (SD)	μΔ (SD)	n	0 wk μ (SD)	16 wk μ (SD)	μΔ (SD)	*d*
FACT-F	11	39.32 (13.88)	38.50 (12.18)	-1.87 (14.23)	13	30.70 (12.81)	33.92 (12.69)	2.75 (10.38)	0.37
FP Physical wellbeing	11	23.00 (6.52)	21.75 (6.40)	-1.27 (6.93)	13	20.00 (6.10)	22.15 (6.40)	1.77 (4.64)	0.60
FP family wellbeing	11	21.46 (7.67)	20.74 (7.61)	-0.24 (11.59)	13	20.84 (4.98)	22.62 (5.09)	1.13 (4.04)	0.16
FP emotional wellbeing	11	19.85 (3.47)	19.08 (4.10)	-0.02 (4.51)	13	17.69 (5.68)	17.31 (4.96)	0.08 (5.44)	0.02
FP functional wellbeing	11	22.92 (4.42)	20.26 (8.34)	-2.08 (7.64)	13	19.63 (7.45)	18.54 (5.87)	-0.54 (5.65)	0.23
FP sub score	11	35.93 (8.34)	33.90 (6.57)	-1.95 (8.52)	13	29.59 (9.97)	30.95 (7.67)	0.68 (7.02)	0.34
FACT-P total	11	123.49 (22.96)	115.73 (24.04)	-5.92 (30.99)	13	107.74 (25.47)	111.57 (25.45)	3.12 (15.19)	0.37

FP - FACT-P; wk - week

3.3.2 Physical outcomes

Data for physical outcome measures are highlighted in table 4.7.

The groups were well matched at baseline on physical outcomes. However, there were differences at baseline for leg press between groups (control μ = 99.32kg [SD = 23.078] vs 74.56kg [41.024]).

All participants had Karnofsky and ECOG data (intervention n =18(100%), control n =13(100%)). Weight and BMI data was available for 12 (67%) intervention and 9 (69%) control participants.

Some participants were unable to attend further physical assessment at 8 and 16 weeks. Subsequently there were 10 (56%) intervention and 8 (62%) control participants with complete data with the exception of the chest press outcome (intervention n =9 (50%) and control n =7 (54%). The reasons for inability to complete the physical assessments were bone pain, illness and progressive disease.

3.3.2.1 Effect sizes for physical outcomes

A moderate effect size was observed for weight (*d* = 0.737) and BMI (*d* = 0.552) both of which increased in the intervention groups versus the control (table 4.7).

A moderate effect size was also observed for the 3RM testing. Both the leg press (*d* = 0.597) and the chest press (*d* = 0.522) increased in favour of the intervention group when compared to the control (table 4.7). Accordingly, changes overtime in both of the 3RM testing showed improvements in the intervention groups vs the control (figure 4.4 and figure 4.5).

There were no other notable effect sizes for all other physical outcomes (*d* <0.49).

Table 4.7 The change in physical assessments from baseline to 16 weeks

Physical assessments	Control				Intervention				
	n	0 wk μ (SD)	16 wk μ (SD)	μΔ (SD)	n	0 wk μ (SD)	16 wk μ (SD)	μΔ (SD)	*d*
Weight (kg)	9	90.02 (13.45)	89.48 (13.01)	-1.13 (1.78)	12	97.10 (16.17)	97.69 (16.23)	0.62 (2.85)	0.74
BMI (kg/m²)	9	29.84 (4.24)	29.57 (4.45)	-0.28 (0.71)	12	31.95 (4.35)	31.98 (3.49)	0.15 (0.84)	0.55
ECOG (n)	9	0.08 (0.28)	0.44 (0.53)	0.33 (0.50)	12	0.22 (0.55)	0.83 (0.84)	0.50 (0.67)	0.28
KPS (n)	9	96.92 (11.09)	92.22 (9.72)	-3.33 (12.25)	12	96.67 (6.86)	87.50 (13.57)	-7.50 (12.15)	0.34
3RM Leg press (kg)	8	99.32 (23.08)	97.50 (43.10)	6.25 (17.88)	10	74.56 (41.02)	93.00 (33.10)	21.75 (32.06)	0.60
3RM Chest press (kg)	7	9.83 (2.54)	10.14 (1.65)	-0.21 (1.22)	9	10.69 (9.72)	8.55 (2.53)	0.72 (2.22)	0.52
Hand Grip Left (lbs)	8	32.82 (8.04)	32.51 (7.77)	0.40 (4.47)	10	29.80 (7.11)	32.45 (5.00)	2.04 (3.44)	0.41
Hand Grip Right (lbs)	8	35.63 (8.83)	36.04 (7.80)	-0.05 (4.86)	10	32.16 (6.14)	34.03 (6.29)	1.19 (4.08)	0.28
SMWT Average (m)	8	379.90 (103.35)	447.00 (215.86)	10.30 (23.49)	10	375.33 (97.79)	361.09 (49.32)	5.26 (75.43)	0.09
CSTS (n)	8	10.15 (2.79)	10.25 (3.91)	1.13 (2.70)	10	9.00 (3.28)	12.27 (4.90)	2.00 (1.56)	0.40
Mid arm circumference (cm²)	8	32.98 (4.65)	34.28 (3.81)	1.04 (0.77)	10	34.39 (4.30)	35.18 (4.09)	1.40 (2.12)	0.23

BMI - body mass index; ECOG - Eastern Cooperative Oncology Group; KPS - Karnofsky performance score; 3RM - Three repetition max; SMWT - Six minute walk test; CSTS - Chair sit to stand

3.3.2.2 Changes in physical outcomes at baseline, 8 and 16 weeks

Graphical data displaying the within group results of mean change from baseline in 8-week and 16-week physical outcomes is shown in figures 4.4 to 4.8.

3.3.2.2.1 Leg Press

Leg press weight was increased in the intervention group from baseline at 8 weeks (μΔ from baseline 21.26 kg) and 16 weeks (μΔ from baseline 21.75 kg), whilst men in the control group saw little change over the same period (μΔ from baseline to 8-week assessment 3.57kg and 16-week assessment 6.25kg).

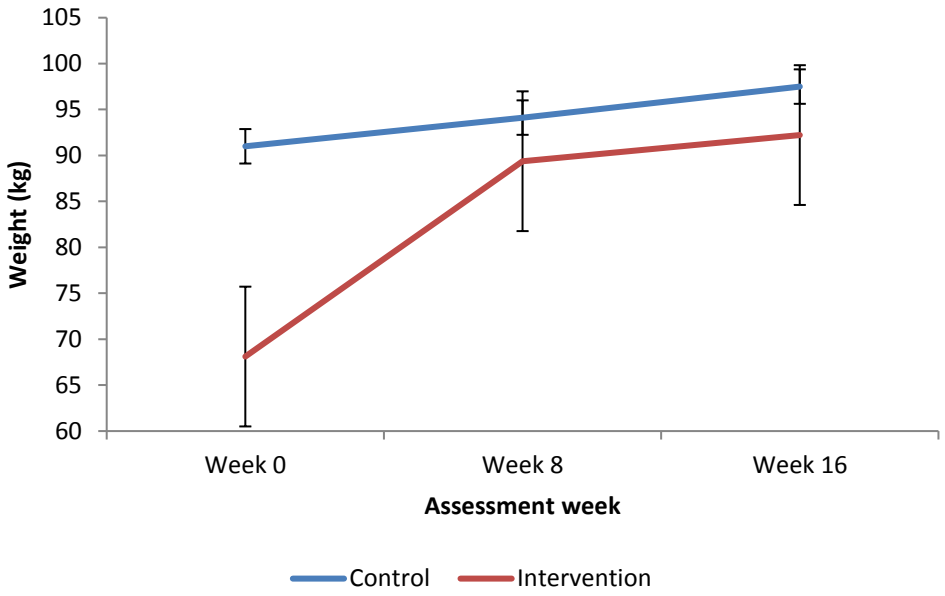

Figure 4.4 Leg press three repetition max testing for the intervention and control groups. Data is displayed as mean in groups and standard error bars.

3.3.2.2.2 Chest Press

For chest press weight was increased in the intervention group from baseline at 8 weeks (μΔ from baseline 0.23kg) and 16 weeks (μΔ from baseline 0.72kg). Men in the control group saw a fall in chest press weight over the same period (μΔ from baseline to 8-week assessment -0.14 and 16-week assessment -0.21kg).

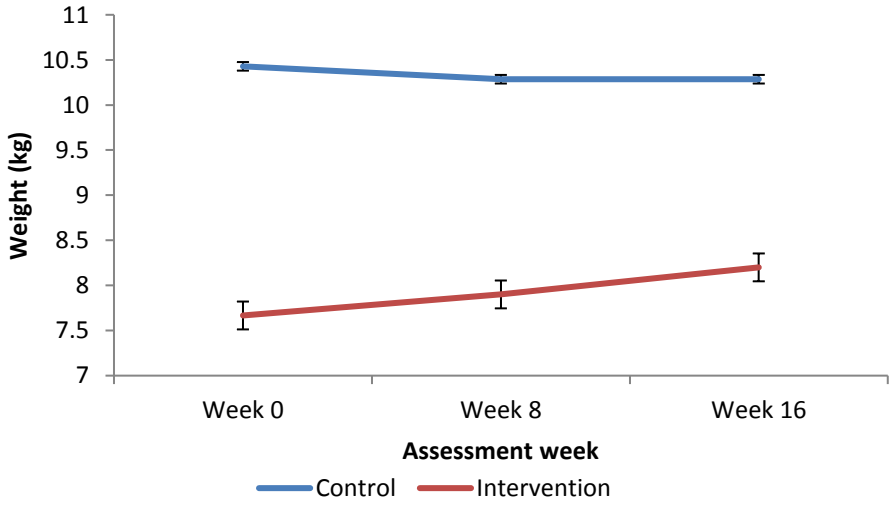

Figure 4.5 Chest press three repetition max testing for the intervention and control groups. Data is displayed as mean in groups and standard error bars.

3.3.2.2.3 Hand grip strength

For hand grip strength in the left hand there was an increase in the intervention group from baseline at 8 weeks (μΔ from baseline 1.70lbs) and 16 weeks (μΔ from baseline 2.04lbs). For the right hand there was no observable change from baseline at 8 weeks (μΔ from baseline -0.10lbs) but by the 16-week assessment the handgrip strength for the right hand had increased (μΔ from baseline 1.19lbs).

However, men in the control group initially saw a larger increase in left hand grip strength at 8 weeks (μΔ from baseline to 8-week assessment 5.00lbs) but this fell by the 16-week assessment (μΔ from baseline 16-week assessment 0.40lbs). A similar result was observed for right hand grip strength with an increase at 8 weeks (μΔ from baseline 6.5lbs) followed by a drop by 16 weeks to lower than the baseline result (μΔ from baseline -0.05lbs).

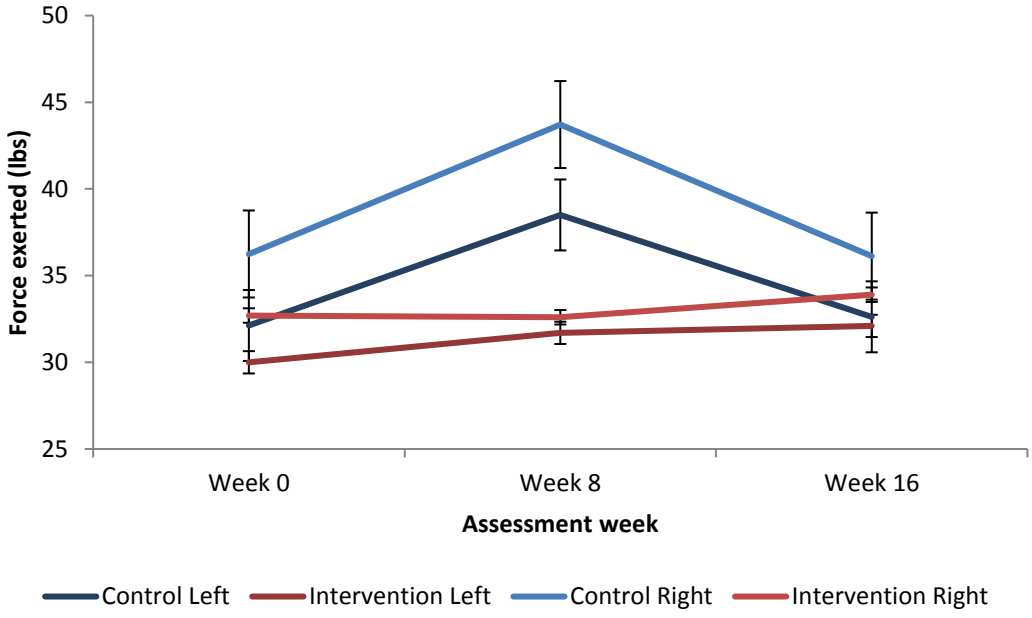

Figure 4.6 Hand grip strength testing for the intervention and control groups. Data is displayed as mean in groups and standard error bars.

3.3.2.2.4 Six minute walk test

For mean distance travelled in the six minute walk test there was no notable change in the intervention group at the 8-week assessment (μΔ from baseline 0.6m) but an improvement observed at 16 weeks (μΔ from baseline 5.40m). However, for the control group, there was a slight decrease in average distance travelled at 8 weeks

(μΔ from baseline -2.50m) with an improvement at 16 weeks (μΔ from baseline 10.30m) greater than that observed in the intervention. However, the effect size for this change was trivial (*d* = 0.090).

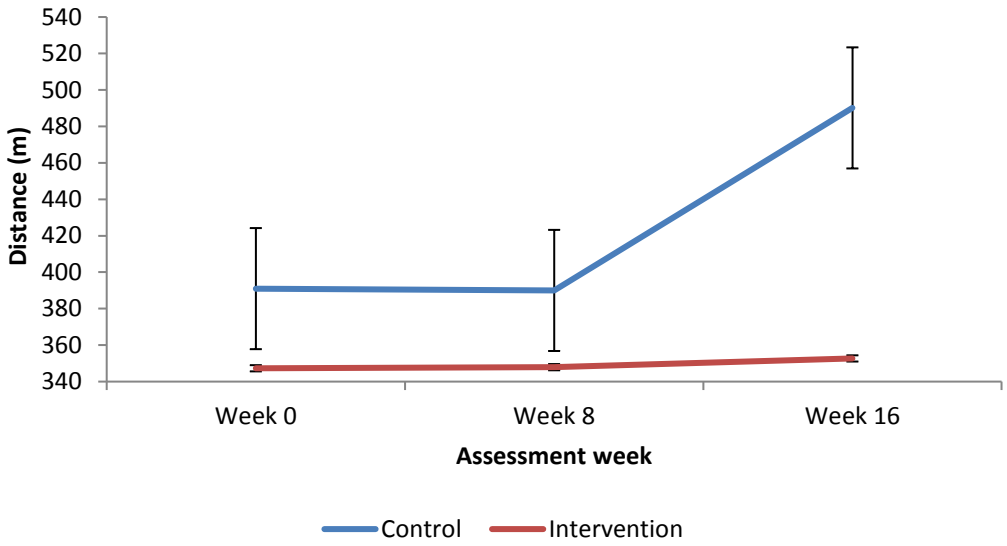

Figure 4.7 Six minute walk testing for the intervention and control groups. Data is displayed as mean of the best score in groups and standard error bars.

3.3.2.2.5 Chair sit-to-stand test

For the chair sit to stand test results had improved from baseline for both the 8-week and 16-week assessments in the intervention group (μΔ baseline to 8 week assessment n =1.10 and 16 weeks n =2.00). In the control group there was also an improvement from baseline to a similar degree to the intervention group at the 8-week assessment but this improved from the 8-week to the 16-week assessment with only marginally (μΔ baseline to 8-week assessment n =1.00 and 16-week assessment n =1.13).

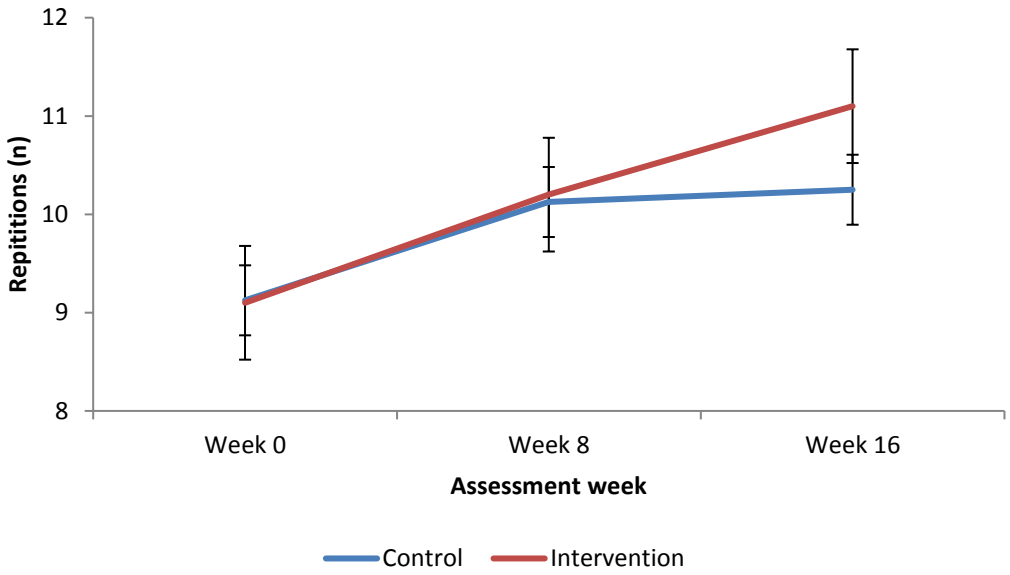

Figure 4.8 Chair sit to stand test for the intervention and control groups. Data is displayed as mean of the best score in groups and standard error bars.

3.3.3 Body composition outcomes

3.3.3.1 Lean indices

Data for lean indices are provided in table 4.8. Groups were well matched with no significant differences in lean indices between groups at baseline. Complete data was available for 9 (69%) control and 12 (67%) intervention participants.

A moderate effect size was observed for left arm (*d* = 0.740), right arm (*d* = 0.604), left leg (*d* = 0.702) and right leg (*d* = 0.604) lean mass which increased in favour of the intervention group when compared to controls. A large effect size was observed for trunk (*d* = 1.124), sub-total body (*d* = 1.529) and whole body (*d* = 1.432) lean mass, from baseline to 16 weeks, which increased in favour of the intervention group when compared to control. Although, with the exclusion of head lean mass, all of the lean indices increased in favour of the intervention group but demonstrated no notable effect size (d < 0.49).

Table 4.8 Change in lean indices from baseline to 16 weeks.

Lean indices	Control				Intervention				
	n	0 wk μ (SD)	16 wk μ (SD)	μΔ (SD)	n	0 wk μ (SD)	16 wk μ (SD)	μΔ (SD)	*d*
Head Lean (g)	9	3751.22 (332.28)	3766.24 (377.63)	-25.40 (143.30)	12	3825.50 (327.47)	3773.96 (274.33)	-38.84 (220.80)	0.07
Left arm lean (g)	9	3317.32 (447.69)	3330.06 (335.34)	-62.95 (260.31)	12	3183.07 (592.93)	3289.24 (583.34)	104.95 (187.86)	0.74
Right arm lean (g)	9	3413.12 (443.63)	3442.40 (437.45)	-41.21 (159.72)	12	3359.56 (605.16)	3448.20 (580.57)	59.82 (174.43)	0.60
Trunk lean (g)	9	29243.00 (26.62)	29495.96 (2773.03)	-431.62 (937.62)	12	29678.68 (3668.57)	30332.72 (4194.10)	1044.41 (1603.01)	1.12
Left leg Lean (g)	9	8578.04 (995.367)	8795.27 (1092.29)	70.94 (385.07)	12	8709.50 (1215.37)	9199.17 (1308.09)	309.80 (288.98)	0.70
Right leg lean (g)	9	8903.35 (1024.21)	9026.77 (919.75)	-41.21 (159.72)	12	8840.22 (1315.40)	9149.63 (1474.75)	59.82 (174.43)	0.60
Sub-total body lean (g)	9	53454.84 (5205.13)	54090.46 (5050.99)	-497.26 (1218.92)	12	53771.03 (7078.64)	55418.96 (7929.48)	1685.98 (1610.49)	1.53
Whole body lean (g)	9	57206.06 (5383.52)	57856.69 (5188.90)	-522.67 (1325.57)	12	57.59.53 (7266.34)	59192.92 (8138.93)	1647.13 (1683.73)	1.43

3.3.3.2 Fat indices

Data for the fat indices are given in table 4.9. There were differences evident in fat indices at baseline between groups for right arm fat % (control 37.40[8.51] vs intervention 43.80[5.23]); left arm fat % (control 32.13[8.93] vs intervention 44.19[5.23]) trunk fat % (control 34.73[8.28] vs intervention 39.74[5.32]); Right leg fat % (control 37.21[7.13] vs intervention 41.81[5.10]); sub total body fat % (control 36.18[7.38] vs intervention 41.00[4.57]) and whole body fat % (control 35.63[7.09] vs intervention 40.27[4.40]). The other fat indices were well matched between the groups at baseline.

A moderate effect size was observed for whole body fat % (*d* = 0.664), subtotal body fat % (*d* = 0.666), right leg fat % (*d* = 0.532), left leg fat % (*d* = 0.636) and left arm fat % (*d* = 0.644) all of which decreased in favour of the intervention group versus the control. A large effect size was observed for right arm fat % (*d* = 0.946) which decreased in favour of the intervention group versus the control. All other fat indices decreased in the intervention group relative to the control group however there were no other notable effects sizes (*d* <0.49).

Table 4.9 Change in fat indices from baseline to 16 weeks.

Fat indices	Control				Intervention				
	n	0 wk μ (SD)	16 wk μ (SD)	μΔ(SD)	n	0 wk μ (SD)	16 wk μ (SD)	μΔ(SD)	*d*
Whole Body fat (%)	9	35.63 (7.09)	34.67 (7.37)	0.10 (1.22)	12	40.27 (4.40)	39.19 (3.67)	-1.08 (2.20)	0.66
Whole Body fat (g)	9	32675.60 (9963.31)	31755.58 (9945.17)	-64.52 (1387.82)	12	39545.64 (9885.24)	38652.68 (8918.81)	-907.87 (3295.17)	0.33
Subtotal body fat (%)	9	36.19 (7.38)	35.20 (7.38)	0.09 (1.27)	12	41.00 (4.57)	39.85 (3.83)	-1.14 (2.30)	0.67
Subtotal body fat (g)	9	31355.28 (9835.67)	30477.53 (9845.37)	-51.59 (1387.86)	12	38092.06 (9806.42)	37238.97 (8866.34)	-884.41 (3263.33)	0.33
Right leg fat (%)	9	37.22 (7.13)	35.93 (7.63)	0.45 (1.80)	12	41.81 (5.10)	40.74 (5.85)	-0.65 (2.33)	0.53
Right leg fat (g)	9	5450.84 (1691.97)	5277.77 (1913.49)	88.51 (287.07)	12	6498.05 (1825.46)	6450.72 (2006.29)	-91.09 (589.30)	0.39
Left leg fat (%)	9	38.29 (6.41)	36.59 (6.81)	-0.22 (1.55)	12	41.61 (4.48)	39.91 (4.57)	-1.23 (1.64)	0.64
Left leg fat (g)	9	5462.6 (1584.02)	5241.19 (1742.99)	-16.55 (277.25)	12	6329.34 (1672.43)	6257.89(1871.70)	-104.33 (460.13)	0.23
Trunk fat (%)	9	34.73 (8.28)	33.89 (8.49)	-0.07 (1.81)	12	39.74 (5.32)	38.72 (3.79)	-1.28 (2.97)	0.49
Trunk fat (g)	9	116258.02 (5723.81)	15828.82 (5562.37)	-143.93 (1021.75)	12	20002.03 (5507.13)	19376.95 (4286.34)	-546.67 (1846.75)	0.27
Right arm fat (%)	9	37.40 (8.51)	37.04 (9.28)	0.63 (1.43)	12	43.80 (5.23)	42.45 (5.41)	-1.198 (2.33)	0.95
Right arm fat (g)	9	2123.70 (743.61)	2096.88 (689.10)	23.19 (152.12)	12	2685.15 (843.83)	2599.16 (765.88)	-103.60 (408.86)	0.41
Left arm fat (%)	9	37.13 (8.93)	36.94 (8.15)	0.59 (2.12)	12	44.19 (5.23)	43.11 (6.01)	-1.11 (3.07)	0.64
Left arm fat (g)	9	2060.08 (773.31)	2032.87 (656.29)	-2.81 (116.94)	12	2577.48 (776.58)	254.25 (766.58)	-38.71 (349.86)	0.14
Head fat (%)	9	26.05 (2.98)	25.36 (3.37)	-0.06 (0.22)	12	27.46 (1.78)	27.22 (2.00)	-0.09 (0.31)	0.10
Head fat (g)	9	1320.32 (179.87)	1278.05 (200.53)	-12.93 (56.29)	12	1453.58 (192.80)	1413.72 (157.71)	-23.46 (99.76)	0.13

3.3.3.3 Bone mineral density

Data for BMD is highlighted in table 4.10. There were baseline differences evident between groups for femoral neck BMD (control .71[.08] vs intervention .90[.14]) and total hip BMD (control .93[.10] vs intervention 1.03[.13]). All other BMD measures were well-matched between groups at baseline.

A large effect size was observed for hip BMD (*d* = 1.575) which decreased in the intervention group versus the control from baseline to 16 weeks. All other BMD measures decreased in the intervention group relative to the control group however there were no notable effect sizes (*d* < 0.49) except for head lean mass which only just reached a moderate effect size.

Table 4.10 Change in BMD from baseline to 16 weeks.

Bone mineral density (g/cm²)	**Control**				**Intervention**				
	n	0 wk μ (SD)	16 wk μ (SD)	μΔ(SD)	n	0 wk μ (SD)	16 wk μ (SD)	μΔ(SD)	*d*
Lumbar spine	8	0.98 (0.11)	1.03 (0.13)	0.01 (0.04)	12	1.01 (0.14)	0.94 (0.10)	-0.00 (0.04)	0.22
Femoral Neck	8	0.71 (0.08)	0.71 (0.08)	0.00 (0.02)	12	0.80 (0.14)	0.15 (0.12)	-0.00 (0.03)	0.12
Hip	8	0.93 (0.10)	0.97 (0.12)	0.01 (0.01)	12	1.03 (0.13)	0.97 (0.12)	-0.02 (0.02)	1.58
Whole body	8	1.14 (0.13)	1.13 (0.07)	0.01 (0.03)	12	1.14 (0.13)	1.09 (0.10)	-0.00 (0.02)	0.47
Subtotal body	8	1.04 (0.13)	1.04 (0.08)	0.01 (0.03)	12	1.03 (0.13)	0.98 (0.08)	-0.00 (0.02)	0.37
Head	8	2.01 (0.212)	2.01 (0.18)	0.03 (0.10)	12	2.15 (0.34)	2.05 (0.32)	-0.01 (0.05)	0.50

3.3.4 Blood serum outcomes

Data for the blood serum results are given in table 4.11. No notable effect sizes were observed between the two groups (*d*<0.49). Complete data was available for 10 (77%) control and 14 (78%) intervention participants.

Table 4.11 Change from baseline to 16 weeks in blood serum values

Blood serum results	**Control**				**Intervention**				
nmol	n	0 wk μ (SD)	16 wk μ (SD)	μΔ(SD)	n	0 wk μ (SD)	16 wk μ (SD)	μΔ(SD)	*d*
PSA (ug/L)	10	100.91 (195.95)	139.34 (385.23)	80.29 (266.55)	14	29.91 (72.28)	14.26 (24.83)	0.50 (21.40)	0.42
SHBG (nmol/L)	10	71.32 (36.85)	73.50 (28.19)	3.98 (29.04)	14	73.00 (47.14)	80.99 (51.32)	2.58 (9.17)	0.07
Testosterone (nmol/L)	10	0.48 (0.20)	0.48 (0.22)	-0.02 (0.32)	14	0.54 (0.22)	0.46 (0.14)	-0.05 (0.17)	0.06
LDH (IU/L)	10	425.77 (130.14)	383.60 (62.01)	-13.40 (41.33)	14	397.39 (81.52)	400.00 (74.92)	0.69 (31.71)	0.38

Blood serum local normal ranges: PSA ug/L (0.1-4.5); LDH IU/L (240-480); Testosterone nmol/L (6.7 - 25.7); SHBG nmol/L (20.6-76.7). * Prostate cancer risk management programme referral pathway PSA values are: 50-59 years 3.0 ug/L, 60-69 years 4.0 ug/L, 70 years and older 5.0 ug/L.*

3.3.5 Dietary outcomes

Data for dietary intake is given in table 4.12. Groups were well matched at baseline. Complete dietary data was obtained from 12 (92%) control participants and 13 (72%) intervention participants.

A moderate effect size was observed for calories (*d* = 0.555), sugars (*d* = 0.573) and fibre (*d* = 0.639) which all increased in favour of the intervention group compared to control. A large effect size was observed in protein intake (*d* = 1.620) which increased in the intervention group versus the control. No other dietary intake had a notable effect size (*d* < 0.49).

Table 4.12. The change in dietary intake from baseline to 16 weeks.

Average daily dietary intake	Control				Intervention				
	n	0 wk μ (SD)	16 wk μ (SD)	μΔ (SD)	n	0 wk μ (SD)	16 wk μ(SD)	IμΔ(SD)	*d*
Calories (kcal)	12	1837.00 (665.70)	1766.70 (645.50)	-111.17 (319.70)	13	1651.90 (355.70)	1782.40 (387.40)	77.92 (360.56)	0.56
Carbohydrates (g)	12	211.50 (88.30)	204.50 (81.70)	-13.17 (32.18)	13	189.60 (36.40)	181.00 (45.00)	-11.92 (53.09)	0.03
Sugars (g)	12	97.60 (60.70)	82.20 (49.60)	-20.57 (23.67)	13	92.10 (22.90)	86.50 (29.40)	-4.98 (30.30)	0.57
Protein (g)	12	82.70 (19.90)	74.30 (20.00)	-9.00 14.62	13	68.60 (18.30)	115.50 (33.50)	38.08 (38.40)	1.62
Fat (g)	12	67.20 (28.50)	68.10 (31.80)	-0.08 22.99	13	62.40 (23.30)	65.90 (22.30)	3.12 (19.14)	0.15
Saturates (g)	12	25.20 (11.30)	25.30 (12.50)	0.21 8.93	13	22.70 (9.80)	26.10 (7.60)	3.32 (6.37)	0.40
Fibre (g)	12	21.50 (7.00)	21.40 (8.90)	-0.94 (3.54)	13	17.10 (4.10)	18.60 (5.10)	1.35 (3.61)	0.64
Salt (g)	12	5.40 (2.00)	5.10 (2.40)	-0.23 (2.07)	13	4.80 (1.50)	5.20 (2.00)	0.34 (1.63)	0.30

3.3.6 Sample size calculation

The planning for the sample size in subsequent phase III RCTs should be based on clinically important changes in key health outcomes and taking into account patient attrition data observed in the phase II feasibility trial (Altman, Schulz et al. 2001). The key health outcome for men with CRPC chosen in the present study were prostate cancer specific QoL (FACT-P). Based on the FACT-P, the following can be calculated.

The power calculation to estimate sample size for a subsequent Phase III RCT was performed using the power calculation software (G*Power v3.0.10, Germany). A two independent samples test was undertaken with 95% power and 5% significance, using effect size (calculated from μΔ and SD) from the intervention and control groups.

When the mean change from baseline to 16 weeks in FACT-P (control μΔ (SD) = -5.92(30.99) vs. intervention 3.12(15.19)) the required phase III RCT sample size is estimated at 191 participants per group. Given a 16% dropout rate in the present study this would require a cohort of 444 in a two arm trial (222 in each group) patients in order to detect significance at α level of 0.05 with 95% power.

4. Discussion

4.1 Overview of the key findings

The primary aims of this present study were to determine the feasibility of a combined programme of dietary guidance, supplementation and resistance exercise in men with CRPC and its effect on key health outcomes in these men. The primary outcomes would address the feasibility of participant recruitment and determine the design for a potential further larger scale trial (Phase III RCT).

There was difficulty in recruiting this population to a feasibility exercise RCT. A recruitment rate of 13.5% was achieved. Of those recruited attendance was relatively good at 69% with the best attendance observed in those who opted to attend sessions three times a week. Adherence during attended sessions was 100% as exercise sessions were adapted per session as described in the methods (section 2.3.1) Adherence to independent exercise was excellent at 78.57%. Additionally, adherence to the supplements was relatively good at 68% for whey protein and 71% for creatine.

As such an intervention has never previously been trialled in men with CRPC, the findings of this study are novel. The study showed improvements within the intervention group in LBM indices and a reduction in fat mass indices corresponding with a decline in weight and favourable changes in BMI. In addition, improvements in 3RM testing and physical wellbeing scores were demonstrated in the intervention group.

Surprisingly, a decline in BMD was observed in the intervention group, although a notable effect size was only observable in the decline for hip BMD. This could be due to progressive disease but the reasons are unclear.

4.2 The feasibility of the lifestyle intervention

4.2.1 Recruitment and eligibility

The recruitment target for this phase II feasibility study was initially set at 50 participants which was not successfully met. A total of 31 participants were successfully recruited. However, a large majority of men with CRPC were deemed ineligible for this study due to extensive comorbidities (figure 4.2 CONSORT diagram). This reflects the complex nature of these patients at such an advanced stage of disease. A primary reason for ineligibility to this trial was unstable/painful bony metastasis, which is a common comorbidity that is extremely detrimental to the wellbeing of men with CRPC (Hotte and Saad 2010).

Other common reasons for ineligibility involved the inability to give informed consent due to the presence of neurodegenerative diseases such as Alzheimer's and dementia. There is some data to suggest that ADT increases the risk of developing such neurodegenerative diseases (Nead, Gaskin et al. 2017). A proportion of those who declined were under full time care (either at home, in a care-home, hospice or as a hospital inpatient). Although these reasons might not be directly linked to the presence of advanced prostate cancer, many within the population of men with CRPC are older adults and therefore have multiple comorbidities to contend with. Recruitment of older participants into research studies has previously been demonstrated to be difficult and more challenging than younger participants (Corbie-Smith, Viscoli et al. 2003, Murthy, Krumholz et al. 2004, Ahsan, Chen et al. 2006). However, despite this the average age of the study participants in this cohort was 70 years in the control and 73 years in the intervention, an average of 72 years, a population often considered under-represented in clinical research (Mody, Miller et al. 2008). This age group has previously been shown to have the lowest participation in cancer research studies with a 0.5% enrolment fraction in the 75 year and older groups (Murthy, Krumholz et al. 2004). In addition, the baseline demographics of the groups demonstrate the trial was able to recruit participants with multiple comorbidities including CVD, MSK comorbidity and metabolic disease (table 4.1).

In comparison to other prostate cancer and exercise studies, the men in this study were older (μ: 70.00 (5.49) control and 73.00 (6.56) intervention), had a higher BMI (μ: 90.00 (13.45) control and 97.10 (16.17) intervention) and a larger proportion had comorbid conditions, were retired, previous CAB/MAB, previous chemotherapy and node positive or metastatic disease (Bourke, Doll et al. 2011, Gilbert, Tew et al. 2016, Taaffe, Newton et al. 2017, Dawson, Dorff et al. 2018). However, these studies included men on ADT at earlier stages of disease, i.e. localised of locally advanced disease, so this was to be expected. This is a positive indication that although there were difficulties from recruiting from such a complex heterogenic population, there was not simply a selection bias for the "healthier" patients. The research team made a concerted effort to achieve a representative sample of men with CRPC undergoing treatment at STH. However, the men recruited into this study were all white and whilst this does represent the majority ethnic group in Yorkshire and the Humber (83.7%) the study failed to recruit any men from other ethnic minorities (Census 2011). This too is a problem commonly seen in the recruitment to research studies, including in prostate cancer trials (Murthy, Krumholz et al. 2004, Lane, Donovan et al. 2014, Hamdy, Donovan et al. 2016).

Men were either identified from oncology or urology clinic lists or from oncology treatment lists. However, in total 3607 patients were screened in the process which was time consuming and labour intensive. Of those screened, only 229 men were considered eligible (a 6% rate of those eligible to those screened) and the rate of recruitment was 13.5%. The rate of recruitment is similar to that which has been observed in previous cancer and exercise studies, reporting between 9.5%-19% recruitment rates (Thomas, Alvarez-Reeves et al. 2013, Gilbert, Tew et al. 2016, Thomas Gwendolyn, Cartmel et al. 2016). Given that men with CRPC are a dying population, it could be that the eligible population to recruit into this trial was too small within STH alone given only 6% screened were initially considered eligible. A solution to this would be a multi-site study.

4.2.2 Adherence

Adherence to the supervised and independent exercise was relatively good at 69% and 78.57% respectively. For supervised exercise, participants who opted to attend the maximum three sessions per week had the best adherence versus those who opted for two or one session a week (78.8%, 63.3% and 51.1% respectively). The

adherence was less than that which has been reported in other prostate cancer exercise trials, ranging from 69%-95% (Bourke, Doll et al. 2011, Gilbert, Tew et al. 2016, Dawson, Dorff et al. 2018, GalvÃO, Taaffe et al. 2018). However, a common reason for non-adherence to the exercise sessions was fatigue and illness. Particularly during the winter period, a number of participants were not able to attend due to ill health, which is common for a group on immunosuppressive therapies (Antonarakis and Armstrong 2011, Auchus, Yu et al. 2014). Furthermore, this finding is reflected in the high number of SAEs and AEs that occurred over the trial period, which included one death (control).

Two patients in the intervention group over this period spent time in hospital due to ill health, one of whom had a diagnosis of pneumonia. However, adherence to the independent exercise was excellent at 78.57%, which includes missing data from two participants. This adherence rate to independent exercise is similar to that which has been seen in trials of combination of supervised exercise and independent exercise in prostate cancer patients (Bourke, Doll et al. 2011, Gilbert, Tew et al. 2016). It could be that for men experiencing fatigue and illness in this study, the independent exercise was more accessible to them where they could fit the exercise around their "good days" rather than a scheduled session. Complete data on the assessment outcomes ranged from 56-92% inclusive of drop-outs, whereby the lowest number of complete data available was for the physical outcome assessments, specifically the 3RM testing. Participants reported common reasons for the non-participation of the physical outcome assessments was bone pain and fatigue. Although the figures completed assessments seem low, previous exercise studies of advanced cancer patients undergoing palliative care showed completion was 69% (Oldervoll, Loge et al. 2011). The adherence to the whey protein supplementation was 68% and creatine supplementation 71% which was comparable to the only other prostate cancer and whey protein supplement trial (72.0 ± 22.8%) (Dawson, Dorff et al. 2018).

4.2.3 Adverse and serious adverse events

There were three AEs associated with taking the whey protein which were all gastrointestinal disturbances consisting of constipation and/or acid reflux. Other than this, the whey protein was well tolerated. There was one episode of vertigo in a control participant who had a history of vertigo problems during his DXA scan. No other AEs or any SAEs were associated with trial procedures. This is more reflective of the

complexity of these advanced cancer patients with multiple comorbidities. Overall the COMRADE trial was viewed as safe.

4.2.4 Attrition

The overall attrition rate was 16% with four drop outs and one death in the control group. This is similar to that which has been observed in previous prostate and exercise trials, which ranged from 10-15% (Bourke, Doll et al. 2011, Gilbert, Tew et al. 2016, GalvÃO, Taaffe et al. 2018). However, the overall attrition was superior to that observed in the study by Taffe et al which was 34% (Taaffe, Newton et al. 2017). Furthermore, these figures were better than those seen in trials of advanced cancer patients however which have been reported to be as high as 36% (Oldervoll, Loge et al. 2011). Reasons for drop out were that the participant could no longer commit the time (n =1), disease progression (n =1), pain as a result of disease (n =1) and psychological morbidity (n =1). For the man that could no longer commit the time, he has specified that this was due to his frequent and ongoing visits to hospital. This again reflects the ongoing complications and burden of advanced and incurable cancer on these men.

4.2.5 Summary of feasibility findings

The feasibility data indicate that the described lifestyle intervention is feasible for men with CRPC. A responsive programme to the changing needs of the participant, with adequate duration, intensity and frequency, at such an advanced stage of disease would improve the programmes accessibility. It may be that for some, with a higher disease or comorbidity burden, a greater emphasis on home based exercise is warranted. In the present study, COMRADE was designed to be flexible as was recommended by the HCPs in Chapter 3. The exercises which were given had both progressions and regressions with a mixture of upper body and lower body exercises. Additionally, alternative exercises could be provided to minimise compressive loads to metastatic lesions whilst still targeting the required muscle groups. This approach was also adopted in the recently published study by Dawson et al (Dawson, Dorff et al. 2018). This approach was demonstrated as being well tolerated and safe in the current cohort. Subsequently, although adherence to the exercise sessions was 69%, compliance in these sessions (i.e. the completion of the exercises) was 100% as the exercises were adapted to the participant on a session by session basis and therefore there was no refusal to perform exercises.

The lack of studies reporting exercise interventions in advanced cancer patients undergoing palliative care has been recognised (Eyigor and Akdeniz 2014, Wittry, Lam et al. 2018). The approach to delivering exercise intervention studies should be different to that typically seen for cancer patients at earlier stages of disease. Advanced cancer populations are more heterogeneous in nature and are less predictable in their natural history, where some men can experience a rapid decline in health. Therefore, longer term interventions are exposed to the effects of disease progression as has been demonstrated in the present study. The present study has developed our initial understanding of how to make exercise programmes for castrate resistant prostate cancer patients feasible and the potential complications arising along the way.

4.3 Effect of intervention on secondary outcomes

4.3.1 Quality of life and fatigue

There were no notable changes in the FACT-P and FACT-F overall although there was a trend for overall improvement or maintenance of scores in the intervention group when compared to the control group which on average had declined. One sub score of the FACT-P questionnaire, physical wellbeing, showed a moderate effect in improvement in the intervention group (*d* = 0.602). Previous studies have demonstrated an improvement in FACT-P and FACT-F scores for men with prostate cancer with exercise training (Segal, Reid et al. 2003, Bourke, Doll et al. 2011, Dawson, Dorff et al. 2018). However, the men recruited into both of these studies were at much earlier stages of disease with a lower disease burden and there was a much larger sample size for all three studies, so it could be that the absence of these findings may be due to the lack of statistical power. Despite this the μΔ in FACT F and FACT P was n =2.75 and n =3.12 for the intervention group which is slightly better than the change reported by Segal et al, 2003.

4.3.2 Physical function

For the physical functioning tests, a meaningful effect size was observed for the 3RM testing in both chest press and leg press, which was also demonstrated in the trend over time at 8-week and 16-week assessments (Figure 5.4 and 5.8). These findings are similar to those in published studies suggesting improvements with exercise in prostate cancer patients with chest press and leg press maximal testing (Nilsen, Raastad et al. 2015, Taaffe, Newton et al. 2017, GalvÃO, Taaffe et al. 2018). Nilsen et

al showed improvement in strength in upper and lower extremities of 0.49 kg, p <0.01 and 0.15 kg, p <0.05, respectively (Nilsen, Raastad et al. 2015). Galvao et al showed significant improvement in leg press of 6.6 kg (95% CI 0.6–12.7; p =0.033) at 3 months (GalvÃO, Taaffe et al. 2018). Furthermore, a combination of physical functioning tests in the study by Taaffe et al which included 1RM testing of chest press and leg press showed significant improvement (p <0.001) with strength progressively increasing at 6 months and 12 months (p <0.001) (Taaffe, Newton et al. 2017).

The 2018 Galvao study in particular had a cohort of patients with metastatic disease, comparable to the cohort in the current study. In addition, Dawson et al also showed improvements in chest press and leg press with resistance exercise and whey protein supplementation in prostate cancer patients (Dawson, Dorff et al. 2018). Conversely the study by Sajid et al failed to showed a change in chest press repetition max testing (p =0.22) however this study was a home-based exercise programme (Sajid, Dale et al. 2016). In the present study, there were however differences at baseline in the leg press, this is likely due to the small sample size and the heterogenity of the CRPC population.

Similar to the present study, previous research in prostate cancer and exercise studies have also found no notable changes in the walk test and chair sit to stand test (timed up and go) (Dawson, Dorff et al. 2018, GalvÃO, Taaffe et al. 2018). The Oldervoll study of exercise in advanced cancer patients undergoing palliative care also showed no significant change in chair sit to stand but there was a significant improvement in the walk test (Oldervoll, Loge et al. 2011). Nilsen et al showed improvements in both chair sit-to-stand and the walk test (Nilsen, Raastad et al. 2015). Regardless, figure 4.8 did show a trend over time for the improvement in the chair sit to stand testing in the intervention compared to control.

For hand grip strength no notable changes were found which was similar in previous studies in prostate cancer groups (Sajid, Dale et al. 2016). However in advanced cancer patients undergoing palliative treatment, exercise interventions have been demonstrated to improve hand-grip strength (Oldervoll, Loge et al. 2011). However, figure 4.8 demonstrated that the change in hand grip strength in the control group whilst initially increasing at 8 weeks, fell to below baseline values at 16 weeks. A similar situation, although to a lesser degree, is observed in the control group values

for the 6 minute walk test. The lack of consistency in the change in mean for both groups may reflect problems and inconsistencies between assessors as multiple assessors were used in the physical function assessments or may be a result of the small sample size.

No notable changes to KPS or ECOG was observed in the present study. However, the association between performance scoring and functional status has been debated, where performance scoring has been deemed insufficient to accurately depict functional status when compared to objective measures (Atkinson, Andreotti et al. 2015, Kelly and Shahrokni 2016). A study in lung cancer patients suggested that objective measures such as $\dot{V}O_2$peak may be a useful in the clinical management of oncology patients and was superior to performance scoring such as ECOG (Roman, Koelwyn et al. 2014). In addition, given that the physical function assessments were conducted by more than one assessor, there were likely inconsistencies between the subjective reporting of PSs which may contribute as to why there was no observable change in PS despite improvements in some of the physical function outcomes.

Due to the low numbers recruited into this trial, it is likely the study was underpowered to demonstrate any notable changes in physical performance outcomes. However, there were changes to 3RM testing in the present study. It may be beneficial in the future to include a more aerobic aspect to the exercise programme if the aim were to facilitate improvement in cardiovascular fitness and therefore potentially physical performance outcomes. In the present study, there was an objective to improve LBM and therefore resistance exercise in combination with the dietary intervention was chosen as guided by the literature. However, it should be noted that compared to the other studies described, the present study is the only study to determine the effects of a resistance exercise and dietary intervention in men with CRPC who have a higher disease burden and have been on multiple treatments for up to two decades. Therefore, where this study has been unable to demonstrate a notable change in physical outcomes in these men, it could be that physiological changes are much harder to achieve over a period of 16 weeks and/or scope to achieve these changes is reduced given the disease burden in these men, compared to that seen in other studies in men at earlier stages of disease.

4.3.3 Body composition

There were favourable changes in body composition in the intervention group demonstrated in the present study. These findings also correlated well with the changes in weight and BMI both of which had a large effect size (d = 2.85 and d = 0.84 respectively).

For the lean indices, a moderate effect size (d > 0.6) was observed for left arm, right arm, left leg and right leg lean mass which increased in favour of the intervention group when compared to controls. In addition, a large effect size (d > 1.1) was observed for trunk, sub-total body and whole body lean mass which increased in favour of the intervention group when compared to controls.

For the fat indices, a moderate effect size (d > 0.5) was observed for whole body fat percentage, subtotal body fat percentage, right leg fat percentage, left leg fat percentage and left arm fat percentage; all of which decreased in favour of the intervention group versus the control. In addition, a large effect size was observed for right arm fat percentage (d > 0.9) which decreased in favour of the intervention group versus the control. However, these results should be viewed with caution as baseline differences were observed between groups in fat percentage for right arm, left arm, trunk, right leg, sub total body and whole body. This could be down to the small sample size and number of available measures for the DXA scan. For all other indices there was a trend in the intervention group for a reduction in fat mass in comparison to the control group.

There was however, no observable change in mid arm circumference which is an indicator for muscle hypertrophy. Previous studies of exercise in cancer patients also found no change in mid arm circumference or in muscle thickness observed by ultrasound (McKenzie and Kalda 2003, Galvao, Nosaka et al. 2006). Given that DXA results indicated changes in lean mass for both right and left arms, this result indicates the ineffectiveness of mid arm circumference in measuring changes of lean mass in this study. This may be due to the short time frame of the intervention but also the corresponding reduction in fat mass which may confound the finding of muscle hypertrophy.

The changes in body composition found in the present study are an important finding. Multiple studies evaluating resistance exercise training or with resistance exercise

included as part of an exercise programme in prostate cancer patients have failed to show any improvements in LBM and/ or favourable changes in body fat indices (Segal, Reid et al. 2003, Nilsen, Raastad et al. 2015, Sajid, Dale et al. 2016, Winters-Stone, Lyons et al. 2016, GalvÃO, Taaffe et al. 2018). These results support the findings which demonstrated improvements in physical function outcomes. The present study was able to demonstrate that despite the long-term effects associated with ADT and chemotherapy these men face, favourable changes to body composition can be achieved with a programme of exercise, dietary guidance and supplementation.

Dawson et al, 2018 demonstrated increases in FFM, LBM and appendicular skeletal mass comparable to the present study. Galvao et al which combined both aerobic and resistance training in prostate cancer patients also showed improvement in total body upper limb and lower body lean mass (Galvão, Taaffe et al. 2010). Another study, of a 12-week endurance training programme, whilst demonstrating a decrease in the intervention group for fat mass failed to demonstrate an increase in lean body mass (Hvid, Winding et al. 2013).

An unexpected finding in the current study was the trend for a lower BMD in the intervention group compared to the control group. For hip BMD, this decline had a large effect size. However, there were differences at baseline between the groups which could account for this finding potentially due to the low sample size. Equally this could be due to changes in medications in the intervention group that have not been accounted for. It seems unlikely that the whey protein, creatine or resistance exercise would cause a decline in BMD due to a large body of evidence to the contrary where BMD is either improved or maintained (Tarnopolsky, Zimmer et al. 2007, Alves, Murai et al. 2012, Cheung, Zajac et al. 2014, Winters-Stone, Dobek et al. 2014, Gwendolyn, Brenda et al. 2017). In essence, it is not clear what may have caused this decline in BMD.

4.3.4 Blood serum

There was no notable effect observed on blood serum results in the present study. Although PSA was maintained in the intervention group when compared to the control which rose, this finding was not of a notable effect size. Similar findings have observed the maintenance of blood serum markers such as PSA and testosterone demonstrating the biochemical safety of exercise interventions in prostate cancer

cohorts (Galvao, Nosaka et al. 2006, Bourke, Doll et al. 2011, Taaffe, Newton et al. 2017). A study with a longer duration might promote a more substantial change in blood serum markers, but it was not an aim of the present study to demonstrate alteration in markers of disease burden, only to ensure the study's biochemical safety.

4.3.5 Dietary changes

A moderate effect size (*d* >0.5) was observed for calories, sugars and fibre which all increased in favour of the intervention group compared to control. A large effect size was observed in protein intake (*d* >1.620) which increased in the intervention group versus the control. It should be noted that the reporting in the three day diet diaries was very poor and therefore was a serious limitation to the accurate analysis of diet. This is not an uncommon finding in research (Schoeller 1990, Subar, Freedman et al. 2015). As a result, the author advises that these results are interpreted with caution. The increase in calories and protein was an expected finding due to the protein supplementation. Aside from this, the results did not differ from that previously reported in dietary analysis of prostate cancer patients undergoing an exercise intervention (Bourke, Doll et al. 2011).

5. Study limitations

As previously mentioned, the major limitation of this study was the number of participants. In addition, there was missing data for a number of the outcomes assessed. This was in the intervention group predominantly which could introduce a bias to the findings, where potentially the men who were less able could not perform the assessment and therefore an inflation of the effects in favour of the intervention group may exist. Alternatively, it is possible that where similar studies were able to demonstrate meaningful changes in outcomes where this study failed, due to the study being under powered. The original target for recruitment was set at 50 participants, which the present study failed to meet. This is despite extensive numbers of patients screened. As mentioned previously, this could be due to these men being in the terminal phase of their disease, with an average 22-24 months life expectancy upon the diagnosis of CRPC. This is reflected in the observation that the rate of recruitment was similar to that seen in other studies of exercise in cancer patients (including advanced cancer patients undergoing palliative care). Whilst it is clear that there is a group of CRPC both eligible and willing to participate in such studies, recruitment from

a single site is a limitation where the required numbers of these men are simply not there. The sample size calculation suggest a sample of n =444 for a two arm trial based on the findings for the FACT-P questionnaire. A phase III multi-site trial design could address the issues of a low recruitment rate and the lack of representation of ethnic minority groups. Where a multi-site trial design may also enable the recruitment of a more ethnically diverse cohort.

An additional difficulty in this study was the use of multiple assessors for the physical assessments. This may have introduced inconsistencies where participants may have had more or less encouragement during physical assessments or where there were inconsistencies in reporting. This may explain the discrepancies in changes at eight and 16 weeks in the control group, where average change dramatically increased at 8 weeks and fell at 16 weeks in hand-grip strength testing and fall at 8 weeks then increase at 16 weeks in the 6 minute walk test.

The lack of availability of researchers was also a problem during the exercise sessions. For safety reasons, the men in this study had to be "spotted" for each exercise involving free-weights which meant there was a limit to how many men could be safely supervised during an exercise session with a single researcher. Although in this study, voluntary exercise instructors were adopted into the trial part way through, they were not dedicated researchers to this trial they were present on an ad hoc basis. Although they were given the study SOP (appendix 13) and briefed/ inducted as to how sessions should be undertaken by the man researcher (RG) for consistency, it would be more beneficial to more formally train all instructors to standardize procedures, which was not feasible in the present body of work. Furthermore, during the exercise sessions no data on RPE were recorded. RPE data (using the BORG scale) would have given a greater insight and help to quantify the intensity of the exercise sessions attended on an individual basis as well as preferences for exercise.

The randomisation procedures in this study were also a logistical limitation. Simple randomisation was adopted, but as a result, the randomisation schedule placed 80% of the first ten men in the control group and 70% of the last ten men into the intervention group. This caused a potential bias in that the last ten men (predominantly intervention), when compared to the first ten (predominantly control) who were recruited over the summer, were in the trial over the winter months and therefore

experienced more AEs due to winter colds and general illness causing a degree of variance between the groups. In addition, this caused problems for an increased workload for the researchers over the winter period which resulted in significantly reduced time available for recruitment. A future trial might adopt a permuted block randomisation procedure to ensure balance across treatment groups where participants are randomly allocated to a group within a time frame. Each “block” of participants would have a specified number of randomly ordered treatment assignments. The example below demonstrates blocks of ten participants: **Intervention group** (A) and **control group** (B)

Block 1: BAAABABBAB.

Block 2: ABABBABABA.

Block 3: AAABBBAABB.

Another limitation experienced in this trial was the adherence to the supervised exercise, whilst the independent exercise had excellent adherence (despite two missing independent exercise diaries). As previously described, a major problem with the complex group of patients recruited into this trial was the comorbid conditions and ill health experienced by these men, reflected in the high number of AEs and SAEs particularly over the winter period. A potential solution to this would be a longer term study, where effects of periods of ill health and therefore a drop in trial adherence may be attenuated. For participants who have fallen to ill health and are therefore required to take time out of the study, upon their return this would also allow the time required to enable the study participants to regain some strength and recover. This would potentially provide a better indication of the changes to secondary outcomes assessed in the present study.

The present study did not adopt behavioural change techniques. It has been recommended that behaviour change be incorporated into studies which aim to increase exercise in cancer patients and confer long-term behaviour change (Bourke, Homer et al. 2013, Roberts, Fisher et al. 2017, Bourke, Turner et al. 2018). Behaviour change techniques have been shown to confer improvements in moderate-vigorous physical activity and promoting better adherence to exercise interventions (Roberts, Fisher et al. 2017).

Furthermore, more extensive preliminary work would have benefitted the trial design with the addition of patient focus groups prior to the trial starting. Earlier preliminary work may have helped to identify the problems that were observed with patient recruitment and helped in defining recruitment techniques. It may also have helped to identify the day to day barriers to exercise patients experience related to their ill health. For example, it may have been possible to develop a more robust at home programme which participants could adopt as a substitute for supervised exercise during periods where their health had declined.

In terms of study outcomes there were two main limitations to this study. The first was the poor reporting of the three day diet diaries. There was significant difficulty in analysing the diet diaries due to poor reporting of portion sizes and lack of detail on foods consumed. For example terms like "fish with broccoli and peas" gave no information on the size or type of fish, how the fish was cooked nor the portion size of the vegetables. As a result, many of the food reported in the diet diaries had to be omitted and therefore there was serious limitation in any conclusions which could be drawn from the dietary analysis. Problems with the underreporting in diet diaries is well known, however currently there exists no form of dietary recall that does is not affected by this limitation (Johnson Rachel 2012). An approach which may better the reporting in future trials would be a higher quality diet diary with a more extensive explanation on correct completion and additional examples given. In addition, this could be supported by the researchers giving a greater deal of time to go through such examples and instructions. Furthermore the adoption of a 7 day exercise diary would ensure that both weekday and weekend dietary data would further enrich the data giving a greater insight into dietary and nutritional changes. However, given the present limitation described, it would likely be more beneficial in proceeding studies to use the 3 day diet diary with a refined and improved approach first, as some men may find 7 days' worth of dietary recording cumbersome.

The use of the DXA scan to obtain data on body composition could present as a limitation. DXA scans, although are able to give data on both fat, bone and muscle, are not the most accurate measure of lean mass changes. CT imaging allows for quantitative assessment of individual muscles and muscle tissue composition can be quantified, either by separate segmentation of muscle and adipose tissue or by analyzing muscle density, both of which cannot be done using the DXA scan (Buckinx,

Landi et al. 2018). However, the DXA scan still provides a much lower dose of radiation compared to CT and is less expensive (Buckinx, Landi et al. 2018).

In addition, no record of changes in exercise behavior were recorded. Particularly for the control group, there is a risk of contamination due to the study being single blinded, a common limitation of exercise trials (Steins Bisschop, Courneya et al. 2015). The adoption of a measure of exercise behavior would help to quantify any contamination in the control group where they may have increased their exercise behavior as a result of being recruited into this study. Exercise behavior could be assessed in a future study with the use of the Godin Leisure Score Index questionnaire which has been adopted in other exercise trials of cancer patients (Bourke, Doll et al. 2011).

6. Conclusions

The aim of this study was to investigate the feasibility of a lifestyle intervention of supervised resistance exercise, dietary supplementation and dietary advice in men with CRPC. The recruitment rate of the present study was similar to previous studies. In addition, adherence to the supervised exercise, independent exercise and supplementation was sufficient in the intervention group. Whilst the number of AEs and SAEs was high in the present study, this predominantly reflects the complex nature of such an advanced cancer population than being related to the study itself. The dropout rate in the present study was also similar to that which has been observed in previous exercise trials.

In conclusion, despite the number of significant barriers these men face, compared to the healthier cohorts often recruited into complex lifestyle interventions of exercise, these men have demonstrated that a trial of exercise, dietary supplementation and dietary guidance for men with CRPC is both feasible and safe however the author suggests that for a subsequent trial changes be made to mitigate the limitations found in the present study.

Chapter 5 Participant reported experiences of COMRADE

1. Introduction

Whilst chapter 4 has reported the quantitative findings of the COMRADE feasibility trial, it did not report the participant's experience of the trial. Participant insights have the potential to further our interpretation and understanding of the observed trial findings within the context of what is acceptable and meaningful to participants (Malterud 2001). A qualitative approach, using participant focus groups can generate an understanding of the processes by which the COMRADE intervention may influence QoL and wellbeing for men with CRPC. Understanding the importance of any lifestyle intervention effects within the participants own personal context by obtaining detailed, information data based upon participants' interpretation of their experiences enables researchers to understand the meaningfulness of any benefits received. In addition, addressing the acceptability and tolerability of the trial procedures provides information for the design and planning of future studies (Moore, Carter et al. 2011). With this information a tailored intervention, with a superior trial design, may help to maximise trial adherence (Sekhon, Cartwright et al. 2017).

In this cohort of men, who are typically under-researched in terms of supportive care we can only hypothesise what barriers to exercise or to the COMRADE trial they have experienced. Furthermore, given the limitations described in chapter 4, namely - difficulty with recruitment, high rate of AEs, poor reporting of diet diaries - it was important to explore further with the participants why they choose to take part in the trial and their acceptability of the intervention procedures and study design. The benefit of focus groups over other qualitative approaches such as interviews are that the participants can share and compare their experiences with each other, develop and generate ideas and explore issues of shared importance (Breen 2006). The use of post study focus groups have been recognised as a valuable methodological approach for understanding participant experiences of complex social interventions (Mays and Pope 2000, Neuman 2013). Therefore, participants' in the COMRADE feasibility RCT were invited to attend post-study focus group to qualitatively share their experiences and views of the trial.

The aim of this study was to explore the experiences, opinions and views of participants in the feasibility RCT to inform the design and running of a potential subsequent study.

Objectives:

1. Determine motivations of the participants for entering the trial.
2. Explore the previous experience of exercise training in men with CRPC prior to participation in COMRADE
3. Explore the current experience of exercise training in men with CRPC within COMRADE (i.e. exercise intervention) and outside of COMRADE.
4. Explore the barriers and facilitators to exercise training and physical activity of men with CRPC both within and outside of the COMRADE trial.
5. Evaluate patient reported acceptability of trial procedures and trial conduct.

2. Methods

In complex interventions, it is crucial that attempts are made to unpick the multiple components effecting the implementation of an intervention. In such cases, an evaluation such as that of participant focus groups or interviews are a valuable research method to make sense of some of the findings and observations experienced in the study. A process evaluation in trials, as recognised by the MRC, "…*can be used to assess fidelity and quality of implementation, clarify causal mechanisms and identify contextual factors associated with variation in outcomes.*" (Moore, Audrey et al. 2015). Although an in-depth process evaluation was not conducted as part of this body of research, the focus groups were used as means to qualitatively explore a detailed understanding of the processes' of the intervention functioning on a small scale (Moore, Audrey et al. 2015). The benefits of using focus groups compared to other research methods such as one to one interviews are the ability for focus groups to capitalize on communication and interactions between research participants (Mays and Pope 2000). The group dynamic of focus groups enable the participants to hear each other's lived experience and perspectives which can stimulate new thinking and insights; creating an environment for sharing, reflecting and refining thoughts.

2.1 Study design

The approach to the analysis of the data was deductive and framework analysis was seen as the most appropriate because the objectives of the focus groups were set in advance rather than emerging from a reflexive research process (Mays and Pope 2000). The overall analytical process however, resonates with the thematic approach, but with the framework approach it is more explicit and informed by *a priori* reasoning

(Mays and Pope 2000). The framework approach involves familiarisation, generating codes and identifying a thematic framework, indexing/coding, charting and finally mapping and interpretation.

2.2 Research governance

2.2.1 Ethics and research and development approval

This study was approved by NRES Committee South West - Cornwall & Plymouth (15/SW/0260) and in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK. All Management permissions were sought from the relevant NHS organisations involved in the study in accordance with NHS research governance arrangements (appendix 14).

2.2.2 Informed consent

Full informed written and verbal consent was obtained from each participant before the commencement of the focus groups (appendix 18).

2.2.3 Confidentiality

Focus Group transcripts were anonymised by allocating each participant a number to protect the identity of all participants. All data was kept on a password protected drive or encrypted on a password protected USB. No identifiable information was released into the public domain or published. No participant withdrew consent, but if they had chosen to their data would have been confidentially destroyed.

2.3 Sample and setting

2.3.1 Sampling

Purposive sampling was used to identify 15 participants in total, from the intervention and control arms of COMRADE, with 4-7 participants per focus group. This included participants who experienced AE/SAEs during the trial, participants with trial completion over six months ago, participants with trial completion within the last six months, those who failed to complete all study trial assessments, and participants who had experienced the exercise sessions on a one-one or group format (where more than one participant in the intervention arm was also undergoing supervised exercise). This was done to facilitate conversation between the participants regarding differences and similarities in experiences.

Men who had dropped out of the COMRADE study were not included in the post study focus groups. Two of these men were not contacted as they had died before they could be invited to take part in the focus groups. Furthermore, two other men whom had dropped out very early into the trial had significant progressive disease and subsequently died in June 2018. The final man was not contactable after he had decided to drop out. All of these men were intervention participants, and two of four of these men did not attend a single exercise session. Furthermore, the men who dropped out of the study were already asked questions regarding reasons for their drop out which are in chapter 4.

2.3.2 Inclusion criteria

- Participants who had been randomly allocated to either the Control or Intervention trial arms of COMRADE and had completed the 16-week follow up.
- Participants who were able to attend the date of the focus group.

2.3.3 Exclusion criteria

- Participants whom were not randomised as part of COMRADE
- Participants who did not successfully complete the 16-week follow up period of COMRADE.
- Participants unable to attend the date of the focus group.

2.4 Recruitment and data collection

2.4.1 Recruitment

Participants were identified from the COMRADE participant log. The participants were initially contacted via a telephone call (by the author); if unavailable a voicemail message was recorded requesting a response if they had an interest in the participation of the focus group. After a briefing over the phone, if the participant expressed an interest in taking part in the focus groups the date and time of the focus group was confirmed to them.

2.4.2 Data collection

Focus groups were conducted face to face with between four and seven participants present and up to two researchers present (the author and a study researcher (RT)). Focus groups were conducted by the author and RT guided by the focus group interview schedule. As new insights were offered these topics were explored. The

focus groups were digitally recorded (encrypted Olympus DM-650 Digital Voice Recorder) and then anonymised.

2.5 Focus group interview schedule

The focus group interview schedule was semi-structured with open ended questions and prompts to allow the participants to express their views and opinions. The focus group interview schedule consisted of 43 questions for the intervention group and 28 questions for the control group. Although all questions were intended to be asked, if the context of a question was addressed in the focus group during discussion then it was omitted. These questions covered motivations and apprehensions before taking part in the trial; previous experience of exercise; evaluation and acceptability of the general trial procedures; acceptability of the COMRADE exercise intervention; engaging with the dietary advice and supplements; support and present experience of exercise post trial. The interview schedule was designed to be inductive with some deductive reasoning. The detailed interview schedule can be reviewed as appendix 28.

2.6 Data analysis

Data analysis using the framework approach is described previously in Chapter 3 section 3.5, but has been summarized below.

Digital recordings were transcribed verbatim by an independent transcription service (JHTS audio and transcription service, www.jhts.co.uk) and the data coded via Nvivo10 software (Version 1.0, by the author). Using the thematic framework analysis approach, familiarisation with the transcripts was first performed and then initial codes were generated.

Initial codes were then related to final themes and sub-themes and analysed according to a thematic framework analysis (Gale, Heath et al. 2013). The analytical framework was then refined and codes grouped together where they were conceptually related. This generated a total of 99 codes in 9 categories. These categories subsequently formed the final three superordinate themes and nine subordinate themes (appendix 27).

All transcripts were double coded by a second researcher (HC) to ensure reliability and rigour of the data analysis. There were no discrepancies in coding between the

author (RG) and HC. The data were then charted into the framework matrix of superordinate themes mapped against verbatim quotes from each focus group. The analytical framework was then refined and codes grouped together where they were conceptually related. An example of an extract from the table is given in appendix 28. The framework was then verified by a third party researcher (DB).

2.6.1 Qualitative data analysis options

As the approach to the analysis of the data was deductive, framework was seen as the most appropriate form of analysis because the objectives of the focus groups were set in advance rather than emerging from a reflexive research process (Mays and Pope 2000). The overall analytical process however, resonates with the thematic approach, but with the framework approach it is more explicit and informed by *a priori* reasoning (Mays and Pope 2000).

2.6.2 The framework approach

Framework analysis is a systematic analytical approach to qualitative research. It is a matrix based method for ordering and synthesizing qualitative data and was developed by Jane Ritchie and Liz Spencer in the 1980s for large scale policy research (Ritchie and Spencer 2002) but is now widely used in health research (Gale, Heath et al. 2013). In the context of these focus groups framework analysis was chosen as it was the most pragmatic approach to systematically facilitate rigorous and transparent data management without losing sight of the "raw data" and enabled the classification of the data into key themes and sub themes, judged comprehensively.

2.6.3 The method of the framework approach

The analysis was carried out in a 6 step approach including familiarising with the data; generating initial codes; searching for themes; reviewing themes; devising and naming themes and producing the report (Braun and Clarke 2006).

2.6.3.1 Familiarisation

Before any attempt to sort through the data was made, there was a process of data familiarisation. Transcripts and observational field notes were read and re-read and recordings were listened to in order to fully immerse oneself with the data in advance of any kind of analytical stage.

2.6.3.2 Generating initial codes and identifying a thematic framework

After initial familiarisation, a process of "open coding" was conducted. This included analysis of a section of an intervention group transcript and the coding of data which was felt to have relevance to the research aims and objectives (such as opinions, attitudes, behaviours or views). Each of these initial codes was accompanied with a note to clarify its meaning.

2.6.3.3 Indexing/coding

Coding aims to classify all the data and enable a systematic comparison between the different data sets. Codes are grouped together in categories which are clearly defined to generate themes and subthemes (Gale, Heath et al. 2013). Coding was conducted electronically using the programme Nvivo by RG. A second researcher (HC) manually coded transcripts. Indexing indicated which themes in the text were being discussed. Once data had been coded a thematic framework was developed consisting of themes and subthemes. Initial themes were more descriptive rather than analytical or abstract.

2.6.3.4 Charting

Once the main themes and subthemes had been identified, reviewed and finalised between the researchers, a matrix was created to help delineate the data set. Each column of the matrix was headed with each theme and each row with each focus group number demonstrated in appendix 28. The relevant sections from each coded transcript were then summarised and entered into the framework matrix so the text can easily be navigated and comparisons can be made between the groups. For each focus group summary, selected information was taken from each transcript in order to reflect meaning without losing content. The transcription conventions were:

- *Italics* - Direct quote
- … - Quote has been abridged
- [word] - Where the author has clarified the meaning or phrase from the quotation

2.6.3.5 Mapping and interpretation

Once charting was complete a more refined analysis of the data set was possible with a deeper immersion into the content of the transcripts. Summaries of each theme were made from identifying relationships between the quotes and links between the data as a whole, providing explanations for the findings and overarching themes (Ritchie and Spencer 2002). This included drawing comparisons between the transcripts

highlighting any conflict/consistencies in key terms/ phrases/ descriptions/ views or explanations. Explanations and conclusions were drawn from the analysis, this can be explicit (originating from the participants descriptive statements) or implicit (identified by the analyst). After the final analysis the data were categorised into a priori themes or new themes were constructed as appropriate (Ritchie and Spencer 2002).

2.6.4 Ensuring quality within qualitative research

Quality in qualitative research is multifaceted and includes consideration of the importance of the research question, the rigor of the research methods, the appropriateness and salience of the inferences, and the clarity and completeness of reporting. Although there is much debate about standards for methodological rigor in qualitative research there is widespread agreement about the need for clear and complete reporting. High quality research which is conducted and assessed systematically would enable researchers to synthesise the data, critically appraise the data with greater ease due to transparency and therefore subsequently ensure reproducibility.

To ensure quality, this qualitative research was conducted following the guidelines for standards for reporting, process and methods from the Consolidated criteria for reporting qualitative research (COREQ) criteria (Tong, Sainsbury et al. 2007). The checklist was used to ensure explicit and comprehensive reporting of the final analysis (appendix 10). The NICE public health development guidance and MRC guidance on the development and evaluation of complex health interventions were used to aid the design of the focus groups (NICE 2012, Craig, Dieppe et al. 2013). The quality of qualitative research is judged fundamentally differently to that of quantitative methods which predominantly look for internal validity, external validity, reliability and objectivity. This study sought to ensure rigour by the four criteria outlined by Shenton i.e. credibility, transferability, dependability and confirmability (Shenton 2004).

3. Results

Of the 31 trial participants, 22 were contacted for their participation after meeting the inclusion criteria. Three focus groups in total were conducted; the first group with control only participants and the second and third groups with intervention only participants. Of the control group, nine men were contacted and of this four agreed to participate (FG1 control, n =4), the remaining men could not participate on the

proposed focus group date due to prior commitments. Of the intervention group, six men were contacted and of this five agreed to participate in the first focus group. Four men subsequently took part in the focus group as one man had been admitted into hospital as an inpatient (FG2 intervention, n =4). For the second intervention focus group seven men were contacted and all seven agreed to participate in the focus group (FG3 intervention, n =7). The characteristics and demographics of participants who took part in the focus group study are detailed in table 6.1.

Table 6.1. Participant demographics

	FG1 control (n =4)	**FG2 intervention (n =4)**	**FG3 intervention (n =7)**
Mean age (y)	70	73	75
Retired	3	4	6
Current or previous Enzalutamide	0	2	6
Current or previous Abiraterone	0	0	1
Current or previous Docetaxel	2	0	1

Three primary themes were identified from the data (table 6.2).These included 1) living with CRPC, 2) experience and opinions of the trial, 3) attitudes and experiences of exercise training and physical activity. Participant's verbatim quotes are provided in order to illustrate the findings.

Table 6.2. Primary and secondary themes of focus groups

Theme 1: Living with CRPC	Physical health
	Psychological health
Theme 2: Experience and opinions of the trial	Motivations and expectations for the trial
	Acceptability of trial procedures
	Perceived benefits of the exercise and dietary intervention
	Critique and suggested improvements for a future study
Theme 2: Attitudes and experience of exercise training and physical activity	Barriers to exercise training and physical activity inside and outside the trial
	Facilitators to exercise training and physical activity inside and outside the trial
	Experience of exercise training outside the trial

3.1 Theme 1: living with castrate resistant prostate cancer

3.1.1 Physical health

When discussing their physical health the most commonly mentioned concern amongst the men was the observed decline in fitness as a result of treatment. In FG1 (control group) this was mentioned 12 times amongst all four participants, in the two other intervention focus groups (FG1 and FG2) it was mentioned a further 6 times in total. The common worry was the inability or increased difficulty in carrying out activities of daily living such as walking the dog, walking to the hospital or performing manual jobs.

"*Yeah, but I used to run and I've found that I just cannot run at all…Since I've been diagnosed with cancer…I couldn't do five minutes and it's just demoralising...*" **Participant 4, control group**

"Well, I'm still working on occasion, touch wood, but when I'm carrying the tiles upstairs or whatever, instead of carrying a box, I carry just maybe four or five tiles because they're large tiles; whereas I used to be able to carry one, maybe two boxes at a time." **Participant 2, control group**

"*…if I had to walk, I used to get off a bus outside the Hallamshire and then walk up to Weston Park and there's those steps aren't there…I was stopping three times or more going up there because I just hadn't got the energy to do it and I was almost crawling up the little gradient after that to get up the hill…And my feeling is that you can be as fit as you like at one point, but it just drops away rapidly if something goes wrong and you can't do anything about it.*" **Participant 3, control group**

These effects were reported as being associated with a combination of problems relating to progression of disease and the AEs of treatment. Disease related AEs, pain and lymphedema were the most commonly mentioned. One man, participant three in the control group, also spoke of the effects of spinal cord compression as a predominant detrimental side effect. In terms of treatment, the AEs effecting activities of daily living were neutropenia resulting from chemotherapy and fatigue resulting from Enzalutamide. For one man fatigue was a very significant problem in FG3, to the extent where he had been asked to be periodically taken off the drug.

"*…I said with my prostate reading being so low, can you not give me a break, can you not take me off this enzalutamide for three months and then we'll have another blood test? Oh no it's working, so you've got it and I said well it really is affecting my quality of life and he said to me well at least you've got a life.*" **Participant 15, intervention group**

Although some positive effects of steroid treatment were mentioned, such as reductions in pain, there were two men in the FG1 who detailed their concerns of excessive weight gain which was perceived to be steroid induced.

"*… the extra weight makes it even harder to do anything...I was on steroids when I had chemotherapy and I clapped two stone on straightaway… I think that, that extra weight is affecting me as much as anything else really, especially my breathing. The breathlessness is the worst thing for me that really gets me down…*" **Participant 4, control group**

Other negative changes to body composition as a result of ADT was mentioned, including weight gain and a loss in muscle, this was also described as a barrier to exercise (see section 6.3.2.1).

3.1.2 Psychological health

For two men in the control group, the detrimental effects of the disease or treatment for disease had had a large impact upon psychological wellbeing. This ranged from feeling low and a lack of motivation to do every day activities to resentment for their disease and their diagnosis.

"I'm either all right or I'm like down on the floor. In the early days I felt awful, terrible, both physically and mentally, I took a right knock." **Participant 4, control group**

The interaction between participants and their consensus is highlighted by the following quotes. It appeared that for one man, there was some resentment for his disease and his declined physical fitness.

"I find it just unfair, if you like. I think why me, what have I done wrong? Just when I ought to be enjoying life more than ever and there's all sorts of things I want to do and it doesn't seem fair." **Participant 3, control *group***

"I agree it doesn't seem fair." **Participant 4, control group**

"I look at young people running or doing things and doing their everyday things. When you come here and you're going past all the students and they're looking all full of life and doing things and laughing and joking and running around and I think you don't know how lucky you are. And I resent it in a way and I'm jealous of people because they're fit and I'm thinking well I know I'm not that young, but there's no reason why I can't feel - I wanted to be as fit as I could be for my age, but this knocked it on the head, all this." **Participant 3, control group**

3.2 Theme 2: experience and opinions of the trial

3.2.1 Motivations and expectations for the trial

The two most commonly mentioned reasons for taking part in the study were to be a part of a research study that could help future prostate cancer patients and to improve their fitness.

"I mean although I've always been relatively fit, I find it quite difficult to maintain the fitness level since I've been on medication. So that was the motivation. Basically that was it." **Participant 8, intervention group**

"… for me I tend to be a bit lazy and by coming to something like this because I'd got to a very low level of fitness and I was very worried about whether I'd ever get out of it and yeah, it got to me do exercise in a more formal way and if it benefits the other people who find themselves in the same boat in future, yeah, then great." **Participant 13, intervention group**

"…I felt like that, it's payback time, got to put something back in for all the years and years that I've had treatment..." **Participant 15, intervention group**

Other reasons for taking part in the trial were the encouragement of family and friends, to improve bone health, to improve psychological wellbeing, to simply get moving again and because the exercise offered was supervised The supervised aspect was felt to beneficial as these men would get individual tailored advice tailored to their needs and abilities.

"...but at the back of my mind I thought it would be nice if there's somebody there who knows what you should be doing and possibly not be doing and what the

best thing is for you. Because we can all, body withstanding, go and get on machines and knock yourself out, but is it really doing you any good?" **Participant 4, control group**

"It was just at the back end of last year, wasn't it and I get pretty low in the winter, I get very low sometimes and I thought this would help pull me through the winter." **Participant 15, intervention group**

The only apprehensions about starting the trial were in reference to being randomised to the control group and for one man whether the weights he would be asked to use in the intervention would be too heavy.

The reasons given for regularly attending the exercise sessions were predominantly the camaraderie experienced with the group aspect of the exercise, the supervised exercise support as well as the beneficial changes to body composition.

3.2.2 Acceptability of trial procedures

There was overall positive feedback given regarding the trial procedures.

Assessments were generally well received although all participants in FG3 agreed that the physical assessments (three repetition maximum testing, six minute walk test, hand grip strength and chair sit to stand test) as being "too easy".

"I think the thing to me was the initial test that [the author] *carried out, where they analyse what you can do and what your physicality is. And I thought that was excellent because it gives you a base to work from."* **Participant 8, intervention group**

"I thought it was handled very well... he just walked me through it in a straightforward way and timed me and adjusted the weights and things like that. So it was excellent yeah." **Participant 7, intervention group**

"*I'd just think well I've done* [the assessment]*, that's been easy, I wish I could have gone further."* **Participant 9, intervention group**

For the questionnaires, there were some difficulties with completing the diet diaries, particularly with fresh food as opposed to packaged, in detailing portion sizes and remembering exactly what was eaten. In addition, there were some difficulties with

gauging how to interpret and complete the rating of items on the FACT-F and FACT-P questionnaires.

"I find them really difficult to judge where I'm putting it at. Am I comparing myself to when I was 20 years old...I'm sometimes tempted to feel that I'm 100%. But I don't know how helpful that would be to you because you don't know what I'm comparing it with. That's what I meant by that, yeah." **Participant 4, control group**

The dietary guidance was very well received but there were some problems for men who were not used to cooking for themselves implying that their lack of cooking skills meant they struggled to make as much of a change as they would have liked.

The interaction between intervention participants in focus group 2 and their consensus is highlighted by the following quotes:

"I think it was a good idea putting that in, I didn't expect that and it was excellent." **Participant 7, intervention group**

"Yeah, I mean it gave you an insight into what…" **Participant 8, intervention group**

"Alternative things to eat. **Participant 7, intervention group**

"*That's right yeah.*" **Participant 8, intervention group**

"Trouble is my wife has got to the age now where she doesn't want, she's always cooked for me; I've never cooked anything. In fact I was in catering corps in army and I couldn't have boiled an egg." **Participant 5, intervention group**

The duration of the trial was thought by the majority to be long enough, with the exception of one who voiced a preference for a longer duration of trial. The structure of the three phase intervention was also received very well by the intervention participants.

"It struck me that they'd been thought through. It wasn't just, oh I'll have a go at this one now, and, oh that one's free, do this, that you had given some thought to the order in which, well not just a day one and day two thing but also doing each exercise…" **Participant 6, intervention group**

The group exercise format (which included up to 6 participants in a session) was also received very positively, and was an aspect enjoyed most by the participants particularly the camaraderie between the participants.

"I thought the group that we've got and the [instructors] *that we got and all the rest of it, I thought it was quite a nice mix. A bit of a laugh here and there or tried to make it so… I think there was a certain amount of camaraderie"* **Participant 8, intervention group**

The interaction between intervention participants in focus group 2 and their consensus is highlighted by the following quotes:

"*I started by myself and you suggested going into the group. I went into the group and I enjoyed it…But it worked well and seeing what other people could do was useful. And seeing how much he could do, I'm pointing at [participant 5] over here."* **Participant 7, intervention group**

"*I think he used to look up to me a little bit*." **Participant 5, intervention group**

"I think there were lots of times when I was with [participant 14] and I think only two or three occasions when there were more, maybe four and certainly the last few there's just been me...I enjoyed it when there were more people in. Now, it's difficult for you to manage that when we're all doing different exercises, but if that could be part of it, so that camaraderie, if that's the right word, the banter, because for me that was an important part of it." **Participant 10, intervention group**

The rapport with the trainers and assessors was also an aspect enjoyed by the participants. It was felt that they were effective at communicating the trial procedures; providing enough information, guidance and support; and adequately contactable when needed (with an appropriate level of contact).

"I found the guys there really helpful and that. And they let you push you as much as you wanted to. And I kept trying to do more of, you know the leg push thing." **Participant 4, control group**

For one participant, it was felt to be of benefit that the trainers were researchers and *"scientifically trained*" where that would not be the case in a commercial gym

environment. In addition, the participants perceived that the trainers in the study had a genuine interest in coaching participants to improve their strength and fitness capability. Overall, the feedback from the participants who took part in the focus groups reported the trial be a very positive experience.

3.2.3 Perceived benefits of the exercise and dietary intervention

The physical benefit arising from the COMRADE exercise intervention most commonly mentioned was perceived improvements in muscle strength and fitness, mentioned by 9 intervention participants. Other physical benefits included improvements in the activities of daily living (mentioned by two), improvements in pain (mentioned by four) and the maintenance of physical fitness. These physical outcomes were felt to be declining prior to the intervention.

"…I certainly feel a lot stronger. I can do things that I couldn't do before." **Participant 7, intervention group**

"But compared to last year, we had to have professional gardeners in to go out to do our garden. Yesterday I mowed the lawn and it's a big lawn. So yeah, I'm a whole lot fitter than I was a year ago. I even did a charity job, a charity auction; I went and chopped somebody's trees down with a chainsaw...Yeah, I'm a whole lot fitter and it's worked for me." **Participant 9, intervention group**

"I wanted to give it a go to see what it was like. Like I said it's been a success up to now. I don't get no pain in bottom of my spine now and I've gone back to gym where I was." **Participant 8, intervention group**

"I realised that when I was first diagnosed 26th of June 2015, I went to the gym and I tested myself on every bit of equipment that I've ever used and I'd been going downhill.... I think now is that I've stopped the decline…on the two occasions I've been to the gym since, I think I was moving fairly close to what had previously been the maximum and they were one rep maxima and, you know, you've been getting me to do between eight and 12 three times. So you were a reminder that I actually have got stronger." **Participant 14, intervention group**

The social and psychological benefits were mentioned by 7 of the intervention participants. Improvements in wellbeing and QoL were mentioned. If seemed from the

conversations that the trial enabled the men to open up about their disease with others who are in a similar situation and therefore were able to support each other.

The interaction between intervention participants in focus group 2 and their consensus is highlighted in the group dynamic demonstrated below. This highlights the commonalities amongst the participants.

"The wellbeing factor. Setting aside the purpose of your project which was bone density and things like that. The wellbeing is overwhelmingly good." **Participant 7, intervention group**

"*It's markedly better isn't it?*" **Participant 8, intervention group**

"…but a lot of people are in the same boat and coping with it 15 years, 12 years or whatever. When you're first diagnosed and you find, you ask the question, well, if I don't have any treatment what are we talking about and the guy says 12 months, that's a good laxative! And the fact that we've got through that …I'm not one personally for support groups in that way - but indirectly this is one to some degree, the fact that you're doing the exercises and then just chatting to people who have been through what you've been through…that's helpful." **Participant 10, intervention group**

"… I think the idea of almost whether or not it works because we don't know whether or not the scans and that will show growth or whatever it might be but the fact that it stops you lying around doing bugger all, actually gets you out of the house and provides that motivation, that in itself, and it's quality of life. Now, whether or not the quality of life, how long we've got is shortened, increased or whatever, the fact that it actually makes you get out of bed when you might not, I think that's beneficial in itself." **Participant 10, intervention group**

One man in the intervention group spoke about how his own progression in the trial, and improvements in physical ability, had inspired others who had also been diagnosed with prostate cancer.

"*I'm very conscious that in the last six months I've improved both mentally and physically. But three of my friends in the last eight weeks have been diagnosed with prostate cancer and I can say to them, look, I've had it for 15 years and I'm still there and you've got lots of hope because I'm still there and feeling better than I was…I'm a*

bit of an example to a number of people just suddenly having the shock, you've got prostate cancer and I can talk to them about it and not everybody can talk about it. And if they can see you coming back then they're thinking well hey, there's hope for me…so it's giving them a hope for the future, I hope, so there are quite a few positives coming out of all this." **Participant 13, intervention group**

3.2.4 Critique and suggested improvements for a future study

As mentioned previously, some participants experienced difficulties completing the questionnaires, as a result, it was suggested that further and more in depth explanation of how to complete them would be of benefit in a future study.

Unfortunately, for some of the men randomised to the control, there was great disappointment that they would not be receiving any diet and supervised exercise support.

"I was devastated. I was gutted, absolutely gutted. I nearly didn't come to the control! I just fancied the idea of somebody telling me what I should and shouldn't be doing and the diet as well just to give something a try, you know, but it is what it is. It's a lottery, isn't it, but yeah, I felt really disappointed. You weren't my friend that day!" **Participant 4, control group**

In the intervention group, problems reported that affected attendance to exercise sessions were illness (3), a family bereavement (1) and poor weather (3). Other problems during the trial included constipation as a result of consuming the whey protein (2), difficulty with travel and parking (8) and the lack of accessible showers (1).

Regarding the intensity of the exercise session, there was a mix of opinion. Some of the men reported that the overall session was not as difficult as they had wanted however there were also some who had difficulty with individual exercises.

" I think you know what I'm going to say. There was one exercise which I found very difficult and I found it very disheartening and I'd been managing everything until then." **Participant 7, intervention group**

"Now in my opinion the [exercise] *I do now* [at the gym is] *harder than when I came here…I took a towel* [to the trial exercise sessions] *because I was expecting*

coming out sweating and sometimes I didn't come out sweating at all " **Participant 5, intervention group**

Although the group format was overwhelmingly preferred and enjoyed by the intervention participants, there was some concern over the number of available instructors present in the sessions. It was felt that sessions would benefit from more instructors to adequately ensure the safe and timely running of the sessions,

"If you've got two or three of you." **Participant 5, intervention group**

"*Yeah, if there's more. But sometimes it depended on how many there were. Sometimes there were too many."* **Participant 8, intervention group**

"*Too many for [the instructor] weren't there?"* **Participant 5, intervention group**

"*Yeah.*" **Participant 8, intervention group**

In addition, it was felt the most benefit would be gained from consistently seeing the same trainer during the intervention period.

"I'm the same with the doctor, I like to see the same doctor because he knows what the criteria is for me, he knows what the situation is. And I think you're better off staying with the same [instructor] *whichever one it was...I do think it would be more beneficial for the individual."* **Participant 8, intervention group**

One participant had also spoken at how he would have preferred for their to have been a longer duration of the intervention.

"I think the duration of it ought to be six months. Seriously because I think it gives you a wider span and a greater depth of knowledge. I mean I understand the cost is going to be substantially more, but I think you would probably find that after six months you would see a substantial improvement in the individual performance. Or when I say performance I'm talking about readings, PSA and all that....But I do think that if you extended it over six months it would eradicate the holidays." **Participant 8, intervention group**

3.3 Theme 3: attitudes and experiences of exercise training and physical activity

3.3.1 Barriers to exercise training and physical activity inside and outside the COMRADE trial

The most commonly mentioned barrier to exercise training outside of the trial (both pre and post study) was lack of motivation followed by fatigue and lack of support and/or advice from treating clinician. Lack of personal motivation was mentioned by 11 participants.

"The motivation to go and do it [exercise]*, it's just too easy to put it off and say oh, I'll do it in a bit…it's just really hard to make you do things that are quite tedious and boring aren't they?"* **Participant 4, control group**

The lack of endorsement to exercise from a clinician or a lack of information which was tailored to men with prostate cancer was a significant concern for three participants.

"...but it's just knowing what the right thing to do is. My wife reads everything, absolutely everything, internet, all the books, we've got every booklet that's ever been published and that. And I find a lot of those things would hold you back rather than encourage you to do anything. So I think it's the degree that you're at. But you don't know what's right and what's wrong, are you doing any harm or are you not, and when your oncologist goes don't do that, and you think…Yeah, that's what she said to me, yeah, don't go on any weights or anything like that." **Participant 4, control group**

"*I think I've found when I've talked to them and mentioned exercise and also the cancer support place, they talk to you as if you can't do anything. And I don't think they recognise the difference between being almost an invalid and being reasonably active. My oncologist told me don't go to the gym, don't do this, don't do that, try some Pilates.*" **Participant 4, control group**

Other barriers mentioned were the gym environment being perceived as too boring, existing co-morbidities (cardiovascular and musculoskeletal), poor mobility, being too old and interfering with holidays.

The barriers specifically associated with prostate cancer and its treatments were reported as fatigue associated with ADT (mentioned by five of the men), disease progression, and side effects of chemotherapy. In addition, body changes associated

with ADT appeared to have significant effects on the body image of four of the men, to the extent where they would not partake in exercise. There was mutual support offered in acknowledging the problem of gynaecomastia amongst the participants, where men shared their common experience and expressed their joint concerns.

"I used to swim, but I won't go in a swimming pool now because, well, I look like a woman because of the treatment. The hormones, the female hormones I'm practically wearing my wife's bra, so I won't go swimming." **Participant 1, control group**

"I don't go in swimming pool now; it's embarrassing a bit isn't it?" **Participants 5, intervention group**

"…I've got quite noticeable boobs." **Participants 8, intervention group**

"Don't worry about that, I could do with a bra." **Participants 5, intervention group**

"…this fatigue problem, you said well exercise, well that's the wrong thing to say to somebody like us if you're really fatigued to say go and do some exercise because that's the last thing you want." **Participant 15, intervention group**

3.3.2 Facilitators to exercise training and physical activity inside and outside the trial

The most common facilitator to exercise as mentioned in the focus groups was encouragement or advice received from their clinical team. Of the 15 men who took part in the focus groups, only three had received support for exercise behaviour from their clinicians. In addition, many of the men felt that exercise should form part of overall care because of its associated health benefits.

"Well my doctor and at Weston Park, they've always said that, when they found out I go to a gym they always said it's a good thing. It's a very good thing to go to a gym while you've got, well you'll always have this." **Participant 4, intervention group**

"I think there should be some link up. I think it ought to be possible to say look you're going to benefit if you can keep fit and do this and we'd like to keep an eye on it

and this sort of thing. But I think the oncologists at the Weston Park Hospital just haven't got time. They've got so many people." **Participant 3, control group**

Alongside the participants desire for clinician input and guidance, was the feeling that supervised exercise would not only be the safest option for men who were unsure of the type and intensity of exercise to do but also help the men to understand which exercises would benefit them the most. This perception was reflected on from their recent experience of supervised exercise in the COMRADE trial

"*…particularly as we were trying to go up the weights, I think if we'd have done that left to our own devices we might have either taken the easy way out or tried to do something too much to do that. So I think it was necessary to* [be supervised] *to know what our own, if you like, for you to manage our limitations*." **Participant 10, intervention group**

3.3.3 Experience of exercise outside the trial

In the intervention group, there was a higher prevalence of men who had chosen to continue with exercise in a gym environment post-study. For three men, they felt that the study had given them the encouragement and confidence to translate their motivation and competence to exercise post participation in the trial. In the control group, there were some negative perceptions of commercial gyms including them being too busy, but also a lack of trust with personal trainers who may not have the empathy or awareness of the clinical condition to achieve the best outcomes for these men. In contrast, the COMRADE trial was perceived as being specifically tailored to achieving benefits in health outcomes relevant to their disease and the related needs of men with CRPC.

"*Yeah, it encouraged me to join the gym doing this. And the main difference I think is expense, it's quite expensive if you include the trainer as well. I'm going three times a week for about an hour*." **Participant 7, intervention group**

The interaction between participants and their consensus is highlighted by the following quotes:

"I joined a gym once and it was just like chucking money away. I had a personal trainer who just walked around with us and that were that. All they wanted was that. **Participant 1, control group**

"I would say when you're talking about other gyms you've got to question, not the motivation of people there, motivation of the trainers, what they're after and obviously the people here know what you're trying to achieve, don't they?" **Participant 4, control group**

Other activities mentioned were home based exercise with the help of equipment such as bikes and rowers and a community based group for cancer patients (Macmillan Active Everyday) which helped to facilitate and encourage exercise.

4. Discussion

4.1 The adverse effects of treatment and disease

It is clear from the findings of this study that the participants who participated in the qualitative focus groups experience a tirade of AEs which are detrimental to both physical and psychological health.

The overall effects leading to a decline in physical fitness was of primary concern for these men, likely leading (in part) to the decline in psychological health that some men experienced. An interesting finding was that this concern was more prevalent in the control group than in the intervention focus groups, despite their being more than double the number of intervention to control participants. Given the perceived benefits described from those in the intervention, it could be that at the time the men engaged in the focus groups there was a perceived mitigation of the decline in physical fitness when compared to the control participants. The perception of this decrease in physical fitness was predominantly perceived as a lesser ability to carry out activities of daily living. A decreased ability to carry out activities of daily living has been shown to have profound effects on QoL in cancer patients, and therefore likely to impact on overall wellbeing (Ulander, Jeppsson et al. 1997). This is compounded by the presence of advanced prostate cancer and the AEs of its associated treatments. Problems like fatigue and lymphedema (which were described in these focus groups) can significantly impede physical function and exercise tolerance in cancer patients and older adults (Stolldorf, Dietrich et al. 2016, Kogure, Hara et al. 2017).

For one man, fatigue brought about by enzalutamide had affected his QoL to the extent where he had asked to be periodically abstain from taking the drug, on this occasion he felt that the impact on his QoL had outweighed the perceived benefits.

This was surprising in light of the findings of chapter 3 where the HCPs interviewed emphasized the importance of balancing QoL and treatment for disease as well as discussions with patients regarding treatment decisions. The fatigue described by this man had affected his functional capacity and ability to carry out everyday activities. This further reflects that which was previously described in chapter 3 where maintaining physical performance and therefore "fitness for treatment" is pivotal.

The psychological health of advanced cancer patients is of significant clinical impact. Low mood, lack of motivation for everyday activities and resentment for the disease and associated effects were all described by these men. In prostate cancer, men with advanced disease and those who have received ADT are much more likely to report greater number of effects which impede QoL (Kornblith Alice, Herr Harry et al. 1994).

4.2 Evaluating the trial experience

The two most common reasons for taking part in the study were to potentially help by contributing to evidence from which informed decisions about therapeutic support for future CRPC patients can be made; and to improve fitness. Similarly, the study by Bourke et al (2012) also reported a motivation for participation in an exercise trial was to contribute to improved treatment for future patients (Bourke, Sohanpal et al. 2012).

As described earlier, the decline in physical fitness is of primary concern for these men and the combination of both the effects of their cancer and the side-effects of drugs can result in a reduced ability to undertake activities of daily living. Improvements in fitness were therefore clearly a priority and motivator to take part in COMRADE for these men. This has also been described as a significant motivator to increase exercise behavior in a previous qualitative study of men with prostate cancer (Bruun, Krustrup et al. 2014). Therefore, a programme which adopts and records continuous progression in exercise training is an important motivator, where men are able to see how they have improved physically over the course of the programme.

Other reasons such as the encouragement of family and friends further reflect the need for support and guidance, not just from their clinical team, but also from their close social circles. It has previously been recognised that the support of family and friends is an important factor the decision making of cancer patients (Hobbs, Landrum et al. 2015, Al-Bahri, Al-Moundhri et al. 2017). In addition, the camaraderie and social

interaction with others due to the group based format of the intervention was an important reason for men to continue to attend sessions.

The group format and social aspect of the intervention was mentioned numerous times in the focus groups. Not only did it bring about peer to peer encouragement, but it also acted as a support network, where the men felt comfortable to talk about their disease openly, which was agreed between the focus groups participants. A previous qualitative study of prostate cancer patients has also demonstrated the value of creating opportunities to share experiences as a psychosocial exercise (McCaughan, McKenna et al. 2015). Whilst the exercise in the COMRADE intervention group was providing meaningful physical health benefits to participants it appeared the social interaction with others and research staff had a valued impact on their psychological health. Wellbeing improvements were described as improvements in quality of life and the ability to do activities of daily living. Such terms were similarly described in the study by (Adamsen, Rasmussen et al. 2001). In addition, the improvements experienced by the men on the trail did not only act as motivators for those also within the study, but one man had also described how his experience had inspired friends outside the study, helping them to have a more positive outlook upon the diagnosis of prostate cancer. Similar findings have also been demonstrated in qualitative analysis of exercise based interventions, demonstrating the group aspect brought both camaraderie and served as a motivational driver in sessions (Adamsen, Rasmussen et al. 2001, Bourke, Sohanpal et al. 2012, Bruun, Krustrup et al. 2014).

These findings suggest that psychosocial support is pivotal for future exercise programmes. Group based formats as well as family and friend encouragement are clear motivators. Furthermore, confidence and support for exercise from treating clinicians is warranted. Future programmes should therefore encourage clinician involvement which is also a key finding in chapter 3. This too would help facilitate exercise in the prostate cancer care pathway, where clinicians who are clinical champions for exercise are able to encourage and advise their patients on exercise and physical activity but also have the knowledge to refer them to local schemes where available. Furthermore, it is important to have family support, this could include the presence of a partner or family member in the initial consultation regarding an exercise programme so they can be a part of the decision making process. In COMRADE it was often the case where men were approached in clinic they were

accompanied by a partner or family member and it was often the case that they were encouraging and in favor of the recruited men to participate in the study. Partners were also receptive and helpful in aspects such as the adoption of a healthy diet, cooking some of the meals suggested in the dietary guidance for their family.

There was a range of benefits experienced by those men who had undertaken the exercise intervention. The most commonly mentioned improvements were physical fitness, muscle strength and ability to undertake activities of daily living. Previous qualitative studies of exercise interventions in prostate cancer patients had also described the positive changes to strength and capacity to do everyday activities (Bruun, Krustrup et al. 2014). An outcome of the COMRADE trial was to determine the effects of the intervention on LBM and physical performance, with the overall aim to improve outcomes in men with CRPC. The findings from the focus groups are encouraging that men in the intervention had reported both physical and benefits including increases in muscle strength. More importantly however, was the unanimous finding of the intervention participants that there were improvements in wellbeing and quality of life.

Despite the barrier to exercise associated with long-term ADT, these men still were still able to undertake exercise training and observed significant benefit from doing so. Although none of these men were on chemotherapy during the trial, two in the intervention had had a previous chemotherapy regimen. This does lead to questions regarding the HCPs perception of physical fitness, given the doubts expressed in chapter 3, where these men have been able to undertake exercise despite significant previous treatment and comorbidity. Despite the significant barriers described in chapter 3, these men were still able to undertake the exercise intervention safely regardless of their comorbidity and physical ability. This demonstrates the intervention was well tolerated, which is further reflected in the lack of SAEs/AEs associated with the trial procedures (with the exception of whey protein causing gastrointestinal problems) in addition to the good adherence described in chapter 3.

The findings from this study and that demonstrated in chapter 5 suggest a need for such supportive interventions for men with CRPC and that with tailored and individualised advice, with supervision initially, can ensure that exercise interventions can be undertaken safely. This includes those burdened by the adverse effects of

treatment and disease. The tolerability of the exercise intervention, despite this, shows how exercise could benefit these men if offered in the care pathway.

4.3 Attitudes and experience of exercise

Personal motivation was the most commonly described barrier to exercise. Although behavior change techniques were not implemented as part of this study, it is recognised they are a key part of improving motivation for increased exercise in cancer patients (Bourke, Homer et al. 2013, Roberts, Fisher et al. 2017).

In addition, lack of support from the clinical care team, was the second most commonly mentioned barrier to engaging in exercise. As previously mentioned, clinicians input and recommendation is an important factor in patient decision making in prostate cancer patients (Blanchard, Labrecque et al. 1988, Ferrante, Shaw et al. 2011). Similar to Bourke et al 2012, none of the men had received specific guidance from their clinical team regards lifestyle changes such as exercise advice, although three of the participant's clinicians had supported the concept of exercise (Bourke, Sohanpal et al. 2012). A study by Koutoukidis et al (2018) showed that whilst HCP's do have the desire to support lifestyle advice, this is not necessarily substantiated with action (Koutoukidis, Lopes et al. 2018). Koutoukidis et al report that HCP's knowledge of healthy lifestyle guidelines, feeling that they were not the ‘right person’ to provide advice, and lack of time and resources are barriers to engaging cancer patients in discussions about exercise; these findings are similarly reflected in chapter 3 of this thesis (Koutoukidis, Lopes et al. 2018). However, given that for some of these men, no advice on physical activity was ever given, it could be that even the most modest discussion regarding increasing physical activity and exercise during routine appointments may improve exercise behavior. This could, in the least, open up conversation for men who may not be aware that such positive lifestyle changes can have a profound effect on their physical and psychological health.

Other barriers included those relating to treatment AEs. A significant barrier relating to the adverse effects of body composition was poor body image. The cessation of activities, such as swimming, was mentioned in two separate focus groups due to effects such as gynecomastia and weight gain. A qualitative study exploring the impact of the AEs of ADT also found that men who suffered gynecomastia avoided "revealing situations" (Grunfeld, Halliday et al. 2012). For these reasons, when considering the

accessibility of exercise for men with CRPC, the type of exercise especially in a public or group environment must be taken into account. For some men who have had unfavorable changes in body composition due to ADT, they may be less likely to participate in exercise programme which may involve activities like swimming. Equally, this could indicate the benefit of exercising in groups who are at a similar stage of treatment, where men may not feel as self-conscious around those in a similar situation. This is prevalent by the fact these men spoke openly with each other about this barrier, even in the presence of two female researchers. This may further indicate that these men felt the researchers were understanding of these types of long-term effects associated with ADT, and therefore were comfortable to talk about it.

Facilitators to exercise most commonly mentioned were advice from the clinical team, this finding has also been previously described in qualitative studies evaluating exercise intervention in prostate cancer patients (Bruun, Krustrup et al. 2014). The participants in this study felt that positive lifestyle behaviors should be an aspect of their "usual care" provided by their clinical care team, indicating it should be integrated into the care pathway. This was in part due to these men having a desire to be informed of how exercise might benefit them as well as guidance on how to safely exercise. In a previous qualitative study of an intervention facilitating prostate cancer patient and clinician decision making, it was recognised that patients welcomed a preference-sensitive and personalised support approach to treatment decision making (Hacking, Scott et al. 2014). The present study highlighted further the need for tailored advice and guidance, which included the need for a supervised aspect to help at least in the initial stages of undertaking exercise which may be unfamiliar. The supervised and tailored aspect of the intervention was in part what motivated some of these men to take part in the trial, where guidance on exercise participation was provided. This motivation has also been described in previous qualitative research in men with prostate cancer who have taken part in an exercise intervention (Adamsen, Rasmussen et al. 2001). Furthermore, for the men who had been randomised to the intervention, it was reported that the trial had provided them with the encouragement and knowledge required to exercise independently post trial, a finding which has also been the case in previous studies (Bourke, Sohanpal et al. 2012). Therefore, the findings suggest that in order to sustain (improve) exercise behavior in these men, a holistic approach to addressing patients health and wellbeing is needed. Such an

approach would allow the clinician to tailor exercise and lifestyle advice relative to the patient's disease history and status. As mentioned in chapter 3, this approach is considered imperative to managing symptoms of disease, treatment related AEs and promoting positive health outcomes (Cockle-Hearne and Faithfull 2010). As one participant commented, when talking of exercise as a supportive therapy as part of their usual care,

"I class it as one really. I think it's all, me personally I think it's all one, all connected." **Participant 11, intervention group.**

Some negative experiences at commercial gyms were described by a few of the men, in particular distrust in the motivations of personal trainers. It is likely that trainers who are qualified and had specific expertise in exercise referral would be the most successful in helping to improve exercise behaviour in these men. This was further reflected in a later comments made by the intervention participants regarding the researchers who were "scientifically trained" which was seen as a specific benefit of COMRADE. Similarly, a previous study in men with prostate cancer found that combination of the training facility and the professional expertise was crucial to the men's faith in an exercise intervention (Adamsen, Rasmussen et al. 2001). Furthermore, having a good rapport with the trainers was a facilitator to exercise for those in the intervention group, by motivating and encouraging them to keep progressing their exercise capacity where they may not have been confident in their physical ability.

4.4 Critique and suggested improvements for a future study

Overall, the procedures in the trial were well received. However, there were a few problems experienced by some participants and some suggestions for improvement in a future trial.

Randomisation to the control arm was a significant set-back for one man. In exercise studies, where it is not possible to double blind, there are ongoing problems where participants are aware they are randomized to the control, and in some studies this has resulted in drop-outs (Bourke, Doll et al. 2011). One possible solution to this is a multi-site study, where the sites are randomised to intervention or control as opposed to individual participants. Not only does this reduce the risk of control contamination, but also of disappointment and subsequent drop outs.

There was some difficulty when completing the questionnaires, such as determining portion sizes in the three day diet diary and determining how to correctly rate the FACT-F and FACT-P questionnaires. For the three day diet diaries, the lack of detail and underreporting during their analysis was a significant problem, as described in the previous chapter. As a result for a lot of the men on this study, accurate detail on dietary intake was not available. In the future, it was agreed with the participants that better guidance on how to fill these out, including better instruction with the diet diaries was warranted for clarity.

With the assessments, some described the assessments as being "too easy" and felt "they could have done more". Particularly with the three repetition max testing, the predominant concern was safety. Although the aim would be to push these men in such physical assessments, with the blinding of the researchers conducting the assessments, it would not have been clear who is deconditioned and in fact who may have been in the intervention and therefore more capable of "pushing further" safely when weights were getting heavier. The best recommendation would therefore be to ensure that the same single researcher is conducting each of the participant assessments, and can therefore become more accustomed to the individuals ability. In addition, establishing a protocol and logistical operations would help stratify by complexity of patient needs.

Although the format of the intervention was well received, some men described wanting a more intense session, whilst others described difficulty during certain exercises. This reflects further the heterogenic of the CRPC population and the difficulty in modifying interventions based on the individual. Given that this study was a feasibility study, it is expected that there would be some men who perhaps did not have a perfectly adapted intervention. Furthermore, as this was the first exercise intervention conducted by the author and that the intensity was determined by the author, more experienced exercise instructors would potentially be able to determine the correct intensity for each participant. Experienced instructors would potentially be able to stratify the intervention better according to disease and physical capability.

In addition, the lack of instructors in a single session to supervise the participants was mentioned as a problem as well as being supervised by different trainers on some

days. Whilst this study lacked the resources to have multiple trainers involved in delivering the intervention, in a future subsequent study if more exercise trainers were adopted this could not only help with achieving the right amount of intensity (or dose) of the exercise suited to the individual as the trainer gets used to the participants own ability but also to track progress and ensure adequate progression and regression where necessary.

The duration of the study was sufficient for the majority of the focus group participants. However, for one participant he had described how a longer study (6 months) would be of greater benefit to achieve the physical improvements and mitigate the effects of absence. As these men are a very complex and heterogeneous group, there were problems with absence relating to ill health. Although not described in the focus groups, for some of the participants in the intervention group, it was very disappointing that they had lost time on the trial and had asked for their intervention period to be extended. Although there was not the resources or time to conduct a study with a longer intervention period, a future study, with a 6 month intervention period would reduce the feelings of "time lost" on the trial due to ill health but equally give men a greater chance of regaining fitness or strength lost due to absence. In addition, an at home programme which could be substituted in periods of absence could offer a pragmatic approach to maintaining adherence and preventing feelings of "time lost"

Despite this, these findings are very encouraging not only that it is feasible to conduct an exercise intervention in men with CRPC safety, but that they are very willing to undertake such interventions for a longer duration of time. It can be said that given no such intervention has been trialed before in men with CRPC and given the limited resources and time available as a PhD study, it is not a surprising finding that there were some difficulty with addressing the right intensity for each individual. However, all sessions were conducted safely. Furthermore, these findings suggest that despite the lack of research surrounding exercise interventions for cancer patients with advanced disease and the exclusion of men with additional comorbidity or those with bone metastasis in previous prostate cancer exercise studies, these men are indeed able to benefit from such interventions. Despite limitations associated with advanced disease and adverse effects of treatment, these men were capable of exercise and had numerous benefits from undertaking the intervention provided in COMRADE.

5. Study limitations

The study included only 15 participants who had taken part in the feasibility RCT and for this reason is limited in its generalizability of the findings not relating to trial procedures. There was a limitation for the available dates for focus group participation, which meant two of the control participants who were invited to take part in the interview could not attend and therefore their views and opinions could not be explored in this study. The interviews included the opinions of only white British men from the South Yorkshire and Humber area under STH care, as this was from the available cohort recruited into the feasibility RCT. The data is therefore biased to the perspectives of this particular group. Due to the nature of how these participants were recruited into the feasibility RCT, it is acknowledged that a self-selection bias may also exist where the opinions of the men who could not participate were not explored. As before, the thematic framework approach to analysing the data was used, although commonly used in healthcare research; this form of analysis is more deductive and therefore stays strongly informed by a priori reasoning (Mays and Pope 2000). It was not pragmatic or feasible to have the focus group participants validate the findings of these focus groups in the context of this PhD, however this does mean the findings are under the interpretation of the author and second researcher (HC) who double coded.

Finally, these were the first focus groups and the second piece of qualitative work undertaken by the author. For this reason, a lack of experience must be taken into account. It must also be noted however that these focus groups contract in both richness and quality of findings compared to the HCP interviews described in chapter 3. This is likely to be due to a difference in set up (i.e. focus groups vs 1:1 interviews), power dynamic (patients vs senior clinicians) and rapport of the interviewer with the participants (given that these men were part of the trial and knew the researchers for over 16 weeks).

6. Conclusions

Overall the feasibility study procedures were well received by the participants, including the assessments, duration and format of the intervention.

Despite the potential barriers associated with advancing disease, long-term side effects of treatment, declining physical fitness and comorbidity, this complex and heterogeneous group were able to undertake the COMRADE study. The study was

well tolerated and despite the high number of SAEs and AEs, none of these were related to the exercise aspect of the intervention, although some where associated with whey protein. Furthermore, these men experienced exceptional physical and psychological benefits.

The group exercise format in particular was very well received bringing about peer to peer support, camaraderie and physical and psychological health. Valuable insights were gained in respect of implementing future exercise intervention studies - participants noted that clinician support, adaptability and supervision of an exercise programme are key processes from a participant perspective that underpin the success of a lifestyle behaviour study such as COMRADE. There are significant physical and psychological problems experienced by men with CRPC due to both the presence of advanced cancer and its associated treatments. As a result there is a need for adequate support and guidance for exercise behaviour from the clinical team, and this a significant facilitator to improvement in the participation of exercise. This includes information specifically tailored to the unique needs of these men due to a currently unmet need for supportive interventions which is of meaningful benefit to men with CRPC. Participant reported experiences here suggest that exercise training for men with CRPC in a supportive, professionally supervised setting, endorsed by clinical team are both feasible and highly valued by patients. Integrating such programmes into NHS cancer care pathways for this group of patients although likely challenging to implement are arguably both valuable and worthwhile means to enhance QoL during the terminal phase of illness.

Chapter 6 General discussion

1. Summary and key findings

1.1 Chapter 1: Introduction

1.1.1 Castrate resistant prostate cancer: treatments and the disease

In the UK, prostate cancer is the most common cancer in men with 47,151 new cases reported in 2015 (Office of National Statistics 2015). CRPC remains the terminal phase of the disease, where patients are typically older, have more comorbidity and can remain on treatments for their disease for over a decade. As a result, these men experience the long-term AEs of ADT, chemotherapy and the presence of their disease as it progresses.

Extensive and detrimental effects of ADT including sexual dysfunction, fatigue, cardiotoxicity, increased FM, decreased LBM, declines in BMD and metabolic comorbidity results in significant morbidity in men with CRPC, effecting QoL (Bagrodia, DiBlasio et al. 2009, Walker, Tran et al. 2013, Bourke, Turner et al. 2018, Dawson, Dorff et al. 2018). In addition, the presence of advanced cancer may exacerbate some of these effects, such as ADT associated LBM loss and development of cachexia. Cachexia can necessitate suboptimal chemotherapy dosage, exacerbating treatment toxicity and at refractory stages ultimately results in death (Suzuki, Asakawa et al. 2013).

1.1.2 Androgens and prostate cancer

The use of ADT as a treatment for prostate cancer results in significant AEs associated with hypogonadism impacting on the QoL in these men. There is emerging data demonstrating the therapeutic effects of testosterone therapy for men with prostate cancer without exacerbating disease progression, contradictory to the "androgen hypothesis" (Agarwal and Oefelein 2005, Morgentaler 2008, Morgentaler and Traish 2009). Studies have highlighted the administration of testosterone as a therapy in men with prostate cancer has failed to initiate tumour progression, and on the contrary showed a drop in PSA (Rhoden and Morgentaler 2003, Agarwal and Oefelein 2005, Balbontin, Moreno et al. 2014). This suggests that treatments which have the potential to promote anabolic changes may not have tumour progressive effects in prostate cancer patients (Morgentaler and Traish 2009, Morgentaler, Lipshultz et al. 2011). These findings indicate that anabolic agents may have a

therapeutic place in treating the AEs associated hypogonadism due to long-term ADT, which may be of significant benefit for men with CRPC with a long history of disease.

1.1.3 Treating lean body mass loss

Pharmacological agents used to address LBM loss and/or cachexia include testosterone, corticosteroids, SARMs, SERMs and supplements promoting anabolic effects such as eicosapentanoic acid and whey protein (Burckart, Beca et al. 2010, Dalton, Barnette et al. 2011, Madeddu, Maccio et al. 2012). Some of these agents have demonstrated beneficial effects in improving LBM and have proven to be safe in preclinical and clinical studies of prostate cancer. In addition, whey protein supplementation has been used to improve LBM in prostate cancer patients with or without resistance exercise (Hanson, Nelson et al. 2017, Dawson, Dorff et al. 2018). Creatine monohydrate has also shown to promote the effect of resistance exercise by improving body composition and improving muscle strength (Brose, Parise et al. 2003, Tarnopolsky, Zimmer et al. 2007).

1.2 Chapter 2: A literature review of exercise and dietary interventions as a supportive therapy for cancer

Supportive programmes which promote "self-care" are lacking in the current prostate cancer care pathway. For men with CRPC, there is a significant need for such programmes tailored to the complex needs of this group.

As men with CRPC are faced with the effects of long-term castration, there is a rationale for the use of exercise and dietary interventions to improve outcomes in these men. Despite data demonstrating the success of diet and exercise interventions in prostate cancer patients in improving prostate cancer specific outcomes such as sexual function, fatigue and QoL, there has been no published RCT data on the effect of such interventions in men with CRPC (Bourke, Doll et al. 2011, Baumann, Zopf et al. 2012, Bourke, Smith et al. 2016).

Although there is an ongoing study underway for men with CRPC (INTERVAL-GAP4), this study, like previous studies of exercise for men with prostate cancer, has neglected to include those men who are more complex. This includes excluding those who have experienced disease progression despite previous treatment whilst receiving therapies such as abiraterone, no previous chemotherapy and a PS of ≤1 (Newton, Kenfield et al. 2018). This potentially, excludes a large proportion of men with CRPC.

In addition, the study adopts a high intensity training approach to exercise. It is likely therefore that this study too risks selecting the "healthiest" or "fittest" within the population and neglects what could be a large proportion of men with CRPC that stand to gain a great deal from such lifestyle interventions. It could be however, that given the study adopts a high intensity exercise programme, it was deemed that not only would the programme appeal to those who are fitter but also could be conducted safely in this cohort. However, this again raises questions on the real world applicability of the study, where it may not be suitable, or appealing, to a large majority of men with CRPC.

1.2.1 A lifestyle intervention in castrate resistant prostate cancer patients: Thesis Overview

Given the evidence, a programme of resistance exercise, whey protein and creatine supplementation, with dietary advice presents an attractive supportive adjunct to the usual care of men with CRPC, where there is a significant clinical need for such interventions. Whilst the prospect of an anabolic drug along-side an exercise intervention was initially an attractive idea, an anabolic drug was not obtainable for the feasibility RCT (due to financial constraints and lack of time), and so whey protein and creatine monohydrate were considered excellent substitutes which were feasible for this study and still promoted anabolic effects on muscle mass.

Given the heterogeneity of men with CRPC whom are older, experience multiple comorbidity and have often been on long-term ADT for a number of years (sometimes over a decade), these men stand to gain a great deal from a supportive therapy aimed at improving outcomes related to their disease and treatment. Despite these men being in the terminal phase of their disease, it's the responsibility of the NHS, as with any advanced disease, to ensure these men live well during this period. The RCT of a lifestyle intervention conducted as part of this PhD was undertaken to provide some evidence for such a supportive therapy.

1.3 Chapter 3: UK healthcare professional opinions regarding exercise provision for prostate cancer patients

The findings of this chapter demonstrated variability within trusts offering chemohormonal therapy. In addition and irrespective of the 2014 NICE guidelines (section 1.4.19 in CG175), it was clear there were significant inconsistencies in the

NHS in how men initiating or undergoing ADT are offered supervised resistance and aerobic exercise if at all.

The survey demonstrated inconsistencies in delivering exercise recommendations amongst all 79 trusts identified. There was also variation in the delivery of exercise recommendations across the 47 sites determined as having an exercise programme or exercise referral scheme which had potential to meet the NICE guidelines. The findings from this study suggested that there is a need to standardise exercise programmes which can be fully integrated into the cancer care pathway for all men initiating or undergoing ADT regardless of the stage of disease.

The views and opinions of HCPs highlighted a lack of current supportive therapies for men with CRPC where such programmes could improve fitness and mitigate some of the long-term effects of their cancer/cancer therapy. The interviews demonstrated the need for an individualised and adaptable lifestyle intervention which employs a self-care approach to empower these men to be an active part of their own health management. In addition, muscle wastage is of significant clinical impact, affecting fitness for treatment and in some cases compromises current therapy. The HCPs were receptive to the idea of anabolic agents being consumed whilst completing a programme of exercise to reduce LBM loss in the context of a clinical trial. Furthermore, fitness for treatment in advanced prostate cancer remains a significant barrier for access to available therapies in those with a poor PS. Given the effects of long-term therapy and competing comorbidity in CRPC patients effecting PS, considerations into the timing of an exercise intervention must be made. This includes considerations into the safety of an intervention during chemotherapy due to the risk of neutropenia. Although generally it was felt that exercise throughout the prostate cancer care pathway would benefit patients.

Despite the lack of available exercise programmes for prostate cancer patients in the UK, the HCP survey and interviews suggest there is support for such intervention amongst the clinical community. However, considerations into the timing of such interventions must be made, such as the stage of disease and treatment. Although the HCP interviews revealed the need and the support for, a cost effective, individualised and adaptable exercise programme for men with CRPC, one HCP did express some concern over the "unfair allocation of resources" to cancer and another considered it

more of a luxury. Overall, the findings suggest that HCPs perceived advocating a self-care approach would empower these men to be an active part of their own health management. In order for such a programme to be successful it was concluded that education of both patient and clinicians would be essential.

1.4 Chapter 4: The feasibility study - COMRADE

The aim of COMRADE was to investigate the feasibility of a lifestyle intervention of supervised resistance exercise, dietary supplementation and dietary advice in men with CRPC. Recruiting this population was difficult with a recruitment rate of 13.5%. However, this was similar to previous exercise studies in cancer cohorts (Thomas, Alvarez-Reeves et al. 2013, Gilbert, Tew et al. 2016, Thomas Gwendolyn, Cartmel et al. 2016). Of those successfully recruited, adherence was less than that observed in other prostate cancer trials at 69%, with the best adherence observed in those who opted to attend sessions three times a week (Bourke, Doll et al. 2011, Gilbert, Tew et al. 2016, Dawson, Dorff et al. 2018, GalvÃO, Taaffe et al. 2018). Adherence to independent exercise was 78%. Additionally, adherence to the supplements was 68% for whey protein and 71% for creatine. Whilst the number of AEs and SAEs was high in the present study, this predominantly reflects the complex nature of such an advanced cancer population than being related to the study itself. The dropout rate in the present study was also similar to that which has been observed in previous exercise trials (Bourke, Doll et al. 2011, Gilbert, Tew et al. 2016, GalvÃO, Taaffe et al. 2018).

The study demonstrated improvements in LBM indices and a reduction in FM indices with the intervention corresponding with a decline in body mass and favourable changes in BMI. Previous studies have failed to show beneficial changes in body composition with exercise interventions in prostate cancer patients (Segal, Reid et al. 2003, Nilsen, Raastad et al. 2015, Sajid, Dale et al. 2016, Winters-Stone, Lyons et al. 2016, GalvÃO, Taaffe et al. 2018). In addition, improvements in 3RM testing and physical wellbeing scores were demonstrated, which is similar to findings in previous studies (Nilsen, Raastad et al. 2015, Taaffe, Newton et al. 2017, GalvÃO, Taaffe et al. 2018). Surprisingly, a decline in BMD was observed in the intervention group, although a notable effect size was only observable for hip BMD, but the reason for this decline was not determined.

The favourable changes in LBM suggest that resistance exercise with dietary guidance and supplementation has the potential to reduce the associated effects of LBM loss with ADT. Compared to healthier cohorts often recruited into complex lifestyle interventions of exercise, a trial of exercise, dietary supplementation and dietary guidance for men with CRPC was both feasible and safe. However, it is to be expected that there will be non-trial related SAE's and AE's due to the age and comorbidity profile of the participants.

1.5 Chapter 5: Participant focus groups

The focus groups demonstrated that the feasibility study procedures were well received. Improvements in the instruction and design of questionnaires, continuity of instructors and assessors throughout the trial, and an increased duration of exercise intervention programme were recommended.

The exercise programme was well tolerated overall. However, where some men had felt the programme was not physically challenging enough, others struggled with some of the exercises. This finding was also observed by the exercise instructor and author (RG). Some men appeared to progress in the exercises more rapidly than others and also tolerate changes in intensity much better, and others progressed much slower and struggled with increased intensity or starting new exercises as part of a new phase. However, the men perceived themselves as fitter and stronger, which reflects and is supported by the increased LBM and muscle strength discussed in chapter 4. The supplements were not tolerated as well as the exercise programme in the intervention group, with some men completely ceasing the whey and some reducing their dosage as shown in chapter 4. This was also reflected in the discussion during the focus group intervention participants.

Similar to previous exercise studies for men with prostate cancer, the camaraderie of the group exercise environment was considered very important by the participants and was of significant psychosocial benefit (Adamsen, Rasmussen et al. 2001, Bourke, Sohanpal et al. 2012, Bruun, Krustrup et al. 2014). Although the men did not explicitly state that the lifestyle intervention should be considered a treatment, it was felt to be a part of their overall care and the QoL and physical wellbeing benefits were highly valued. The physical changes described by these men were a contributing factor to their continued motivation and participation in the trial. Furthermore, the guidance from

trained individuals with the expertise and knowledge of their disease was another motivator to initial and continued participation in the trial.

The focus groups also showed that these men experienced significant physical and psychological problems due to both the presence of advanced cancer and its associated treatments. This included fatigue, gynecomastia, lymphodema, spinal cord compression and bone pain as well as the associated detrimental effects to wellbeing and QoL. Many of these effects were also associated as barriers to the participation in exercise and have been previous described as barriers in other studies (Grunfeld, Halliday et al. 2012, Stolldorf, Dietrich et al. 2016, Kogure, Hara et al. 2017). Other barriers included lack motivation and lack of clinician support for exercise behaviour.

The findings indicated there is a need for adequate support and guidance for exercise behaviour from the clinical team, and this is likely to be a significant facilitator in supporting men with CRPC to initiate and sustain exercise. Previous studies have also described a lack of support for exercise from a patients clinical team and the importance of such conversations in promoting exercise behaviours (Bourke, Sohanpal et al. 2012, Koutoukidis, Lopes et al. 2018). In particular, information specifically tailored to the unique needs of these men, taking into account the individuals needs and abilities to achieve the best health outcomes was recommended.

Overall the men's experience of the trial was a positive one, one participant summarised his experience in the quote below:

"… I think the idea of almost whether or not it works because we don't know whether or not the scans and that will show growth or whatever it might be but the fact that it stops you lying around doing bugger all, actually gets you out of the house and provides that motivation, that in itself, and it's quality of life. Now, whether or not the quality of life, how long we've got is shortened, increased or whatever, the fact that it actually makes you get out of bed when you might not, I think that's beneficial in itself."
Participant 10, intervention group

2. Implications for practice

The findings from these studies have added valuable evidence to the current data regarding exercise and dietary interventions for men with prostate cancer. The studies

in this thesis demonstrate the feasibility of an exercise and dietary intervention for men with CRPC. The patient reported experience demonstrated that patients are willing and receptive to exercise behaviour support. Despite this and the NICE guidelines (section 1.4.19 in CG175), there remains a lack of national implementation of exercise programmes for men with prostate cancer. The evidence accrued in the studies undertaken as part of this thesis has made a contribution to identifying some of the barriers as to why exercise is not routinely implemented in prostate cancer care and how such interventions may be conducted alongside standard clinical care. This evidence has the potential to be translated into addressing these barriers in clinical practice and provide some context as to how lifestyle interventions such as COMRADE can be implemented alongside standard care.

The barriers to exercise training in men with CRPC identified in this thesis can be summarised:

- Pathways: Structural and organisational barriers as a result of pathway changes in the NHS.
- Accessibility: The lack of available exercise programmes nationally which are accessible and appropriate for these men.
- Attitudes: Both of patients and HCPs involved in the care of these men. This predominantly surrounds the perceived ability to undertake exercise, with concerns over safety from HCPs, a lack of data supporting exercise interventions, and also in the motivation of patients to take part.
- Availability of exercise specialists: The need for instructors who have vital knowledge on the disease and how to correctly "prescribe" the correct exercises and intensity of exercise.
- Adverse effects of treatments and disease: The adverse effect of treatments impacting men's physical and psychological (attitudinal) ability to conduct exercise training. Disease progression can also result in changes in treatment and physical ability due to adverse effects such as pain or bone metastasis.
- Comorbidity: Increased disability as a result of other health ailments related or not related to their cancer, such as neurodegenerative disease.

From the evidence in the HCP survey and interviews, it is evident that in order for exercise interventions to be most effective, there is a significant need to embed them

into usual care for men with prostate cancer. The NICE guidance talks about the use of exercise interventions in the context of improving symptoms of fatigue, the evidence presented in the present study suggest that further benefits specific to men with CRPC may be possible with a tailored programme of exercise with supplementation.

The pathway changes related to the introduction of treatments and therefore changes in treatment sequencing can result in inconsistencies in patient care and also uncertainties regarding the long-term effects of these treatments. For these reasons, the introduction of an exercise programme should be considered as early as possible, but continued throughout a man's disease, to ensure the maintenance of an active lifestyle and therefore best possible physical and psychological health outcomes.

Furthermore, the HCP survey findings indicated that there are limited exercise interventions accessible for all cancer patients not just for prostate cancer patients. Patients with a poor performance status related to any cancer type have been neglected in exercise interventions. The findings from the studies presented in this thesis could be translated to highlight the potential opportunities to support other advanced cancer patients where LBM loss and cachexia are of clinical significance, such as pancreatic cancer and lung cancer via exercise and dietary intervention (Tan and Fearon 2008, Tan, Birdsell et al. 2009, Baracos, Reiman et al. 2010).

The findings demonstrate that supportive therapies for men with prostate cancer are necessary and exercise programmes present a potential therapeutic option as reflected by a participant in the intervention group.

"…but a lot of people are in the same boat and coping with it 15 years, 12 years or whatever…I'm not one personally for support groups in that way - but indirectly this is one to some degree, the fact that you're doing the exercises and then just chatting to people who have been through what you've been through…that's helpful." **Participant 10, intervention group**

If a programme was introduced, it would require consideration to the current NHS treatment pathway, the barriers described by the HCPs in chapter 3 and the patient reported barriers described in chapter 5 to determine a strategy for successful implementation. This should include training of HCPs involved in the care for men for prostate cancer all the way from diagnosis to the terminal phase of the disease. This

training package would need to discuss concerns regarding the safety of exercise for the more complicated patients and stress the importance of exercise and physical activity as part of standard care, in achieving best outcomes for disease and treatment. Furthermore, where men may ask their clinician for advice on how to safely exercise, such training would prepare clinicians with the information and or tools they need to advise accordingly, with the confidence that the information they are giving their patients is backed up by high quality research evidence. Where it is possible, professionals with a background in an exercise or health specialism should deliver such training working with clinicians to establish appropriate exercise advice.

It is vital that the clinical care team are advocates for exercise as part of a "self-care" approach to enable patients to benefit in both their treatments and disease. Furthermore, assessment of a patient's physical activity level could in the future be an integral part of a comprehensive medical history. It is the clinical teams responsibility to deliver the highest quality healthcare for these men, and therefore to initiate important conversations regarding improving and maintaining physical activity and exercise during routine care. Whilst it may not be feasible for oncologists or urologists to lead an in depth conversation regarding physical activity and exercise, given the time constraints described in chapter 3, where possible they should recommend increasing activity and refer to an appropriate available programme or to another trained member of the clinical team (such as a CNS) for further information.

A clear referral pathway to exercise programmes needs to be established nationally within Trusts, ideally supported by all members of the patient's MDT. What is less clear is who should provide such a programme which these men can access, the NHS or local authority. This could be determined through a robust economical evaluation of such programmes, which warrants further research. As part of an implementable programme, exercise professionals such as gym instructors and personal trainers, would also need the necessary training to understand some of the barriers which these men may be faced with due to their cancer, both treatment and disease related. This would ensure an understanding and empathetic approach as well as ensuring the participants in the programme feel the professionals have the appropriate experience and qualifications and understand their physical challenges and needs. This would include an understanding of the barriers faced regarding poor body image, debilitating fatigue and bone metastasis for example. Where instructors or trainers are adequately

trained this is likely to instil confidence in the participants. Exercise instructors who are trained in at least the level 3 exercise referral diploma would be recommended to undertake the programme sessions.

Prior to this study, there has been no published RCT data which has demonstrated the benefit of exercise training / physical activity in these men. Not only do the findings from this thesis demonstrate it is possible for men with CRPC to undertake exercise safely but also that patients report this kind of supportive therapy is needed and valued. The findings from the present body of work, with confirmatory evidence from future studies, could provide the impetus for clinicians to discuss exercise as a self-care approach with their more advanced patients and encourage patients to be receptive to support in improving or maintaining levels of activity. Considerations should be made when designing an exercise programme for these men, such as ensuring flexibility in the programme around current therapies, competing comorbidities and symptoms of disease. By tailoring exercise specific to the needs of men with CRPC, it may be possible to potentially manage LBM loss and slow the trajectory toward poor PS. Where men are able to tolerate treatments better due to superior PS and therefore fitness, we can aim to potentially improve OS.

The choice of the design of the resistance exercise aspect of the intervention was not only to utilise multiple muscle groups ensuring a full body approach was adopted but also to allow for regressions and progressions dependant on the individual. As was evident in the focus groups, some men were better at certain exercises than others and therefore responded better to certain exercises. As men with CRPC are a very heterogeneous group, there will be some physical variability of these men at baseline. An adapted approach to exercise training would enable men to adhere to the exercises and confer physical improvements (in weights and repetitions). For this reason, when developing future exercise programmes for men with CRPC (or other advanced cancer patients) it will be important to ensure the exercises chosen are adapted to suit the needs of the individual. As these men have complex needs due to their long history of disease, the approach should be different to that of earlier stage disease. It is therefore vital that those conducting the exercise programmes are adequately trained. Ensuring this will not only instil confidence in the clinical team when referring to the programme, but also in the individuals taking part. Such trained individuals would be able to sufficiently adapt exercise sessions, have an

understanding of the disease and treatment related barriers and facilitate exercise sessions safely.

3. Future research recommendations

3.1 Evidence for successful implementation of exercise in the prostate cancer care pathway

Despite an aim of COMRADE being to inform a larger scale trial, considering the findings of this thesis in its entirety, the immediate logical next steps for research may not be scaling up COMRADE to a larger RCT. Although the findings of these studies have given an insight into the value of lifestyle interventions for men with CRPC, there remain a number of broader questions to be answered. These specifically surround the successful implementation of future exercise programmes.

There have been a number of studies which have evaluated exercise interventions in cancer patients, however as demonstrated in the findings, a lack of implementation evidence has led to failures in research translating to clinical practice. Without such data there are potential risks involved in implementing future programmes. These can include equity harms, where exercise programmes may benefit those who need it least such as those who already partake in exercise or had the intention to do so (Bonell, Jamal et al. 2014). This also encompasses inequities in the intervention benefits, where although all men may benefit, some benefit much more than others, which could arguably be the case in COMRADE where some men progressed much better than others (Bonell, Jamal et al. 2014). Finally, opportunity harms where ineffective interventions may take the place of those which are more effective (Bonell, Jamal et al. 2014). Therefore, it is important to better understand the mechanisms of implementation but also of pathways of potential harm to optimise future interventions.

Future research should evaluate the differential effects of using different professional roles in exercise programme implementation. As highlighted in the HCP interviews, there is uncertainty as to who should deliver exercise advice and/or the programme itself. Although it was concluded that each member of the clinical team should play a part, to what degree is less clear. Furthermore, it is unclear if the intervention itself should be a community or NHS commissioned programme, where there lacks comparative data of the two. We do not know the differential effects of using different

professional groups in different settings, and this question will surely need to be answered for national implementation to be feasible.

In absence of such information, cost comparisons cannot be made and whether such interventions are even deemed viable at all in light of the financial restrictions in the NHS and local authorities. This also poses the question as to how cost effective a tailored prostate cancer specific programme compares to a programme that may include multiple cancer types. It may be that given the economical restrictions, a tailored programme is not justifiable and, as put by one of the clinicians in the HCP interviews, considered "more of a luxury". Regardless of what the most cost effective approach to implementing a programme is, these programmes need to be accessible enough to enable the NHS to signpost men appropriately.

The findings from the HCP interviews suggest that men are offered exercise programmes throughout their patient journey. Considerations should be made as to how these programmes may be positioned in the context of other guidelines/ programmes and initiatives, such as activity in older adults or other cancer types. If a prostate cancer specific programme is to be run separately, what is the justification for doing so and how is this more effective?

A significant limitation of these studies was the small sample sizes which limited the scope of the findings to select populations. Future considerations should be taken into how we may approach interventions to populations of different race, ethnicity, socioeconomic status, sexual orientation, religion/belief or other characteristics. Such considerations are fundamental to health equality, a key component of NICE recommendations and guidelines, and therefore for successful national implementation. Future research should consider how the characteristics of different populations can alter the effectiveness of a prescribed intervention.

Finally, the findings in this body of work have raised some questions on what benefits we should aim to achieve with such interventions for men with CRPC. There is some suggestion from the focus groups that the most valued outcome of the intervention were the psychological benefits, with men describing benefits in mental wellbeing. Future studies should address the outcomes that are most meaningful to these men; the physical, the psychological, or both and to what degree? Pre-study focus groups with CRPC patients would have been valuable in addressing this, but was not viable in

the time constraints of this body of work. Perhaps if these men consider wellbeing as a factor they would most like to improve, then the design of an intervention may look different to that of COMRADE. The intervention may focus less on a regimented exercise training programme and encompass a more casual group based aspect, where men can choose the type of activity for example with a focus on more social factors such as team orientated activity; particularly as the group format of the intervention was valued highly by the men in COMRADE. A less regimented and flexible approach may also encourage men who feel they are less physically capable or struggle with motivation or accessibility to still participate. As mentioned previously, the key component must be that the exercise is tailored to the individual, but this should also encompass individual goals. Future research should question what these men would like to achieve, what is clinically meaningful to them, and how do we achieve this with an intervention. Throughout the disease trajectory of prostate cancer, from diagnosis to death, the outcomes these men consider most important will likely change. For men with CRPC, improvements and maintenance of QoL is imperative and future interventions should strive to reflect that.

3.2 Future trials

The findings of this body of work indicate that a supportive lifestyle intervention for men with CRPC are both needed and have the potential to be of therapeutic benefit. Despite the lack of implementation data as described in the previous section, further research into the specific impact that resistance exercise and dietary interventions in men with CRPC is recommended given the findings in COMRADE.

3.2.1 Optimising the exercise dose

The findings of this thesis suggest a fundamental need for more robust mechanistic evidence. Primarily, this type of research and evidence could enhance greater clinician "buy in". Clinicians rely on plausible physiological rationales in addition to empirical data. This was highlighted by medical oncologist 2 in the HCP interviews who stated a lack of data surrounding exercise as a therapeutic for men with prostate cancer. The data surrounding exercise interventions in cancer groups thus far has predominantly been single dose exercise interventions with a progressive increase in intensity and a one size fits all approach (Buffart, Galvao et al. 2014, van der Leeden, Huijsmans et al. 2018). Such an approach is unlikely to confer a robust effect in outcomes as cancer in itself is heterogenic in nature and numerous studies have shown individual

differences to exercise stimuli (Buffart, Galvao et al. 2014). Patients are therefore likely to respond to a relative intensity/ exercise stimulus differently and what works well for one, might not for another. This further corresponds with the HCP interviews where they had voiced a need for an adaptable programme, and particularly for the advanced cancer patients where they are contending with multiple health ailments.

Future research considerations may like to explore quantifiable data at the molecular level demonstrating a dose response relationship between the optimal type and intensity of exercise for cancer cohorts to promote physiological changes (Friedenreich and Orenstein 2002, Courneya 2003, Buffart, Galvao et al. 2014). The mechanisms which underlie the observable improvements in health outcomes with exercise in cancer patients are not established. For example, there is no established mechanism for why exercise reduces pain or fatigue (Twomey, Martin et al. 2018). Furthermore, in the present trial it is not clear why this was a finding for some men and not others. Without a deeper understanding of the molecular and physiological changes resulting from exercise training in cancer patients, questions regarding the causal relationship will remain unanswered. As a result we are no closer to determining the optimal dose (intensity, duration and method) and type of exercise to confer the greatest benefit for individuals (Courneya 2003, Buffart, Galvao et al. 2014). A personalised approach to exercise prescription might confer the greatest beneficial effect and therefore the most robust evidence for exercise as a supportive therapy.

3.2.2 A trial to deliver the prescribed dose

Previous studies adopting an adapted exercise programme approach have also shown improvements in advanced cancer patients with complex needs (Touillaud, Foucaut et al. 2013, Twomey, Martin et al. 2018, van der Leeden, Huijsmans et al. 2018). Evidence which described the optimal exercise dose adapted to the individual would also be encouraging for clinicians, where the observable effects of the RCT data can be underpinned with basic science mechanistic data which suggests a causal relationship. In addition, such an approach would likely confer an even larger effect size on health outcomes of interest, perhaps beyond that which has been observed in the current literature. Questions on optimal implementation of exercise programmes for greater efficacy and efficiency can then be adequately addressed (Buffart, Galvao et al. 2014). In this case, it may be more appropriate to conduct a small (n ≤100) single arm trial with a more robust real-time evaluation which could therefore respond to the

continually evolving cancer pathways, as demonstrated by the HCP survey and interviews. In addition, such an approach would allow for flexibility and adaptive doses of exercise to be implemented at a relatively low cost compared to a large scale phase III study.

Although RCTs remain the gold standard study design for pharmaceutical research, there is significant criticism for their use in other areas of medicine and they have been considered inappropriate for more complex long-term highly individualised studies (Bothwell, Greene et al. 2016). RCTs have their challenges, from establishing appropriate inclusion criteria to standardising interventions and determining the most relevant outcomes in addition to being both expensive and time consuming, with these limitations being well documented (Bothwell, Greene et al. 2016). The proposed study design would evaluate the effectiveness of the intervention and provide an ongoing timely narrative to the data. Issues arising in the study such as lack of efficacy, poor adherence, or study failings would be addressed and allow for programme improvement from formative evaluations of intermediary results (Ling 2012). In addition, the removal of the control arm would remove the prospect of contamination and the disappointment experienced by those who are subsequently not offered the intervention. The purpose of such a study design would be to observe the molecular and physiological changes observed with a prescribed adapted programme of exercise training. For example, the relationship between increased LBM and inflammatory cytokines with a prescribed exercise dose for an individual. Although this data would not directly demonstrate efficacy of the dose of exercise prescribed for each participant as the trial is not controlled and randomised, it could provide indicators to potential mechanisms underpinning exercise and the corresponding clinical outcomes. Furthermore, the flexibility in the trial would allow for changes to be made (real-time) for best implementation and participant adherence.

The combination of the data regarding optimal exercise prescription underpinned by findings at the molecular level could therefore be used to inform the design of a further study, which would likely be a larger scale RCT (Friedenreich and Orenstein 2002, Courneya 2003, Buffart, Galvao et al. 2014). This study would address the implementation of an individualised exercise programme, with a prescribed dose underpinned by mechanistic findings, for men with prostate cancer. The findings could be used to educate clinicians prior to study recruitment, increasing clinician "buy in"

and helping them to advocate individualised exercise training for their patients. This subsequent study would also draw on the suggested improvements which have been discussed in the present body of work such as a multi-site study, increased intervention duration, adequate numbers of trainers and trainer/assessor continuity, improved instruction for filing out questionnaires, permuted block randomisation and a four arm trial for example.

5. Research evaluation

The research question for the body of work was can a lifestyle intervention of resistance exercise, dietary supplementation and dietary guidance improve outcomes in men with CRPC? This body of work has demonstrated that a lifestyle intervention of resistance exercise, dietary supplementation and guidance can improve outcomes of wellbeing, muscle strength, LBM and body fat.

The first aim of this body of work was to describe exercise in the usual care pathway for men in the UK with prostate cancer who have undergone ADT; including if, how and in which trusts exercise is part of "usual care". The findings determined that nationally supervised exercise for men with advanced prostate cancer undergoing or initiating long-term ADT is not routinely offered in UK trusts and not a part of "usual care". Furthermore, there is a significant lack of available exercise programmes which men with prostate cancer can access.

The second aim was to explore the perspectives of HCPs on the use of exercise training for the management of CRPC. The findings show that HCPs are supportive of exercise as a supportive adjunct to standard care to improve outcomes in these men. However, such a programme would need to be adequately tailored to the needs of the individual taking into consideration comorbidities, disease burden and current and previous treatments and their associated AEs.

The final aim was to determine the feasibility and participant acceptability of a 16-week programme of resistance exercise training, dietary supplementation and dietary guidance as a novel supportive therapy in men with CRPC. There were significant problems with recruitment in the RCT were the study was unable to make its target recruitment of 50 participants; there were a high number of AEs/SAEs; and the adherence to supervised exercise was lower than that seen in previous exercise

studies. However, the advances stage of disease of these men must be taken into account, and with the suggested adaptations to a future trial, it is likely that some of these feasibility outcomes could be improved. Furthermore, the focus groups have established that the study procedures were very well received by the participants.

5.1 Dissemination of findings

The HCP survey and interview findings have been published in two peer reviewed journals (Bourke, Turner et al. 2018, Greasley, Turner et al. 2018). The findings of the COMRADE RCT and focus groups have been accepted for poster presentation at the 2018 National Cancer Research Institute conference and will be published as a full manuscript in due course.

4. Summary

The studies contained within this thesis are a novel contribution to knowledge and provide data on the feasibility of a programme of exercise, dietary guidance and supplementation for men with CRPC. The findings of the studies indicate that whilst it was safe and feasible to conduct such an intervention in these men, significant barriers exist to the implementation of exercise programmes for men with prostate cancer within the NHS and there is a lack of data underpinning the associated physiological changes associated with exercise training in men with prostate cancer. Further research, should address problems associated with national implementation of exercise programmes. This includes creating an NHS culture whereby exercise is seen as a therapeutic adjunct to standard care, whereby it is endorsed by the entire care team. It is likely that this will need to include training HCPs and upskilling the NHS workforce to enable the conversation of exercise with patients but also to refer to appropriate programmes. In order for a referral to be made, there must be available programmes accessible to these men that are facilitated by trained individuals, aware of the unique challenges these men face related to their treatment and disease.

To encourage clinician "buy in" for exercise as part of standard care, future research should also look to determine the optimal "dose" of exercise to warrant the best clinical outcomes in each individual. Part of this may encompass a future study with an adapted trial design, underpinned by the investigation of mechanistic outcomes to further the literature and aid in the successful implementation of exercise programmes in the NHS. With such evidence, we can develop a future prostate cancer care

pathway where exercise is a fundamental aspect of care, ensuring continuity between trusts and exercise programmes across the country which is accessible by all men affected by the disease.

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A lifestyle intervention to improve outcomes in men with castrate-resistant prostate cancer

Rosa Greasley

Volume 2: Appendices

A thesis submitted in partial fulfilment of the requirements of Sheffield Hallam University for the degree of Doctor of Philosophy

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Supervisors: Dr David Broom, Prof Derek Rosario and Dr Helen Crank

Collaborating organisations: Sheffield Teaching Hospitals NHS Trust and The University of Sheffield

Sheffield Hallam University

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Appendix 1 The Clinvivo report (including the 27 item survey)

Sustained exercise training for men with prostate cancer on androgen deprivation (STAMINA) survey

Final Report

Clinvivo Ltd

3rd March 2016

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1. Preamble

This report describes the invitation, collection and analysis of data from respondents invited by Clinvivo, on behalf of the STAMINA investigators, to participate in a survey to explore issues around delivering prostate cancer care in NHS practice.

2. Methods

2.1 Sampling, recruitment and material

The STAMINA Investigators provided Clinvivo with the text of the questionnaire along with a list of invitees and wording of the e-mail invitation (Appendix). Clinvivo sent the invitation email to the invitees along with personalised links to the questionnaire presented on the Clinvivo platform. Clinvivo also prepared and sent customised links to contacts in professional organisations to be circulated to their members, and one link to be shared by the investigators to their Twitter followers.

Individual e-mail invitations were sent out to 392 invitees on 26th November 2015, and invitations for members of four professional organisations were sent to their contacts on 1st December 2015. A Twitter link was shared with the investigators on 11th December 2015. The first reminders to the emailed invitees were sent on 10th December 2015 and the final reminders on 22nd December 2015.

Panellists were invited to comment on the availability and management of exercise therapy for men with prostate cancer on Androgen Deprivation Therapy (ADT) in the NHS.

2.2 Statistical analysis

Descriptive statistics were used to report all responses. The proportions and denominators of categorical variables, and the means and ranges of continuous responses are presented in this report. Graphical categorical proportions have been presented graphically, using pie charts for mutually exclusive categorical data and bar graphs for responses where selection of multiple outcomes was allowed. All analyses were conducted in Stata v13.

3. Results

A total of 95 practitioners agreed to participate in the survey. The individual email invitations contributed to 44.2% of responses, and the the emails to professional

organisations elicited 47.4% of responses. The remaining 8.2% of responses were elicited via Twitter.

Table 1: Mode of invitation of respondents to the survey

Referrer	**n**	**%**
BAUN	13	13.68
BAUS	24	25.26
BUG	4	4.21
E-mail	42	44.21
PCUS	4	4.21
Twitter	8	8.42
Total	**95**	**100**

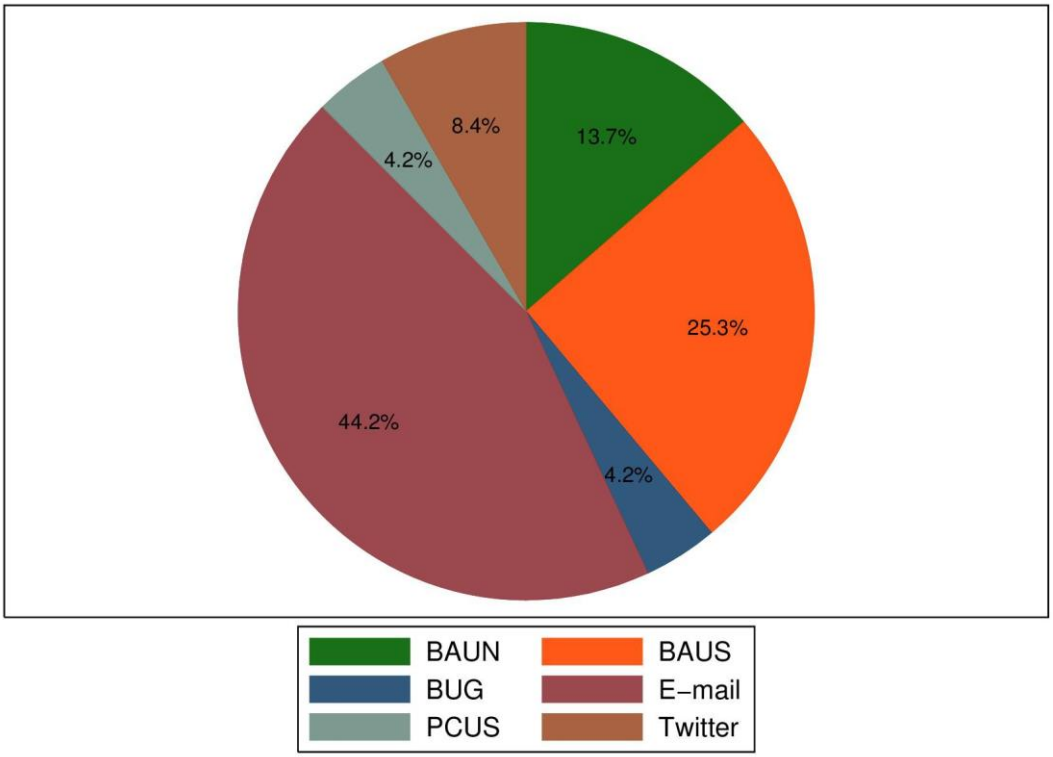


Figure 1: Mode of invitation of respondents to the survey

Most of the respondents were urologists (36.8%) perhaps reflecting the subject area of the survey. Nurses were the next largest group (21.1%), while 16.8% of respondents did not fall under any of the listed professions.

Table 2: Professional roles of respondents

Profession	**n**	**%**
Allied Health Care Professional	3	3.16
Cancer Care Commissioner	3	3.16
Exercise Physiologist	3	3.16
General Care Commissioner	1	1.05
General Practitioner (GP)	7	7.37
Nurse	20	21.05
Oncologist	4	4.21
Physiotherapist	3	3.16
Urologist	35	36.84
Other	16	16.84
Total	**95**	**100**

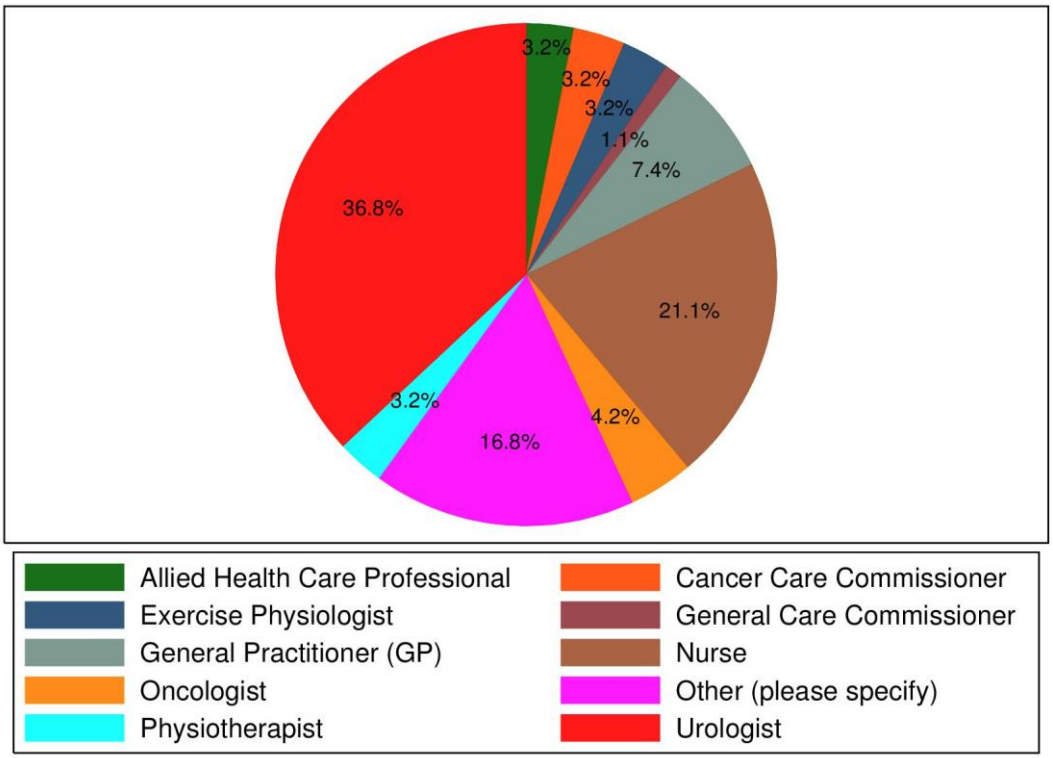


Figure 2: Professional roles of respondents

Respondents were reminded of the recent findings of the CHAARTED and STAMPEDE studies which showed a survival advantage for hormone-naive men with metastatic prostate cancer on chemohormonal therapy (Taxane based chemotherapy plus ADT) rather than ADT alone. Respondents indicated that on average 23.3% of men currently commencing long-term ADT were

also receiving Docetaxel or a similar agent at initiation of ADT, although this ranged from 0% to 87%.

The commonest reasons given by the 39 respondents who indicated that men were not receiving chemohormonal therapy were that the patient was unfit for it (48.7%) and lack of funding (43.59%)

Table 3: Reasons for not giving chemohormonal therapy

Reason	**n**	**%**
No funding	17	43.59
Unconvincing evidence	3	7.69
Updating guidelines	8	20.51
Clinician resistance	5	12.82
Patient resistance	5	12.82
Patient unfit	19	48.72
Other	10	25.64
Number of responses (multiple selection allowed)	**39**	

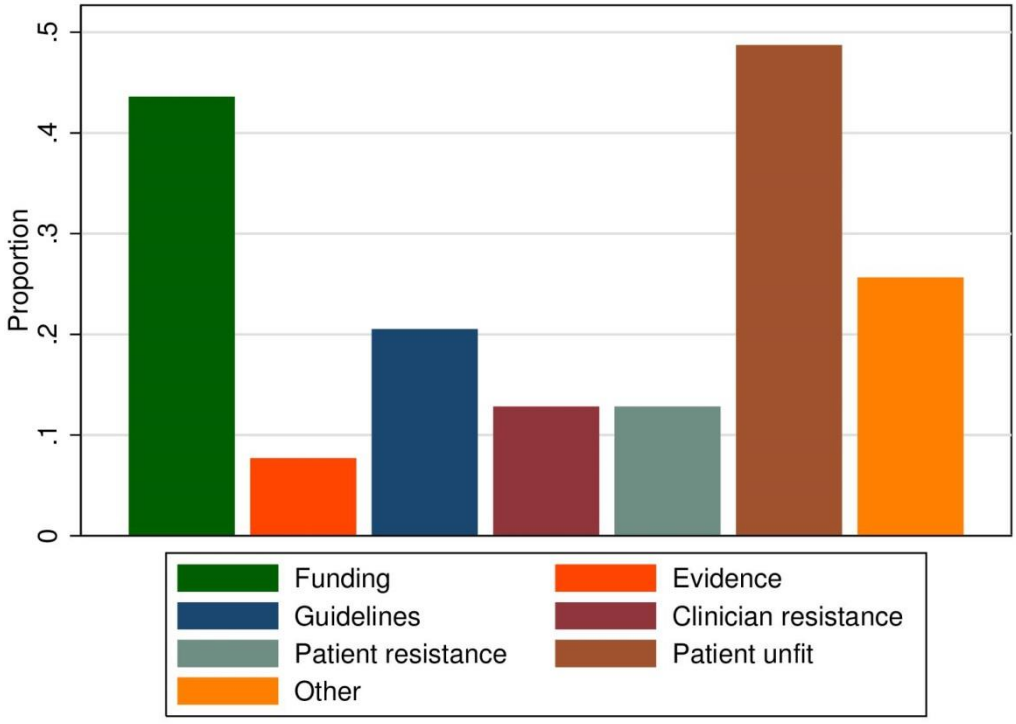


Figure 3: Reasons for not giving chemohormonal therapy

Respondents were asked to indicate the proportion of men on long-term ADT receiving treatment in primary care in their area. A total of 64 respondents reported a mean percentage of 84.5%, ranging from zero to 100%.

In most of the local prostate cancer pathways staffed by the respondents, urologists (93.9%), oncologists (77.2%) and clinical nurse specialists (63.6%) were involved in initiating ADT. General practitioners were involved to a lesser extent (19.7%) and practice nurses were barely involved (4.6%). However, a wider range of specialities were involved in delivering ADT.

Table 4: Healthcare professionals involved in initiating ADT

Profession	**n**	**%**
Oncologist	51	77.21
Urologist	62	93.94
Clinical Nurse Specialist	42	63.64
General Practitioner (GP)	13	19.70
Outpatient Nurse	0	0.00
Practice Nurse	3	4.55
District Nurse	0	0.00
Other	0	0.00
Number of responses (multiple selection allowed)	**66**	

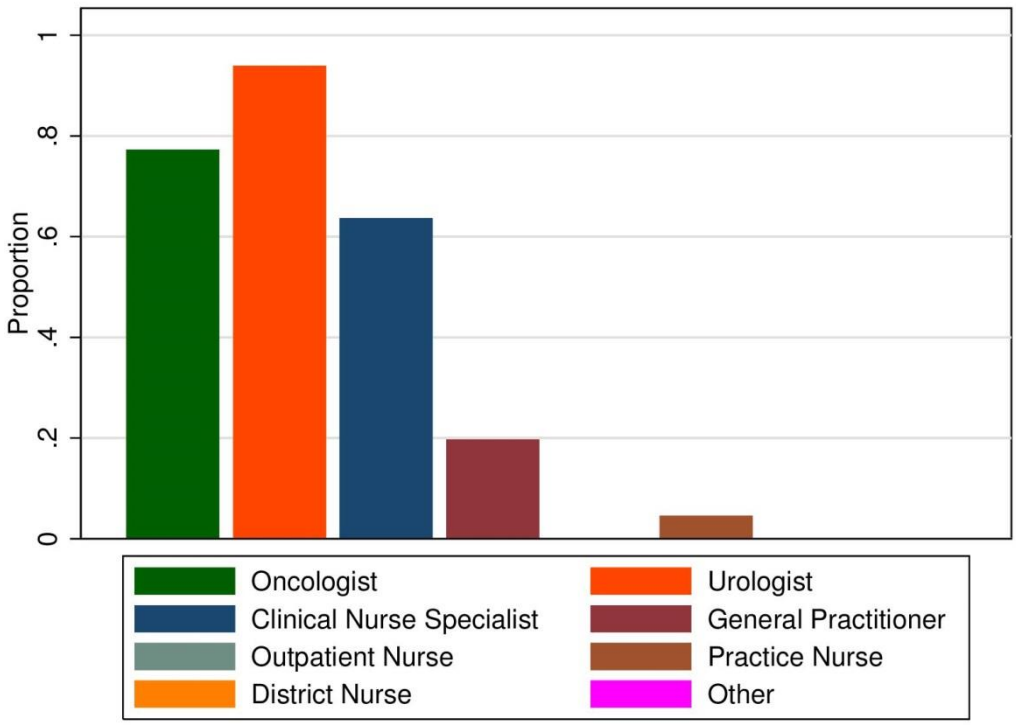


Figure 4: Healthcare professionals involved in initiating ADT

Table 5: Healthcare professionals involved in delivering ADT

Profession	**n**	**%**
Oncologist	19	28.79
Urologist	24	36.36
Clinical Nurse Specialist	46	69.70
General Practitioner (GP)	56	84.85
Outpatient Nurse	10	15.15
Practice Nurse	49	74.24
District Nurse	24	36.36
Other	1	1.52
Number of responses (multiple selection allowed)	**66**	

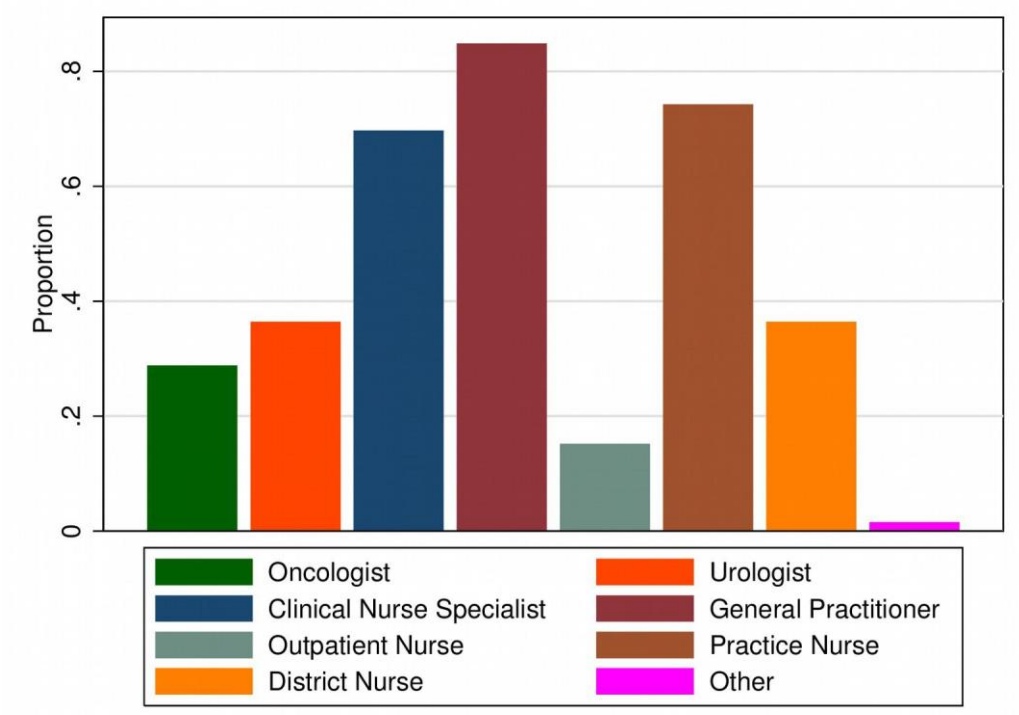


Figure 5: Healthcare professionals involved in delivering ADT

A total of 70 out of 95 respondents (73.6%) stated that they were aware of the new NICE guidelines on Prostate cancer (cg175). Slightly fewer, 58 respondents (61.1%) said they were aware of NICE recommendation 1.4.19 which states that men who are starting or having androgen deprivation therapy should be offered supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue and improve quality of life. Asked to rate on a scale of 10 their ability to deliver this recommendation in their locality, the mean response was 4.87.

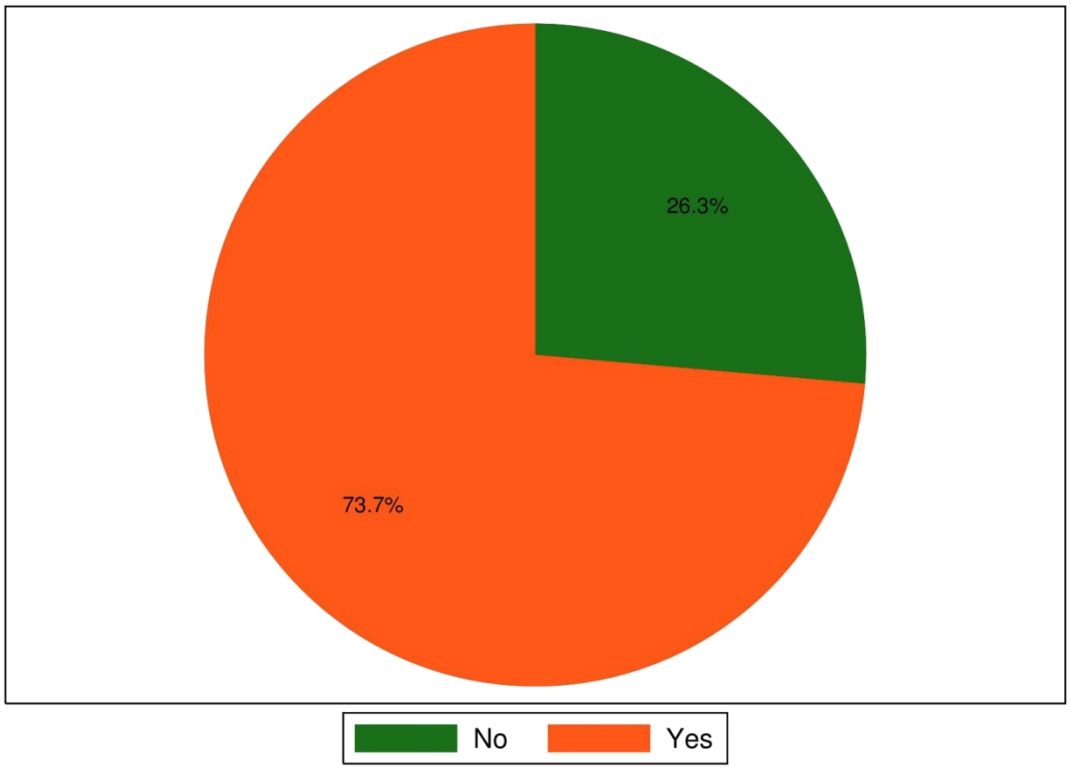


Figure 6: Respondents' awareness of NICE guidelines on prostate cancer (cg175)

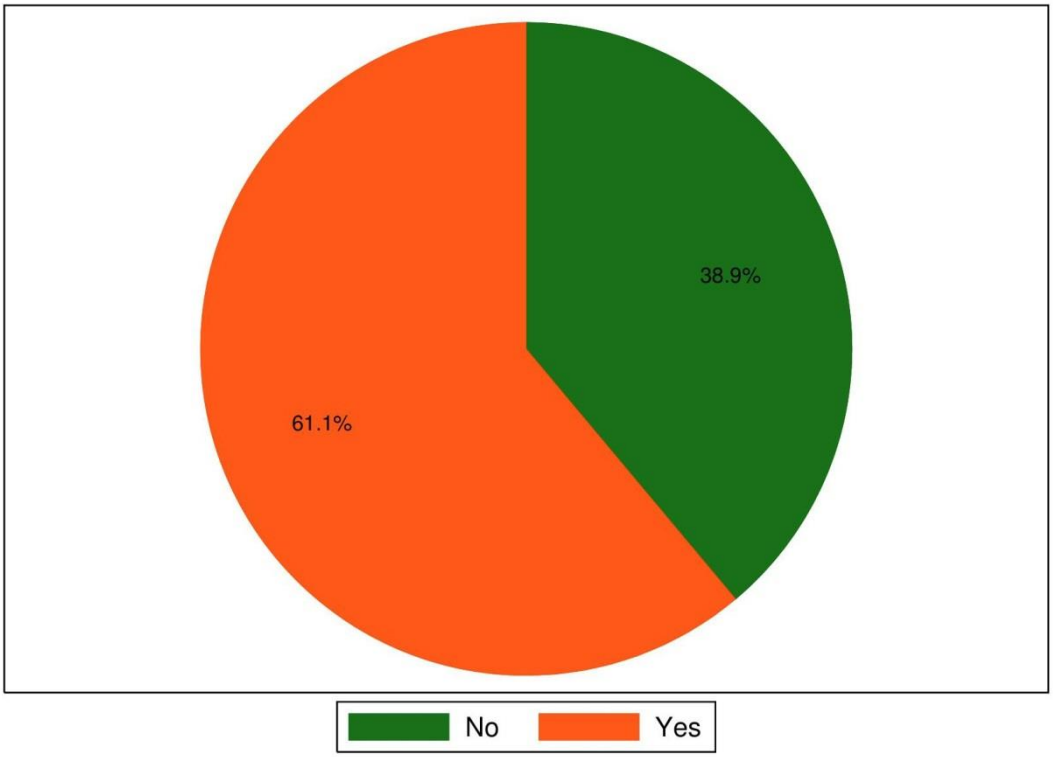


Figure 7: Respondents' awareness of NICE recommendation 1.4.19

About half of respondents were aware of current exercise referral or prescription schemes for patients with cancer in their locality.

Table 6: Respondents' awareness of current local exercise referral/prescription schemes for patients with cancer

Aware	**n**	**%**
Yes	47	49.47
No	37	38.95
Unsure	11	11.58
Total	**95**	

Among those who were aware of the existence of an exercise programme, 80.6% reported that there were schemes accessible to men with prostate cancer on ADT.

Table 7: Accessibility of the available exercise referral/prescription schemes to men with prostate cancer on ADT

Accessible	**n**	**%**
Yes	38	80.85
No	8	17.02
Unsure	1	2.13
Total	**47**	

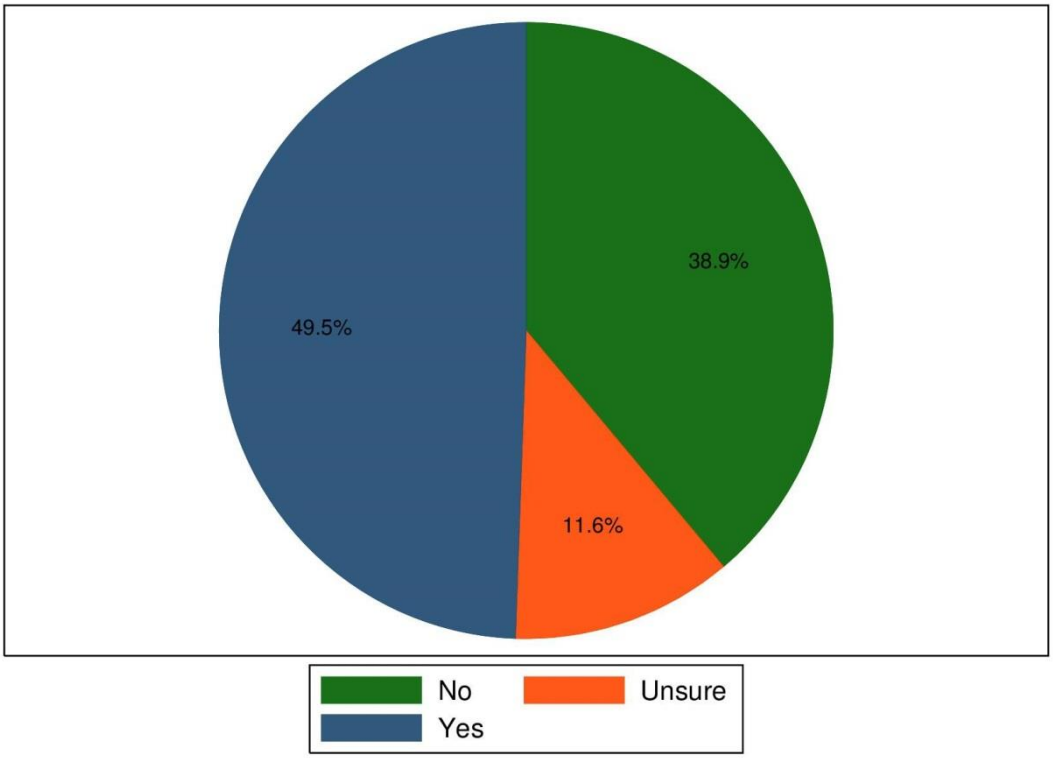


Figure 8: Respondents' awareness of current local exercise referral/prescription schemes for patients with cancer

Most of the exercise referral schemes were available in the community (53.2%), local authority (34.0%) and hospital (21.3%).

Table 8: Where the exercise referral schemes are based

Location	**n**	**%**
Not applicable – these services are not available in my area	0	0.00
Unsure	6	12.77
Hospital	10	21.28
Community	25	53.19
Both hospital and community	6	12.77
Charity sector	3	6.38
Local authority	16	34.04
Other	3	6.38
Number of responses (multiple selection allowed)	**47**	

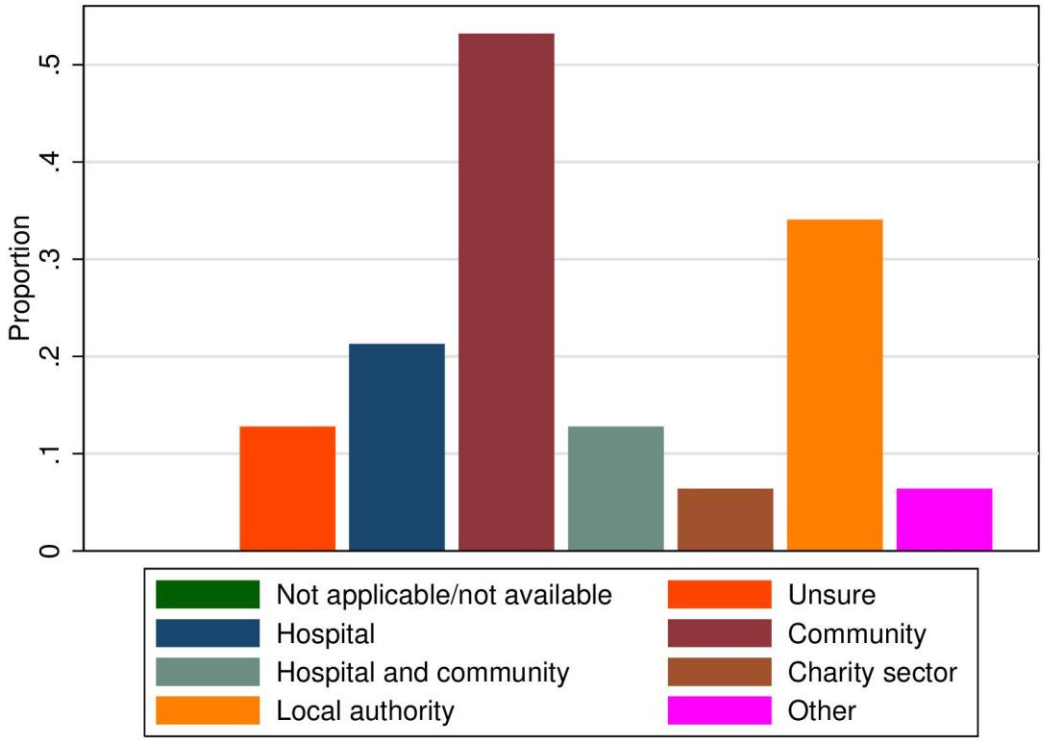


Figure 9: Where the exercise referral schemes are based

Nurses, GPs, physiotherapists and hospital consultants were the clinical specialists most commonly reported to be involved in the exercise referral pathways. Non-clinical specialists, including gym instructors (44.7%) and personal trainers (25.5%) were also involved in the referral pathway.

However, it was the non-clinical professionals, chiefly gym instructors who were reported to be responsible for setting the frequency, intensity and duration of the exercise programme (66.0%), and for supervising the delivery of exercise and tailoring and monitoring individuals' programmes (68.1%). Majority of exercise programmes were offered in group sessions (59.6%).

Table 9: Healthcare professionals involved in exercise referral pathway

Healthcare professional	**n**	**%**
Hospital consultant	16	34.04
Nurse	28	59.57
GP	20	42.55
Physiotherapist	18	38.30
Clinical Exercise Physiologist	8	17.02
Other	6	12.77
Number of responses (multiple selection allowed)	**47**	

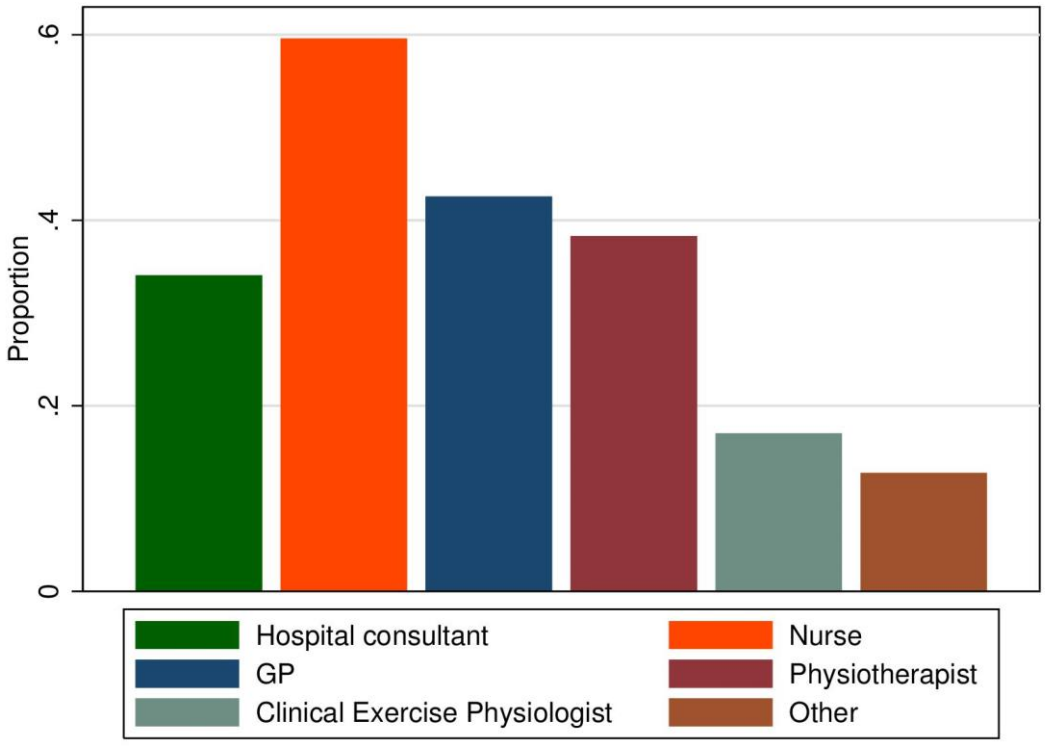


Figure 10: Healthcare professionals involved in exercise referral pathway

Table 10: Non-clinical professionals involved in exercise referral pathway

Non-clinical professional	**n**	**%**
Gym Instructor	21	44.68
Personal Trainer	12	25.53
Other	23	48.94
Number of responses (multiple selection allowed)	**47**	

Figure 11: Non-clinical professionals involved in exercise referral pathwa

Table 11: Professionals responsible for setting frequency, intensity and duration of exercise programmes

Professional	**n**	**%**
Consultant	0	0.00
Nurse	5	10.64
GP	3	6.38
Physiotherapist	11	23.40
Clinical Exercise Physiologist	13	27.66
Gym Instructor	31	65.96
Other	8	17.02
Number of responses (multiple selection allowed)	**47**	

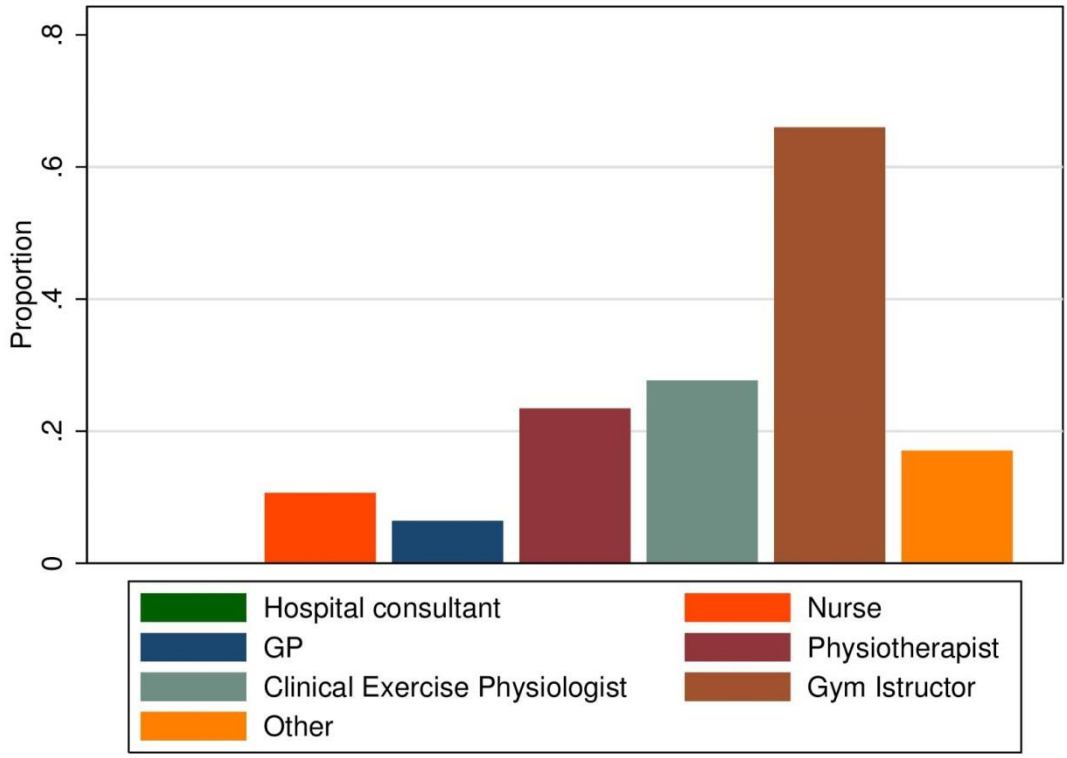


Figure 12: Professionals responsible for setting frequency, intensity and duration of exercise programmes

Table 12: Professionals responsible for supervised exercise delivery, tailoring and monitoring of an individual's programme

Professional	**n**	**%**
Consultant	0	0.00
Nurse	1	2.13
GP	1	2.13
Physiotherapist	11	23.40
Clinical Exercise Physiologist	12	25.53
Gym Instructor	32	68.09
Other	8	17.02
Number of responses (multiple selection allowed)	**47**	

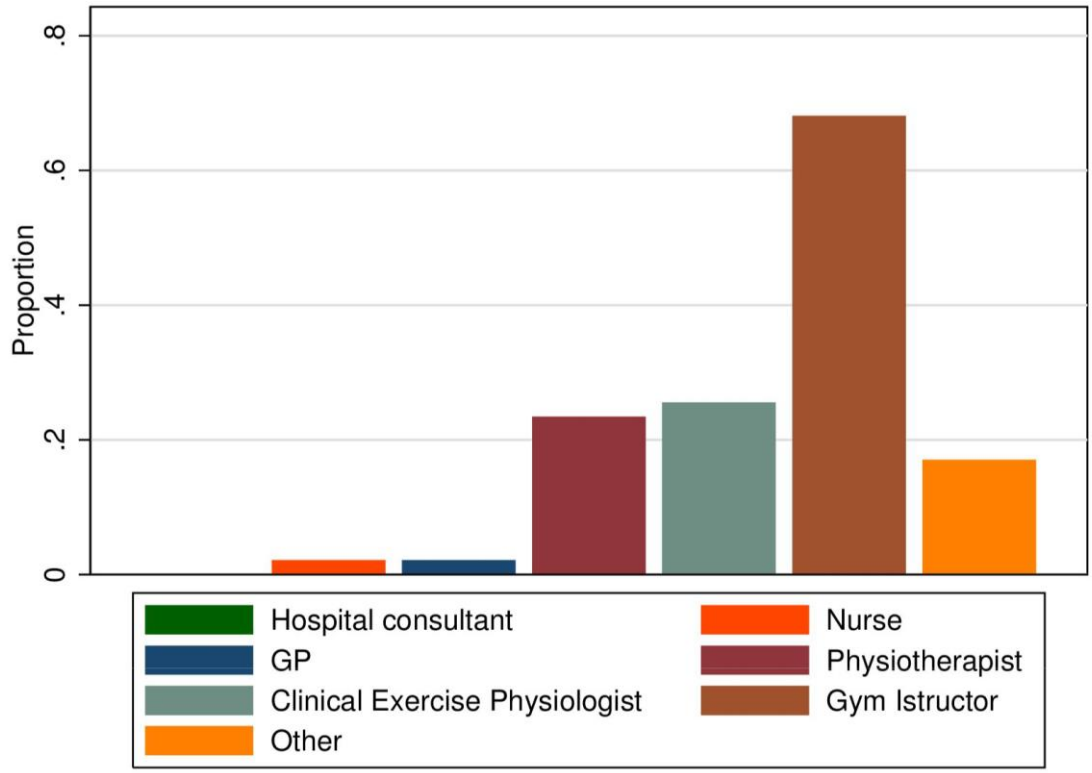


Figure 13: Professionals responsible for supervised exercise delivery, tailoring and monitoring of an individual's programme

Table 13: How the exercise sessions are offered

Session type	**n**	**%**
Group	28	59.57
One-to-one	14	29.79
Both group and one-to-one	1	2.13
Other	1	8.51
Total	**47**	**100**

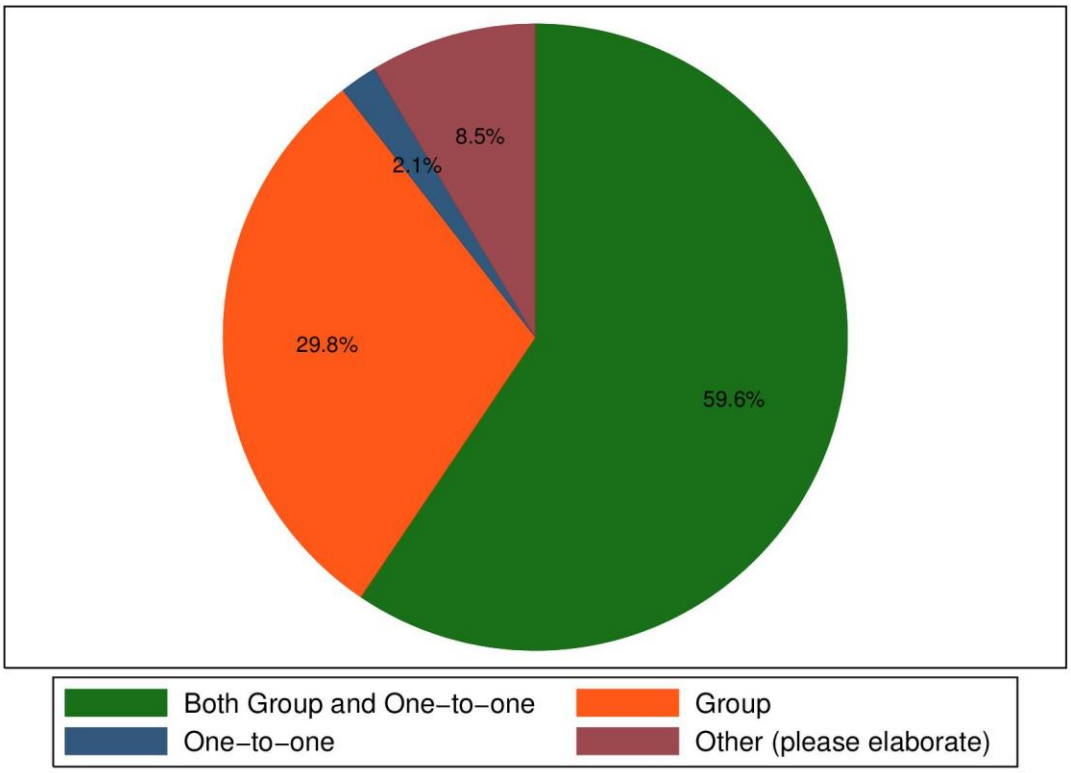


Figure 14: How the exercise sessions are offered

Over half – 72.3% – of the 47 respondents who knew about exercise referral programmes were not aware or were unsure of the existence of training schemes in their organisations for staff on exercise interventions in cancer populations. A third of these respondents (32.4%) reported that instead these facilities were based in the community or local authority, just under 20% reported that they were available in primary care, secondary care, charities or private sector, while most (44.1%) reported that these facilities were based in other places.

Table 14: Respondents' awareness of training schemes in their organisations for staff on exercise interventions in cancer populations

Aware	**n**	**%**
Yes	13	27.66
No	25	53.19
Unsure	9	19.15
Total	**47**	**100**

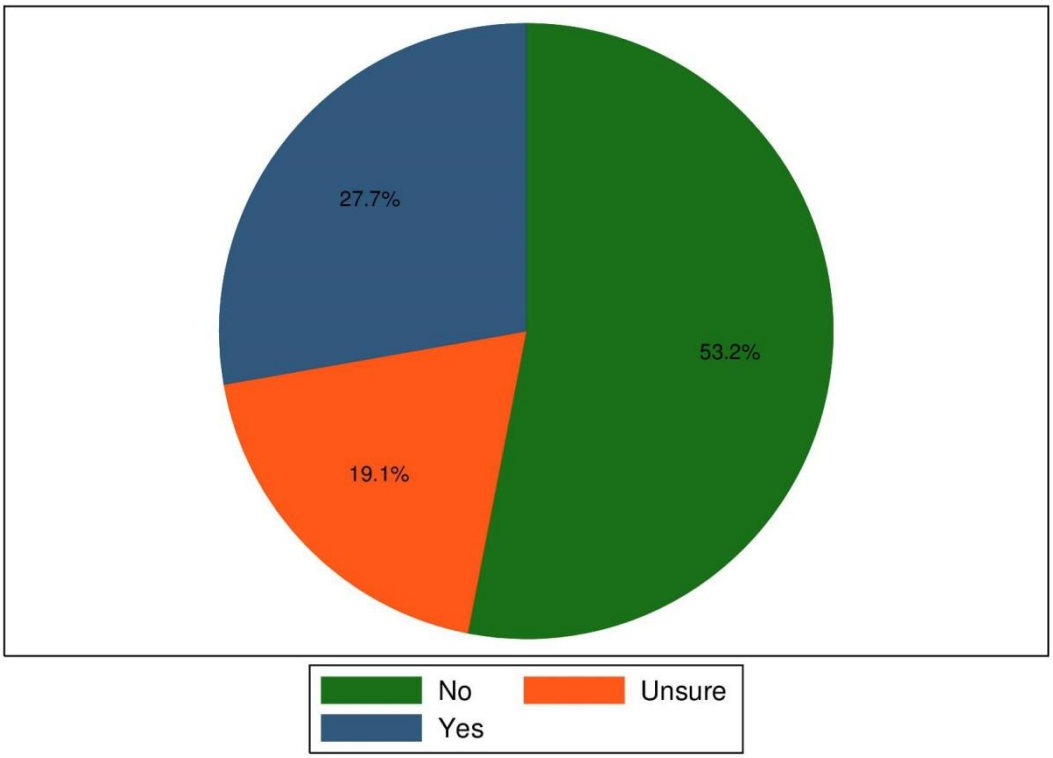


Figure 15: Respondents' awareness of training schemes in their organisations for staff on exercise interventions in cancer populations

Table 15: Where training facilities (not located in respondents organisations) are based

Location	**n**	**%**
Community/local authority	11	32.35
Primary care	1	2.94
Secondary care	1	2.94
Charitable organisation	5	14.71
Private sector	0	0.00
Other	15	44.12
Number of responses (multiple selection allowed)	**34**	

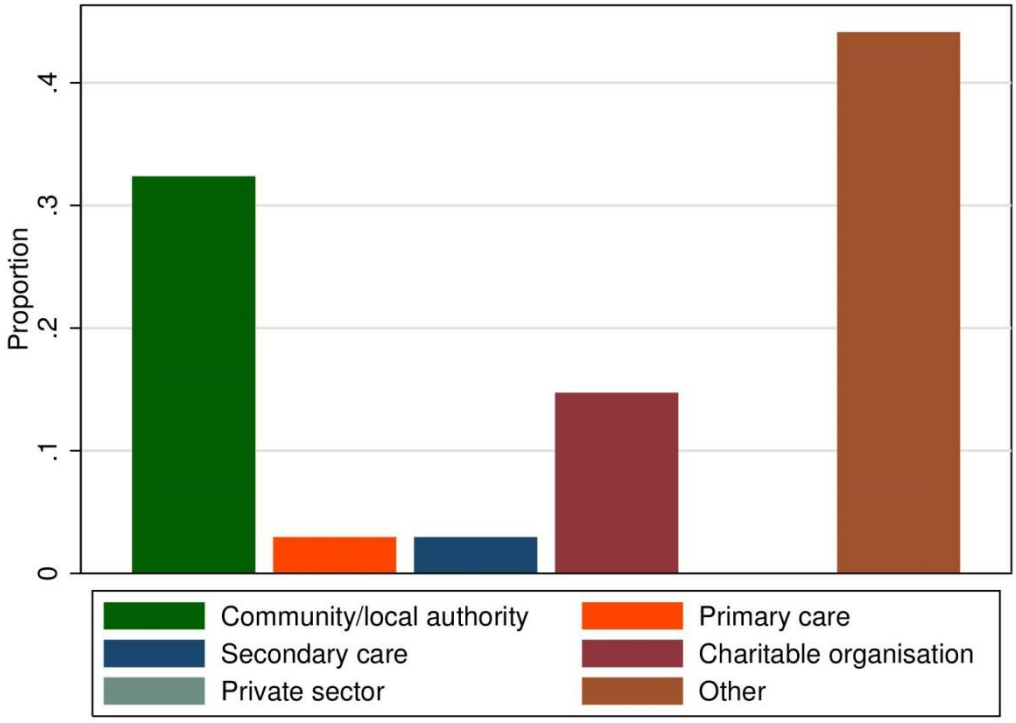


Figure 16: Where training facilities (not located in respondents organisations) are based

A majority of respondents were aware of current (55.3%) or future (63.8%) local service evaluations around exercise programmes for men with prostate cancer. Only 45.3% of respondents were aware of behaviour change support services available to their local population to promote active lifestyle; of these 79.1% of respondents indicated that these services were available to men with prostate cancer.

Table 16: Respondents' awareness of current local service evaluations around exercise programmes for men with prostate cancer

Aware	**n**	**%**
Yes	12	25.53
No	26	55.32
Unsure	9	19.15
Total	**47**	**100**

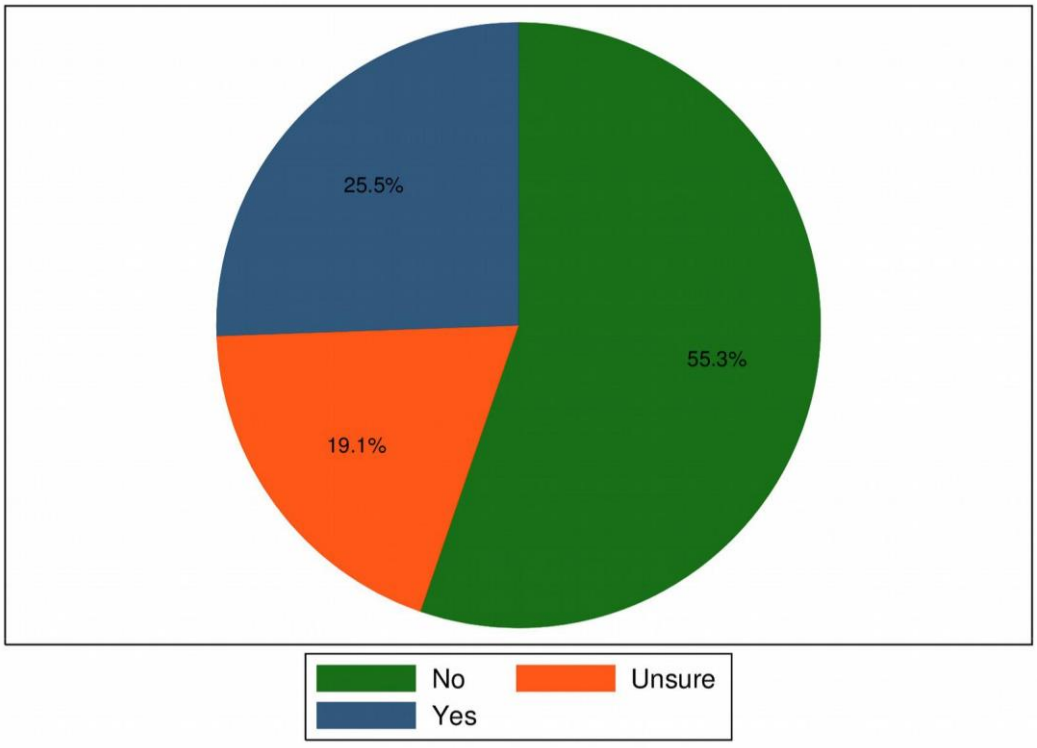


Figure 17: Respondents' awareness of current local service evaluations around exercise programmes for men with prostate cancer

Table 17: Respondents' awareness of future local service evaluations around exercise programmes for men with prostate cancer

Aware	**n**	**%**
Yes	6	12.77
No	30	63.83
Unsure	11	23.40
Total	**47**	**100**

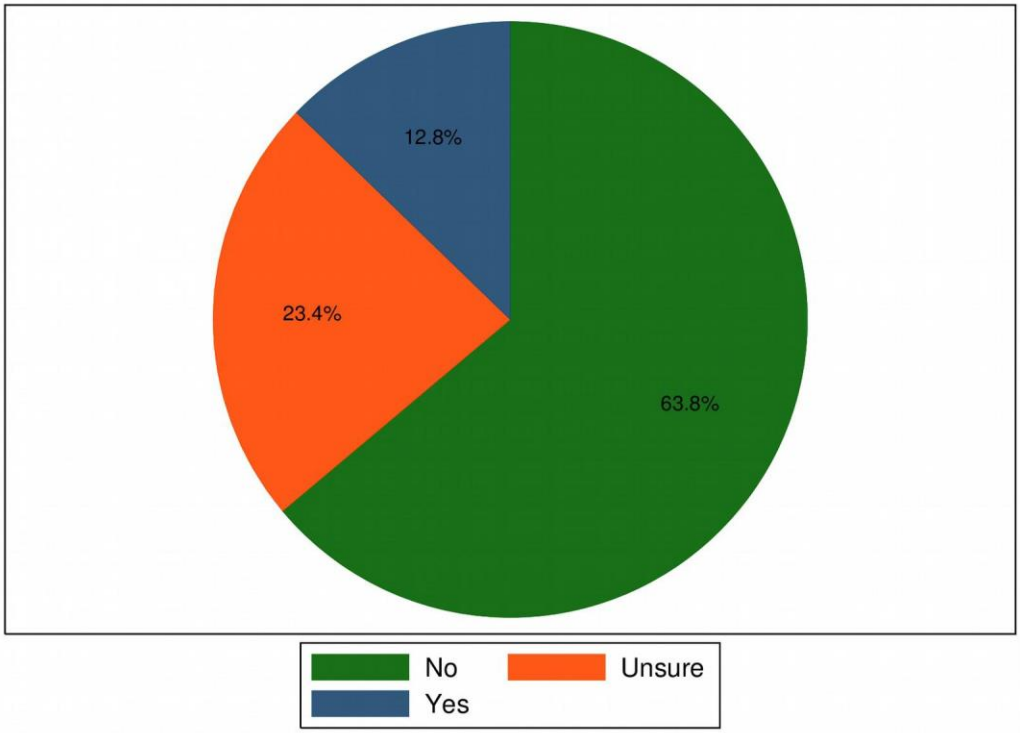


Figure 18: Respondents' awareness of future local service evaluations around exercise programmes for men with prostate cancer

Table 18: Respondents' awareness of behaviour change support services available to their local Awarepopulations to promote active lifestyle

Aware	**n**	**%**
Yes	43	45.26
No	36	37.87
Unsure	16	16.84
Total	**95**	**100**

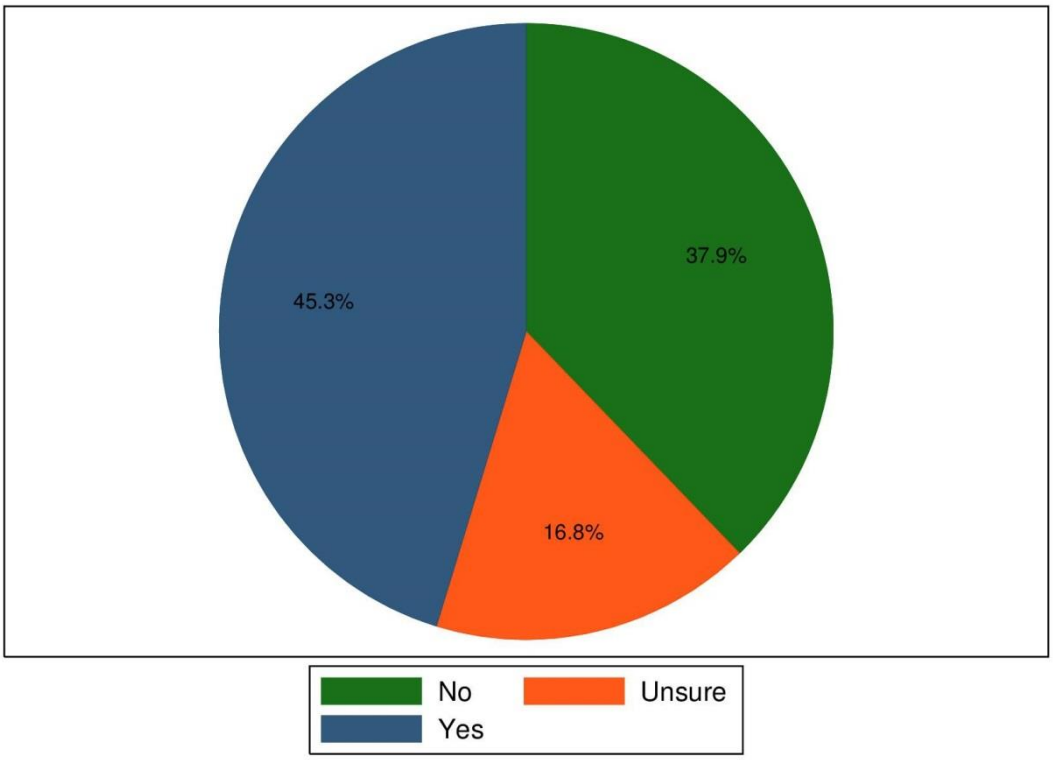


Figure 19: Respondents' awareness of behaviour change support services available to their local populations to promote active lifestyle

Table 19: Availability of behaviour change support services to men with prostate cancer

Available	**n**	**%**
Yes	34	79.07
No	9	20.93
Total	**43**	**100**

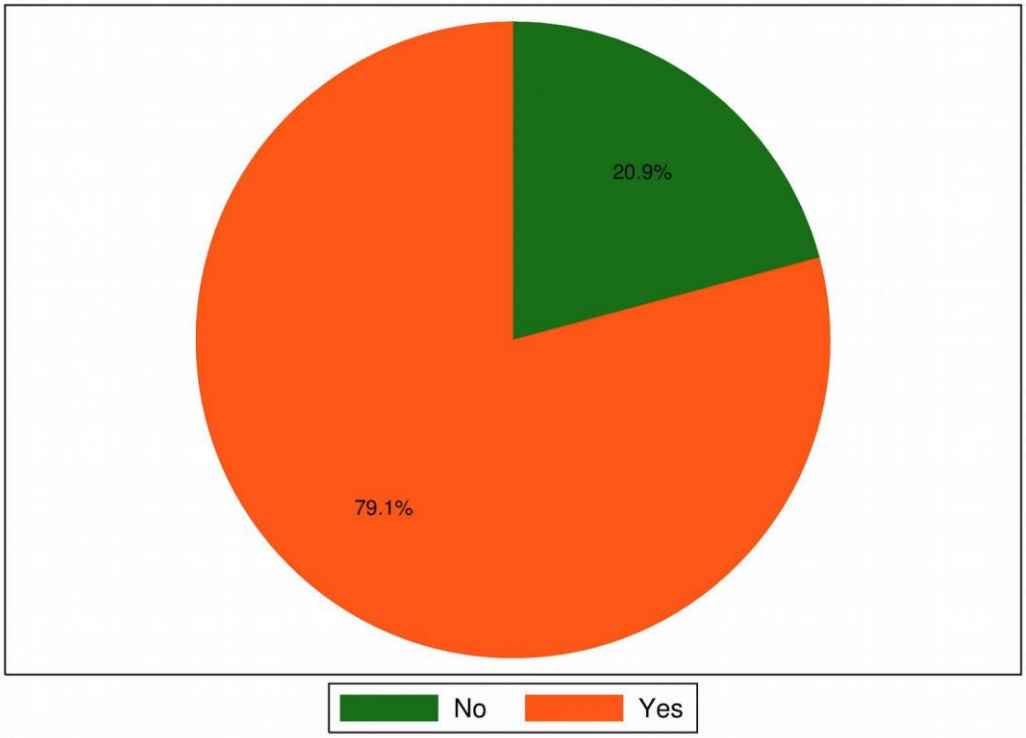


Figure 20: Availability of behaviour change support services to men with prostate cancer

Just over half – 50.3% – of respondents do not believe that charity services for lifestyle support without NHS resources would fulfil the NICE guidelines on exercise for men with prostate cancer.

Table 20: Respondents' opinion on whether charity services for lifestyle support without NHS resources would fulfil NICE guidelines on exercise

Charity services sufficient	**n**	**%**
Yes	24	25.26
No	48	50.53
Unsure	23	24.21
Total	**95**	**100**

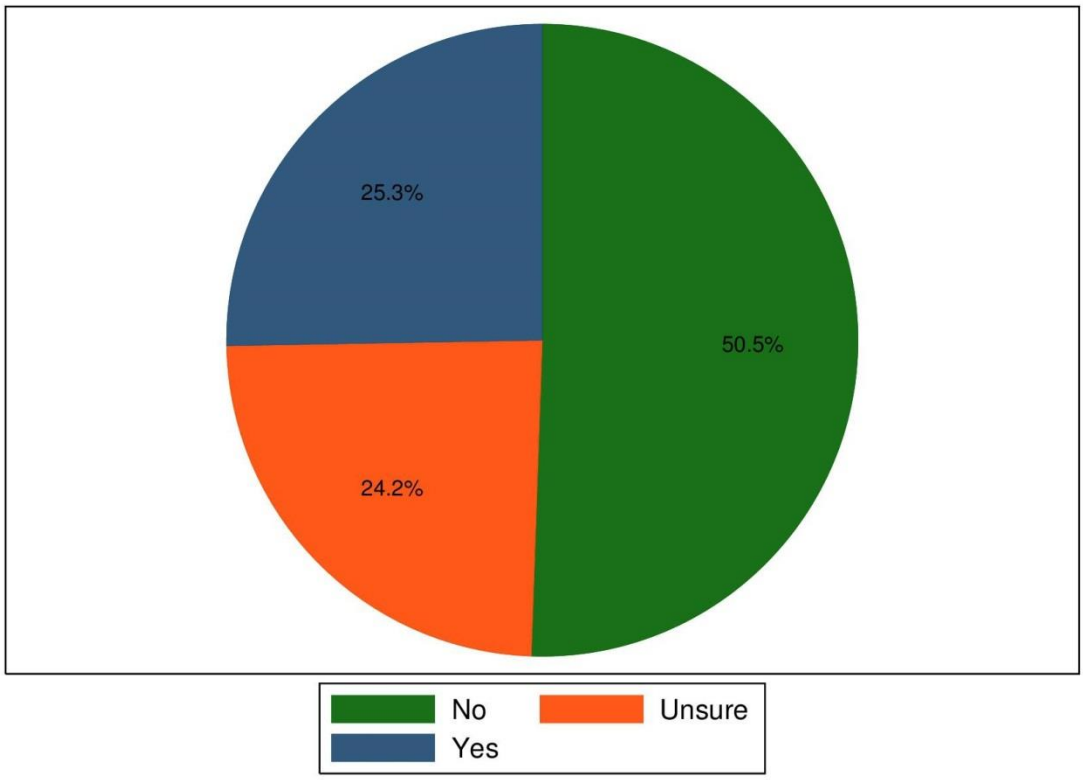


Figure 21: Respondents' opinion on whether charity services for lifestyle support without NHS resources would fulfil NICE guidelines on exercise

About half of the respondents agreed to take part in a future interview.

Table 21: Respondents' willingness to take part in interview to explore issues in detail

Willing	**n**	**%**
Yes	48	50.53
No	47	49.47
Total	**95**	**100**

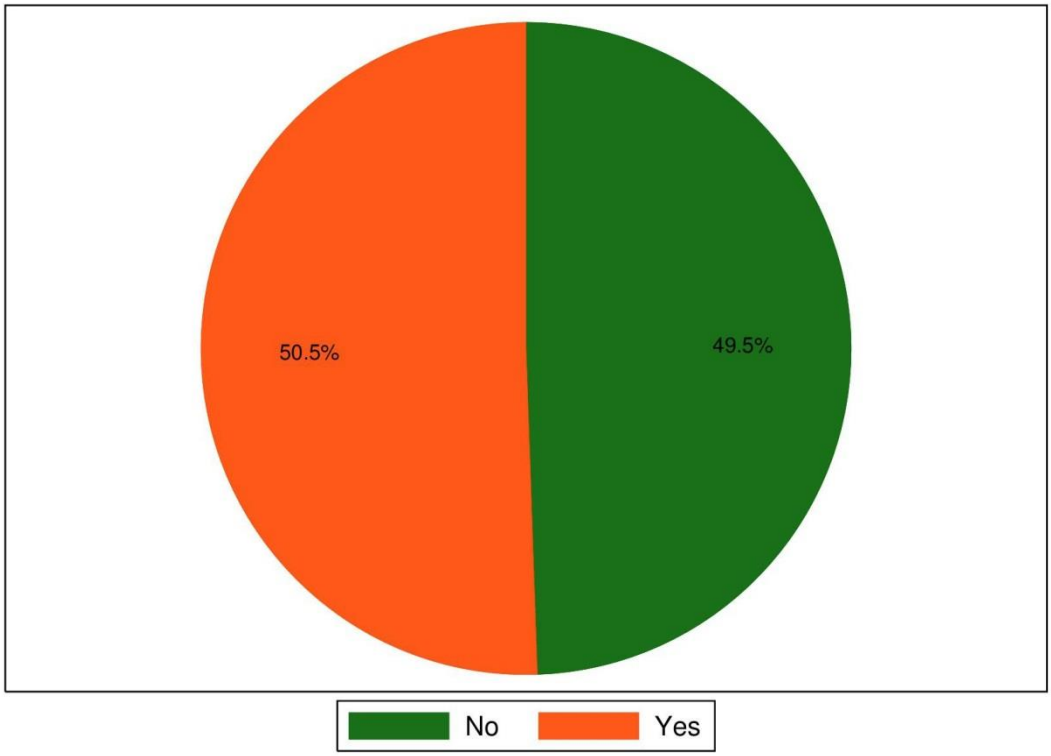


Figure 22: Respondents' willingness to take part in interview to explore issues in detail

4. Transfer of files and data

All items referred to in this report may be found in a Dropbox folder using the following link. The files will be available for 30 days (or longer on request)

https://www.dropbox.com/sh/ddox7t7jb9bxk0o/AAAFcPyRzDbZy5sNmH76Z52xa

It has been a pleasure working with you on this project, we trust that the data, results and report that we have provided are useful.

5. Appendix

5.1 Text of invitation email provided to Clinvivo

Dear [Name] [Surname],

This is to let you know that you have been invited by the University of Sheffield to participate in STAMINA - NIHR programme development grant evaluating exercise therapy for men with prostate cancer on Androgen Deprivation Therapy (ADT) in the NHS within England.

You can access the questionnaire by going to https://www.clinvivo.co.uk/stamina/auth/ [redacted].

The questionnaire will be available until 23rd December 2015.

Kind Regards,

The Clinvivo Team.

5.2 Text of reminder email provided to Clinvivo

Dear [Name] [Surname],

This is to let you know that we have yet to receive your response to our NIHR survey being carried out by the University of Sheffield, regarding the recent NICE guidelines on prostate cancer (CG175) with specific reference to supervised exercise, and its implementation throughout England.

This survey will close on 23rd December 2015.

I hope you would agree this is quite an important piece of work, and we would really appreciate your professional input on this. Thank you!

Please click the following link to be taken directly to the survey: https://www.clinvivo.co.uk/stamina/auth/ [redacted].

Kind regards,

Rebecca Turner, Liam Bourke and Derek Rosario
On behalf of The STAMINA Study Team at the University of Sheffiel

5.3 Text of invitation emails to professional organisations provided to Clinvivo

[Name of Professional Organisation]
[Name of Contact Person]

Dear [Name],

Thank you for agreeing to distribute the questionnaire for STAMINA, NIHR programme development grant to members of BUG as discussed previously, it is greatly appreciated. It would also be very helpful if you could provide us with a figure of the number of people this is distributed to - the reason we ask this is so we can calculate a response rate.
Please find the wording and link below ready to distribute to your BUG members.
Thank you.

___

Dear Members of [Organisation acronym],

At the University of Sheffield we are carrying out a national survey on behalf of the National Institute for Health Research, NIHR (STAMINA programme development grant). We are looking to see how the recent NICE guidelines on prostate cancer (CG175), with specific reference to supervised exercise, are being implemented throughout England.

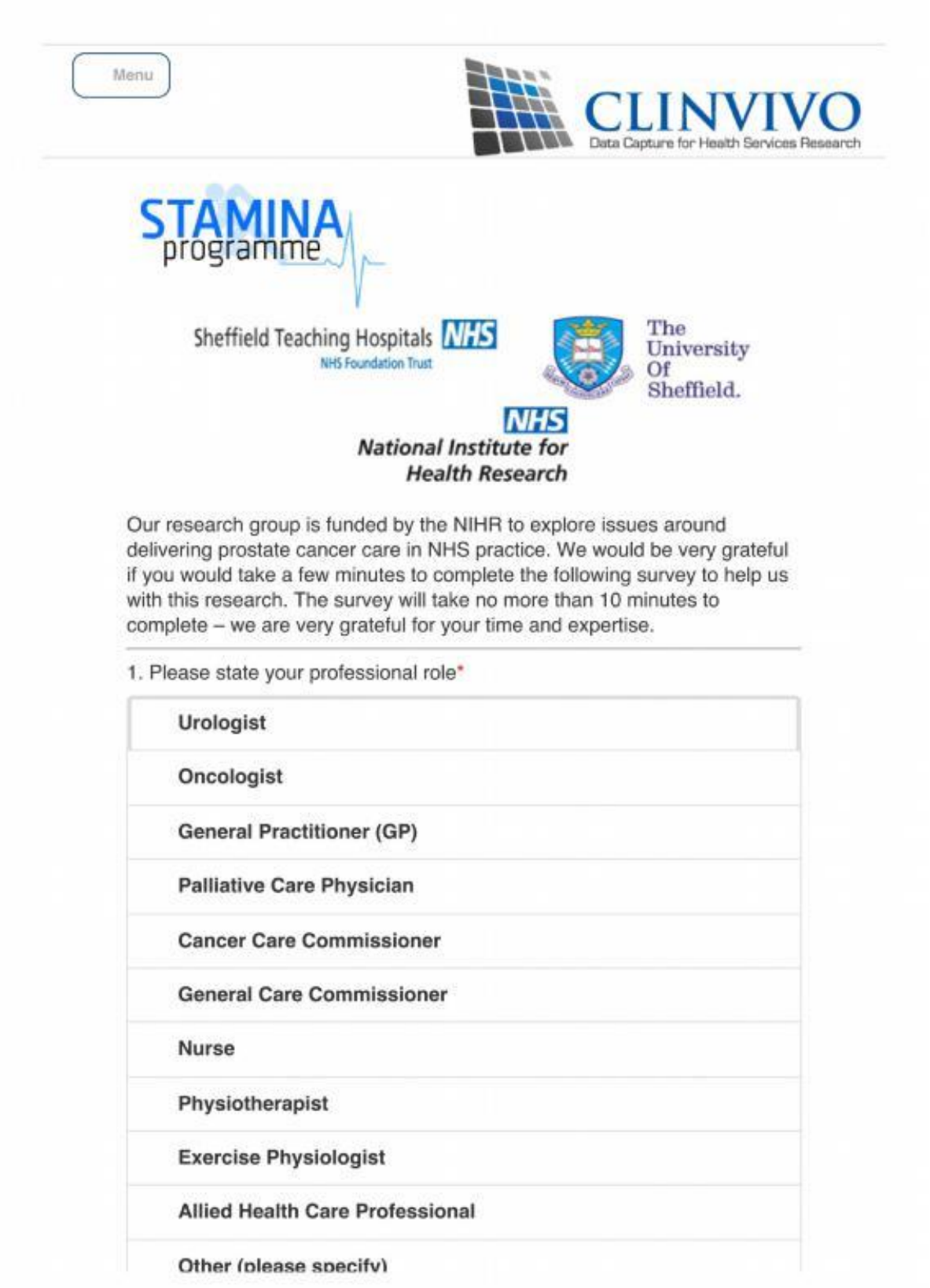
You have been invited to participate in the survey. You can access the questionnaire by going to https://www.clinvivo.co.uk/stamina/ [redacted].

The questionnaire will be available until 23rd December 2015.

Kind regards,

Rebecca Turner, Liam Bourke and Derek Rosario
On behalf of The STAMINA Study Team at the University of Sheffield

5.4 Content of the survey as viewed by participants



Other (please specify)

2. Please state the full postcode of your primary place of work*

3. Recent findings of the CHAARTED and STAMPEDE studies have shown a survival advantage for hormone-naïve men with metastatic prostate cancer started on Chemohormonal therapy (Taxane-based chemotherapy with ADT) rather than ADT alone. Bearing these in mind:

What proportion of men currently commencing long-term ADT are also receiving Docetaxel or a similar agent at initiation of ADT?

Your answer: 0%

(Please drag the blue slider)

0 100

4. Could you please outline the main reasons why men do not receive chemohormonal therapy?

Please tick all that apply*

- **No Funding**
- **Unconvincing Evidence**
- **Updating Guidelines**
- **Clinician Resistance**
- **Patient Resistance**
- **Patient Unfit**
- **Other (please specify)**

5. Can you give a percentage of how many men on long term (>6mth) ADT receive their ADT treatment in primary care in your local area?

Your answer: 0%

Your answer: 0%

(Please drag the blue slider)

0 100

6. In your local prostate cancer pathway, which health care professionals are involved in **initiating** ADT?

Please tick all that apply*

- **Oncologist**
- **Urologist**
- **Clinical Nurse Specialist**
- **General Practitioner (GP)**
- **Outpatient Nurse**
- **Practice Nurse**
- **District Nurse**
- **Other (please specify)**

7. In your local prostate cancer pathway, which health care professionals are involved in **delivering** ADT?

Please tick all that apply*

- **Oncologist**
- **Urologist**
- **Clinical Nurse Specialist**
- **General Practitioner (GP)**
- **Outpatient Nurse**
- **Practice Nurse**

District Nurse
Other (please specify)

8. Are you aware of the new NICE guidelines on Prostate cancer (cg175)?*

Yes
No

9. NICE recommendation 1.4.19: "Offer men who are starting or having androgen deprivation therapy supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue and improve quality of life"
Were you aware of these recommendations until now?*

Yes
No

10. To what extent do you feel you are in a position to deliver this recommendation on exercise for men on ADT in 2016/2017 in your locality? Please click the appropriate number.*

Extremely unlikely									Highly likely
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

11. Are you aware of any current local exercise referral/prescription schemes for **ANY** patients with cancer?*

Yes
No
Unsure

12. Are any of the available exercise referral/prescription schemes accessible to men with prostate cancer on ADT?*

Yes
No

Unsure

13. Where are these exercise referral schemes based?

Please tick all that apply*

- Not Applicable - these services are not available in my area
- Unsure
- Hospital
- Community
- Both Hospital and Community
- Charity Sector
- Local Authority
- Other (please elaborate)

14. Can you tell us which health care professionals are involved in any exercise referral pathway?

Please tick all that apply*

- Hospital Consultant
- Nurse
- GP
- Physiotherapist
- Clinical Exercise Physiologist
- Other (please elaborate)

15. Are non-clinical professionals involved in this pathway? If so who are these individuals?

Please tick all that apply*

- [ ] **Gym Instructor**
- [ ] **Personal Trainer**
- [ ] **Other (please elaborate)**

16. Who would be responsible for setting the frequency, intensity and duration of the exercise programme?

Please tick all that apply*

- [ ] **Consultant**
- [ ] **Nurse**
- [ ] **GP**
- [ ] **Physiotherapist**
- [ ] **Clinical Exercise Physiologist**
- [ ] **Gym Instructor / Professional**
- [ ] **Other (please elaborate)**

17. Who would be involved in the supervised exercise delivery, tailoring and monitoring of an individual's programme?

Please tick all that apply*

- [ ] **Consultant**
- [ ] **Nurse**
- [ ] **GP**

- Physiotherapist
- Clinical Exercise Physiologist
- Gym Instructor / Professional
- Other (please elaborate)

18. Are these supervised sessions offered on a one-to-one basis, in a group setting or both?*

- Group
- One-to-one
- Both Group and One-to-one
- Other (please elaborate)

19. Are you aware of any training schemes for staff that your organisation offers or that you can access around exercise interventions in cancer populations?*

- Yes
- No
- Unsure

20. If not provided by your own organisation, where are these staff training facilities based?

Please tick all that apply*

- Community/Local Authority
- Primary Care
- Secondary Care
- Charitable

- **Private sector**
- **Other (please specify)**

21. Are you aware of any **current** local service evaluation around exercise programmes for men with prostate cancer?*

- **Yes**
- **No**
- **Unsure**

Any comments?

22. Are you aware of any **future** planned local service evaluation schemes around exercise programmes for men with prostate cancer? *

- **Yes**
- **No**
- **Unsure**

Any comments?

23. Are you aware of **any** behaviour change support services available to your local population to promote engagement and maintenance of an active lifestyle?*

- **Yes**
- **No**
- **Unsure**

24. If yes, are these services available to men with prostate cancer?*

- **Yes**

- [ ] **No**

25. National charities such as Macmillan and Prostate Cancer UK provide support and information for active lifestyles. Do you consider using these services exclusively, without any further NHS resources, would fulfil the NICE guidelines on exercise for men with prostate cancer on ADT?*

- [ ] **Yes**
- [ ] **No**
- [ ] **Unsure**

Any comments?

26. Would you be prepared to take part in an interview which would explore some of the questions in this survey in more detail? The interview will last around 30-45 mins (time reimbursable) , can be done over the phone and can be arranged at a time of your convenience.*

- [ ] **Yes**
- [ ] **No**

27. If yes, please provide your contact details, all time will be reimbursed. Email Address:*

Telephone number (optional):

Save

Appendix 2 STAMINA ethics approval

NHS
Health Research Authority

NRES Committee South West - Cornwall & Plymouth

Level 3 Block B Whitefriars Lewins Mead

Bristol BS1 2NT

Telephone:
01173421390
Fax:01173420445

24 August 2015

Mr Derek J Rosario

Senior Lecturer and Hon. Consultant
Urological Surgeon University of Sheffield

Department of Oncology School of Medicine

Royal Hallshire Hospital, Sheffield S10 2JF

Dear Mr Rosario

Study title:	**Sustained exercise TrAining for Men wIth prostate caNcer on Androgen deprivation: the STAMINA programme**
REC reference:	**15/SW/0260**
Protocol number:	**STH18391**
IRAS project ID:	**178340**

The Proportionate Review Sub-committee of the NRES Committee South West - Cornwall & Plymouth reviewed the above application on 24 August 2015.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Georgina Castledine, nrescommittee.southwest-cornwall-plymouth@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study 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.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

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).

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”).

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [POSTER (WS2)]	1	29 July 2015
Copies of advertisement materials for research participants [POSTER (WS3)]	1	29 July 2015
Covering letter on headed paper [Covering letter]		29 July 2015
IRAS Checklist XML [Checklist_13082015]		13 August 2015
Letter from funder [funding letter]	1	31 July 2014
Letters of invitation to participant [Invitation letter (WS2)]	1	15 July 2015
Letters of invitation to participant [Invitation letter (WS3)]	1	15 July 2015
Other [Email from Sponsor]		13 August 2015
Other [Response to validation queries]		13 August 2015
Participant consent form [Informed consent (WS2)]	1	15 July 2015
Participant consent form [Informed consent (WS3)]	1	27 May 2015
Participant information sheet (PIS) [Health Professionals]	1.1	21 August 2015
Participant information sheet (PIS)	1.2	21 August 2015
REC Application Form [REC_Form_13082015]		13 August 2015
Referee's report or other scientific critique report [Feedback report]	1	31 July 2014
Research protocol or project proposal [Protocol]	1	11 June 2015
Summary CV for Chief Investigator (CI) [CI CV]		29 July 2015

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

There were no declarations of interest.

Statement of compliance

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

After ethical review

Reporting requirements

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
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

15/SW/0260	**Please quote this number on all correspondence**

Yours sincerely

Canon Ian Ainsworth-Smith Chair

Email: nrescommittee.southwest-cornwall-plymouth@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers" [SL-AR2]

Copy to: *Ms Jemima Clarke, Sheffield Teaching Hospitals NHS Foundation Trust*

NRES Committee South West - Cornwall & Plymouth Attendance at PRS Sub-Committee of the REC meeting on 24 August 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
Canon Ian Ainsworth-Smith	Retired Hospital Chaplain	Yes	
Dr Hilary Sanders	Retired Senior Lecturer in Statistics	Yes	
Miss Rosalyn Squire	Research Nurse	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Georgina Castledine	REC Manager

NHS
Health Research Authority

South West - Cornwall & Plymouth Research Ethics Committee

Level 3 Block B Whitefriars Lewins Mead

Bristol BS1 2NT

29 February 2016

Mr Derek J Rosario

Senior Lecturer and Hon. Consultant Urological Surgeon University of Sheffield

Department of Oncology School of Medicine

Royal Hallshire Hospital, Sheffield S10 2JF

Dear Mr Rosario

Study title:	**Sustained exercise TrAining for Men wIth prostate caNcer on Androgen deprivation: the STAMINA programme**
REC reference:	**15/SW/0260**
Protocol number:	**STH18391**
Amendment number:	**2**
Amendment date:	**18 February 2016**
IRAS project ID:	**178340**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee reviewed the following amendment:

1. Added questions to semi-structured interview schedule.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [WS2 SSI 100216 v3]	3	10 February 2016
Notice of Substantial Amendment (non-CTIMP)	2	18 February 2016
[AmendmentForm_ReadyForSubmission]		

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

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

15/SW/0260: Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

Yours sincerely

pp. L Roberts.

Canon Ian Ainsworth-Smith Chair

E-mail: nrescommittee.southwest-cornwall-plymouth@nhs.net

Copy to: *Ms Jemima Clarke, Sheffield Teaching Hospitals NHS Foundation Trust*

South West - Cornwall & Plymouth Research Ethics Committee Attendance at Sub-Committee of the REC meeting via correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Canon Ian Ainsworth-Smith	Retired Hospital Chaplain	Yes	
Mrs Sheila Bullard	Clinical Research Project Manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Lucy Roberts	REC Assistant

Appendix 3 HCP interview consent form

The University Of Sheffield.

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

NHS National Institute for Health Research

PARTICIPANT CONSENT FORM: HEALTH PROFESSIONAL INTERVIEWS

Version 3: 29/02/2016

Sustained exercise TrAining for Men with prostate caNcer on Androgen deprivation: the STAMINA programme

Please initial

1	I confirm that I have read and understood the information sheet (Version 3) for the above study, have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time.	
3	I understand that information collected during the study may be looked at by authorised individuals from this NHS Trust or regulatory bodies in order to confirm that the study is being carried out correctly. Responsible representatives of the sponsor may also have access to this information for the purposes of monitoring and auditing. I give permission for these individuals to have access to my records.	
4	I understand that the information I provide will be confidential and that my identity will not be used in any outputs from the research.	
5	I give permission for research personnel to retain my personal details only for the purposes of participation in the research study. I understand these details will not be passed on to third parties under any circumstances. I understand that my identifiable data will be kept securely by the study co-ordinating centre in hard copy only.	
6	I agree that my anonymised responses may be used for research purposes and publication.	
7	I agree to the interview being digitally recorded.	
8	I agree to take part in the above study.	
9	I understand if I withdraw from the study, all data taken from my participation in the study will be retained for analysis.	

Name of participant (PRINT)	Date	Signature
Name of individual taking consent (PRINT)	Date	Signature

2 copies to be kept; original for site file; 1 for participant

Appendix 4 HCP interviews participant invitation letter

Department of Oncology & Metabolism
The Medical School
Beech Hill road
Sheffield
S10 2RX

Dear [name]

I am writing to inform you about a new research study to explore the potential of delivering exercise training for men with prostate cancer on androgen deprivation therapy (ADT).

We would like to invite you to take part in an interview with a member of the research team, lasting approximately 30-40 minutes. This can happen at a time and place convenient to you, or over the phone.

We will discuss your perspectives on roles and responsibilities in primary and secondary care in regards to referral and provision of supervised exercise programmes as part of cancer care for men on ADT.

Please find enclosed a participant information sheet, which describes the study in detail and answers the most frequently asked questions.

If you are interested in participating in this study, or wish to discuss it further please contact the research team using the details below. One of the study researchers will gladly answer any further questions you may have.

Yours sincerely,

Mr Derek Rosario (Consultant Urologist and study Chief Investigator)

Ms Rosa Greasley via email stamina@sth.nhs.uk or R.Greasley@shu.ac.uk

Appendix 5 HCP interview participant information sheet

PARTICIPANT INFORMATION SHEET: HEALTH PROFESSIONAL INTERVIEWS

Version 3 29/02/2016

Sustained exercise TrAining for Men with prostate caNcer on Androgen deprivation:
the STAMINA programme

We would like to invite you to take part in a research study. Before you decide, you need to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully.

What is the purpose of the study?
In July 2014, NICE published updated guidelines for the diagnosis and treatment of prostate cancer. This included a recommendation that men with prostate cancer on androgen deprivation therapy (ADT) should be offered 12 weeks of supervised resistance and aerobic exercise at least twice a week, to reduce fatigue and improve quality of life.

The aim of this study is to understand the perspectives of different health care professionals in primary and secondary care regarding their role in providing supervised exercise programmes as part of cancer care for men on ADT. This will be done using semi-structured interviews.

What are the possible benefits of taking part?
We cannot promise that taking part in this study will help you personally, but the information you provide will be very useful to the research team in terms of evaluating if exercise training can be part of improving cancer care in the NHS.

What are the possible disadvantages of taking part?
We will ask you to give up your time to take part in the interview. We hope not to take more than 40 minutes.

Why have I been invited to take part?
You have been invited to participate because of your role as a health professional and your expertise in cancer, exercise or primary care.

Do I have to take part?
It is up to you to decide whether or not to take part in this research. If you agree to be interviewed you will be asked to sign a consent form to show that you have read this information sheet and agreed to take part. You are free to withdraw from the study at any time, without giving a reason. Taking part in this study will not affect your legal rights.

What will happen to me if I take part?
If you decide to take part in the study, one of the research staff will ask you to let us know when we can visit you to perform the interview or tell us when you could be interviewed over the phone. The discussion will last around 30-40 minutes and will take place at a time and date convenient to you.

The topics to be discussed will include your current role in treating or supporting men with prostate cancer on ADT and your perceptions of how their quality of life can be positively or negatively affected, as well as your views regarding the role of exercise within treatment and support.
You do not have to answer or comment on anything that you would prefer not to. You will be asked to agree to the discussion being audio recorded by signing the consent form.

What if I change my mind during the study?
You are free to withdraw from the study at any time.

Will my involvement in the study be kept confidential?
Yes. We will follow legal and ethical practice and all information about you will be handled in strict confidence.

We will transcribe the recordings of the interviews and will be writing up a report of the findings but we will not use your real name anywhere in the report. When we are analysing the data it will only be seen by the research team and it will be stored securely according to the Data Protection Act.

What will happen to the information from the study?
The results of the study will be used to develop research which will test if we can effectively deliver exercise training for men on ADT as a brand new supportive cancer therapy. The overall (and anonymised) results will be written up for publication in scientific journals, will be fed back to patient groups, charities and also be fed back to national bodies such as the National Cancer Research Institute. We will be able to provide you with the overall results on request. You can request a copy of your interview transcript and let us know if you would like to amend anything you said.

What action will be taken if the interviews find that the NICE guidelines are not being followed?
All the results from these interviews will be anonymised and fed back to the clinical team providing care for men with prostate cancer in your area. No specific action will be taken by the research team.

Who has reviewed this study?
This study has been reviewed by the South West – Cornwall and Plymouth Research Ethics committee.

Who is funding the study?
This study has been funded by the National Institute for Health Research.

Who has checked the ethical implications of this study?
The South West – Cornwall and Plymouth Research Ethics committee has reviewed and approved this study.

What if I have further questions or would like more information about the study?
If you would like more information about the study you are invited to contact:-

Dr Liam Bourke	Project Supervisor	Tel: 0114 225 5396
Mr Derek Rosario	Chief Investigator	Tel: 0114 271 3223

What happens if I have a complaint?

If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, please contact the project supervisor Dr Liam Bourke 0114 2255396.

THANK YOU FOR TAKING THE TIME TO CONSIDER PARTICIPATING IN THIS STUDY
MR DEREK ROSARIO

Appendix 6 HCP interview schedule

Health Care professional semi-structured interview questions

Introduction

Thank you for your time in taking part in this interview. We are interested in your perspective regarding roles, responsibilities and training needs associated with providing supervised exercise programmes for men with metastatic castrate resistant prostate cancer (mCRPC). By supervised exercise, we mean a structured programme of exercise training delivered and overseen by a professional. We are also interested to establish the views and opinions of such interventions in combination with pharmacological agents with the aim to improve outcomes of a structured exercise programme.

We would like to audio record the interviews but these will be completely confidential and all data will be anonymised in transcription and analysis. Can you please confirm you have read, understood and signed the informed consent form and are happy to proceed?

Questions

STAMPEDE trial data

- The standard of care for advanced hormone sensitive prostate cancer is long term-androgen deprivation therapy. How much do you agree with this statement?
- Recent data from the STAMPEDE and CHAARTED trial suggest there to be a survival benefit in initiating chemotherapy earlier in the hormone sensitive advanced PCa pathway. Do you feel the recent findings of the trials will change the standard of care, and to what extent?

  [PROBE]

  - How might you change your own practice?

The HCPs role and current pathway for men with metastatic castrate resistant prostate cancer (mCRPC)

- What is your role within the care pathway for men whose cancer has relapsed (i.e. become castrate resistant)?

  [PROBE]
  - Involved in the treatment of these men: How do you typically sequence treatment for men with mCRPC? [Chemotherapy first? 2nd line ADT first? Other?]
  - Will this change based on the STAMPEDE and CHAARTED trial data?

- For these men (mCRPC), what are the most common reasons that effect not only the initiation of 2nd line treatment but also the duration?

  [PROBE]
  - Fitness - How might you assess these men for fitness to initiate 2nd line treatment and what specifically might you find that would prevent you in prescribing such treatment?
  - Impact on QoL - What specifically may result in a poorer QoL?
  - Clinician's advice - What specifically may influence the clinician?

- In your experience what do you consider to be the most important outcome for men with mCRPC?

- What supportive and/or palliative programmes for men with mCRPC do you know of?

  [PROBE]
  - Would you refer routinely into such programmes and if so what factors might prompt you to?
  - Local / National?
  - In your opinion how successful have they been?

Muscle loss and cachexia in mCRPC

- In your experience, what adverse effects do you consider to have the most impact on men with mCRPC?

  [PROBE]
  - Treatment specific?
  - Disease specific?

- What impact does muscle wastage have on these men?

  [PROBE]
  - Do you consider it to be clinically important?

- What do you do currently to address muscle wastage in men with mCRPC? **[PROBE]**
    - Do you consider the cause of muscle wastage? (do you distinguish between muscle wastage associated with ADT and inactivity or cachexia and sarcopenia) - is there any merit to that?
    - How do you assess?
    - What treatments might you implement?
    - How successful have you found these? Adverse effects?
    - What might prompt you to initiate such treatments?
    - Are there any barriers to addressing muscle wastage?

- Are there any specific therapies you might offer for a man with mCRPC with suspected cachexia or early onset cachexia? (different to treatment strategies for muscle wastage)

  [PROBE]
    - What therapies?
    - How successful have you found these therapies?

Prostate cancer and exercise interventions

- What do you know about the role of exercise in treating men with PCa?

  [PROBE]
    - Could you describe any guidance or recommendations you are aware of for these men?

- What is your organisation already doing with regards to exercise for men with prostate cancer on ADT?
- How beneficial do you think exercise/exercise programmes would be for your patients with mCRPC?

  [PROBE]
    - Would you be prepared to directly advocate and be personally involved in exercise programmes for men in your clinics?
    - Where do you think exercise should fit in the treatment pathway for men with mCRPC? (Before initiation of chemotherapy/2nd line ADT, during or after?)
    - Are there any additional behavioural change strategies you feel might complement exercise programmes?

- Which health care professional do you feel should be responsible for referring and following up exercise interventions in men with mCRPC?

  [PROMPT] Urologist/Oncologist/GP/other?

- What are the barriers you foresee for men with mCRPC in enrolling in a 12-week exercise programme?

  [PROBE]

  - Practical/resource (Is there currently capacity?)
  - From staff, patients, systems?
  - Patient related personal barriers?

Novel pharmacological agents in combination with exercise

- How would you feel about allowing your patients take novel pharmaceutical agents with anabolic effects that might improve the response to exercise?

  [PROBE]

  - Would you be concerned with androgenic effects? (Which ones and why?)
  - [Dependant on response] What anabolic agents do you have specific knowledge of to make you feel this way?

- If there was an evidence based intervention that clearly improved patient outcomes, do you think there is a place for such a combination of therapies in the NHS?

Our research team are hoping to evaluate how a 12-week supervised exercise programme, potentially in combination with a pharmaceutical agent to improve response, can be delivered in the NHS for men initiating 2nd line treatment for mCRPC. This will require professionals in your role to support this process.

- How would you feel about referring your mCRPC men to a study which would investigate:

  a) An exercise intervention alone

  b) An exercise intervention in combination with a SARM (describe if not known)

  c) An exercise intervention in combination with an anabolic steroid

- Given what we have spoken about today, how would you move forward to improve outcomes in men with mCRPC?

  [PROBE]
  - What would be the best approach?
  - Where should research be focussed?

- Is there anything else you would like to add?

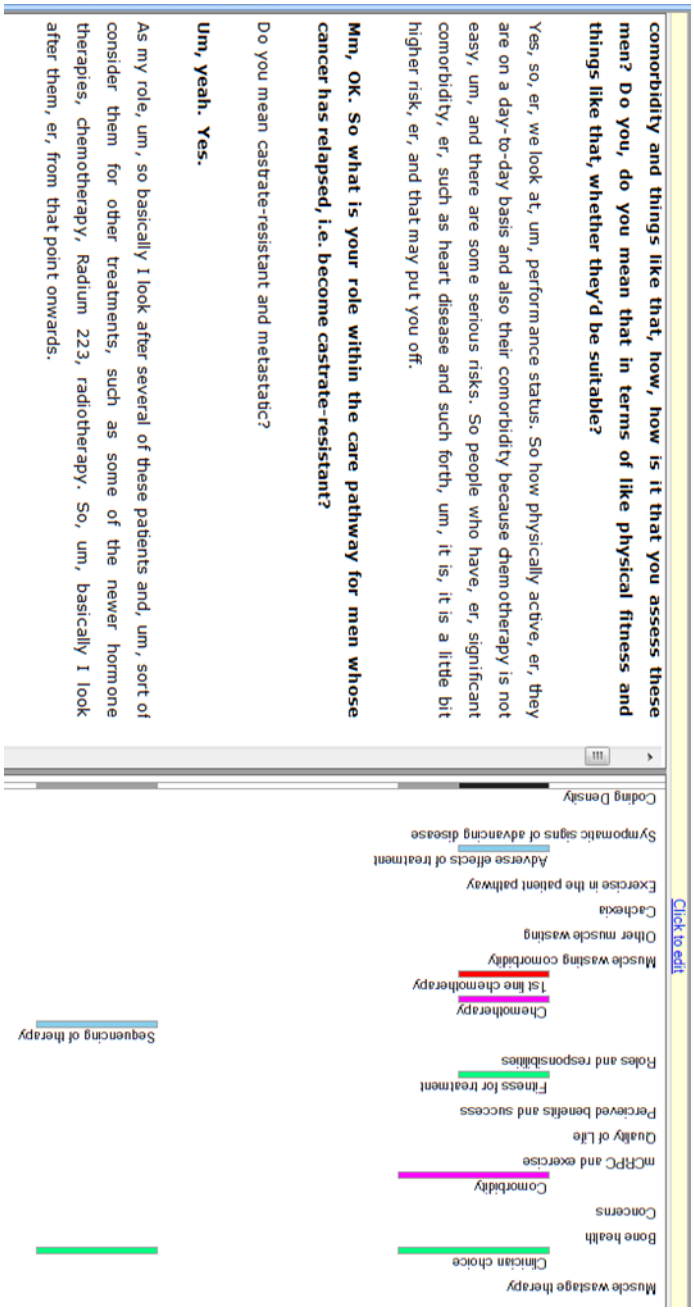
Appendix 7 Initial codes from familiarisation for HCP interviews

Look for: | Search In | Nodes | Find Now | Clear | Advanced Find

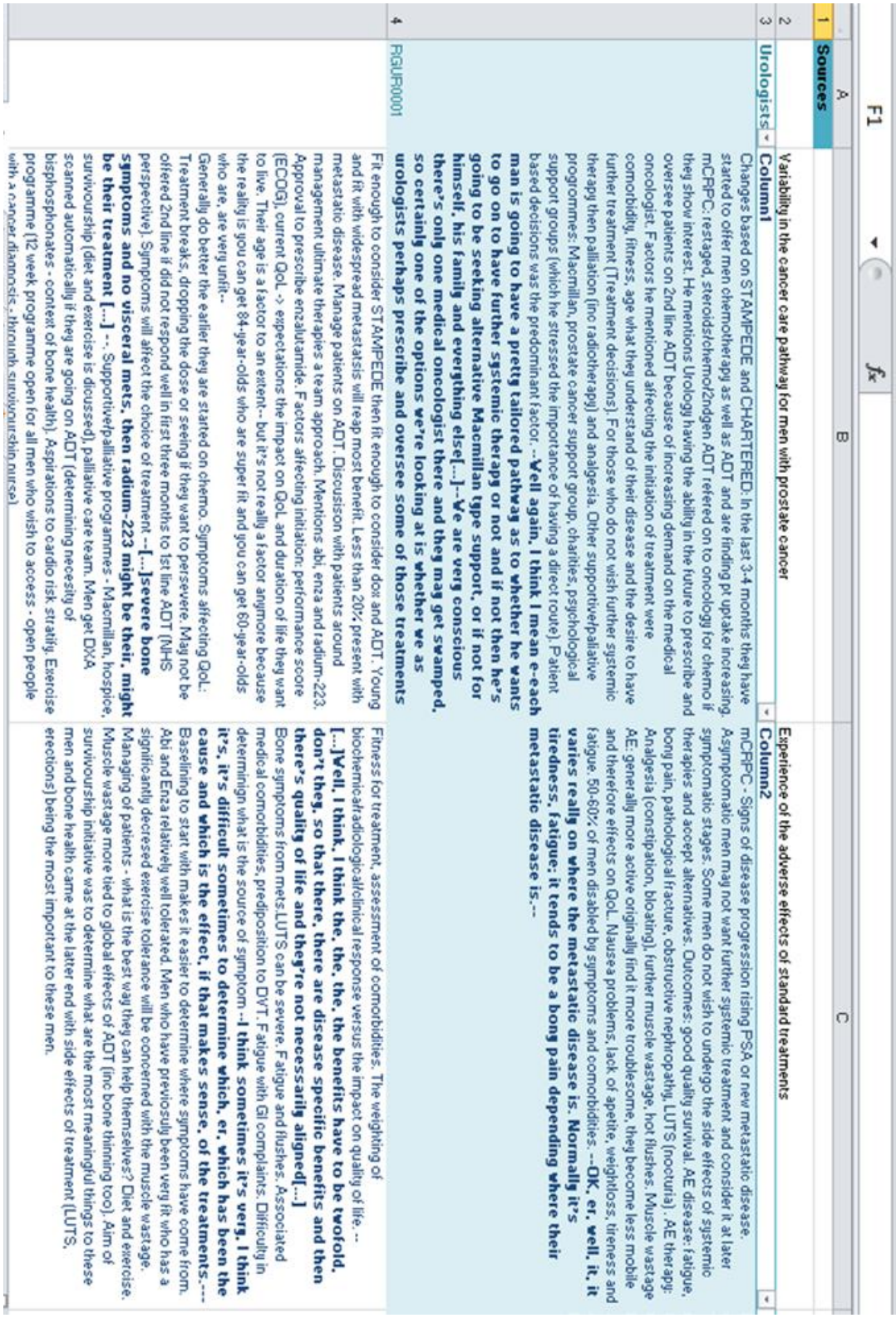
Nodes

Name	Sources	References
1st line chemotherapy	7	19
2nd line treatment	4	6
2nd line ADT	5	12
Chemotherapy	4	14
Adverse effects chemotherapy	4	8
QoL 2nd line ADT	0	0
Quality of Life	2	3
Other 2nd line treatments	1	2
Adverse effects of disease	9	24
Disease progression	1	1
Adverse effects of treatment	9	35
Alternative therapies	1	1
Anabolic agents	0	0
Concerns	8	29
Current therapeutic use elsewhere	0	0
Percieved benefits	3	3
Use in cancer	9	29
Androgen Deprivation Therapy	3	4
Castrate Resistant PCa	4	8
Hormone sensitive PCa	6	16
Assessing fitness for treatment	4	8
Bone health	4	6
Radium 223	2	4
Cancer care pathway	9	23
Comorbidity	1	1
Comorbidities	4	16
Muscle wasting	7	24
Assessment	4	9
Cachexia	10	30
High priority	5	9
Low priority	3	8
Muscle wastage therapy	5	18
Other muscle wasting	7	15
Therapy for comorbidity	6	24
DXA Scans	1	2
Exercise and cancer	0	0
Complemetary programmes to exercise	4	4
Exercise and other cancer	0	0
Current programmes	4	4
Knowledge of benefit and success	0	0
Where current projects have failed	0	0

Appendix 8 Indexing and coding of transcripts in Nvivo



Appendix 9 A section of the frame work matrix



	A	B	C
1	**Sources**		
2		Variability in the cancer care pathway for men with prostate cancer	Experience of the adverse effects of standard treatments
3	Urologists	**Column1**	**Column2**
		Changes based on STAMPEDE and CHARTERED: In the last 3-4 months they have started to offer men chemotherapy as well as ADT and are finding pt uptake increasing. mCRPC: restaged, steroids/chemo/2ndgen ADT refered on to oncology for chemo if they show interest. He mentions Urology having the ability in the future to prescribe and oversee patients on 2nd line ADT because of increasing demand on the medical oncologist. Factors he mentioned affecting the initiation of treatment were comorbidity, fitness, age what they understand of their disease and the desire to have further treatment (Treatment decisions). For those who do not wish further systemic therapy then palliation (inc radiotherapy) and analgesia. Other supportive/palliative programmes: Macmillan, prostate cancer support group, charities, psychological support groups (which he stressed the importance of having a direct route). Patient based decisions was the predominant factor.--**Well again, I think I mean e-each man is going to have a pretty tailored pathway as to whether he wants to go on to have further systemic therapy or not and if not then he's going to be seeking alternative Macmillan type support, or if not for himself, his family and everything else[...]--We are very conscious there's only one medical oncologist there and they may get swamped, so certainly one of the options we're looking at is whether we as urologists perhaps prescribe and oversee some of those treatments**	mCRPC - Signs of disease progression rising PSA or new metastatic disease. Asymptomatic men may not want further systemic treatment and consider it at later symptomatic stages. Some men do not wish to undergo the side effects of systemic therapies and accept alternatives. Outcomes: good quality survival. AE disease: fatigue, bony pain, pathological fracture, obstructive nephropathy, LUTS (nocturia). AE therapy: Analgesia (constipation, bloating), further muscle wastage, hot flushes. Muscle wastage AE: generally more active originally find it more troublesome, they become less mobile and therefore effects on QoL. Nausea problems, lack of apetite, weightloss, tireness and fatigue. 50-60% of men disabled by symptoms and comorbidities.--**OK, er, well, it, it varies really on where the metastatic disease is. Normally it's tiredness, fatigue; it tends to be a bony pain depending where their metastatic disease is.--**
4	RGUR0001	Fit enough to consider STAMPEDE then fit enough to consider dox and ADT. Young and fit with widespread metastasis will reap most benefit. Less than 20% present with metastatic disease. Manage patients on ADT. Discussion with patients around management ultimate therapies a team approach. Mentions abi, enza and radium-223. Approval to prescribe enzalutamide. Factors affecting initiation: performance score (ECOG), current QoL -> expectations the impact on QoL and duration of life they want to live. Their age is a factor to an extent-- but it's not really a factor anymore because the reality is you can get 84-ye-ar-olds who are super fit and you can get 60-ye-ar-olds who are, are very unfit-- Generally do better the earlier they are started on chemo. Symptoms affecting QoL: Treatment breaks, dropping the dose or seeing if they want to persevere. May not be offered 2nd line if did not respond well in first three months to 1st line ADT (NHS perspective). Symptoms will affect the choice of treatment --**[...]severe bone symptoms and no visceral mets, then radium-223 might be their, might be their treatment [...]** --. Supportive/palliative programmes - Macmillan, hospice, survivourship (diet and exercise is dicussed), palliative care team. Men get DXA scanned automatically if they are going on ADT (determining necesity of bisphosphonates - context of bone health). Aspirations to cardio risk stratify. Exercise programme (12 week programme open for all men who wish to access - open people with a cancer diagnosis - through survivourship nurse)	Fitness for treatment, assessment of comorbidities. The weighting of biochemical/radiological/clinical response versus the impact on quality of life.--**[...]Well, I think, I think the, the, the, the benefits have to be twofold, don't they, so that there, there are disease specific benefits and then there's quality of life and they're not necessarily aligned[...]** Bone symptoms from mets.LUTS can be severe. Fatigue and flushes. Associated medical comorbidities, predisposition to DVT. Fatigue with GI complaints. Difficulty in determinign what is the source of symptom --**I think sometimes it's very, I think it's, it's difficult sometimes to determine which, er, which has been the cause and which is the effect, if that makes sense, of the treatments.**--- Baselining to start with makes it easier to determine where symptoms have come from. Abi and Enza relatively well tolerated. Men who have previously been very fit who has a significantly decreased exercise tolerance will be concerned with the muscle wastage. Managing of patients - what is the best way they can help themselves? Diet and exercise. Muscle wastage more tied to global effects of ADT (inc bone thinning too). Aim of survivourship initiative was to determine what are the most meaningful things to these men and bone health came at the latter end with side effects of treatment (LUTS, erections) being the most important to these men.

Appendix 10 COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	
Occupation	3	What was their occupation at the time of the study?	
Gender	4	Was the researcher male or female?	
Experience and training	5	What experience or training did the researcher have?	
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	
Sample size	12	How many participants were in the study?	
Non-participation	13	How many people refused to participate or dropped out? Reasons?	

Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	
Field notes	20	Were field notes made during and/or after the inter view or focus group?	
Duration	21	What was the duration of the inter views or focus group?	
Data saturation	22	Was data saturation discussed?	
Transcripts returned	23	Were transcripts returned to participants for comment and/or	

Appendix 11 Trusts identified from the survey

B

Barts Health NHS Trust

Bedford Hospital NHS Trust

Bolton NHS foundation Trust

Bradford Teaching Hospitals NHS Foundation Trust

Burton Hospitals NHS Foundation Trust

Buckinghamshire Healthcare NHS Trust

NHS Bury and Bury Leisure

C

Calderdale and Huddersfield NHS Foundation Trust

Cambridge University Hospitals NHS Foundation trust

Chelsea and Westminster Hospital NHS Foundation Trust

The Cheltenham NHS Trust

The Christie NHS Foundation Trust

City Hospitals Sunderland NHS Foundation Trust

Cornwall Partnership Trust

County Durham and Darlington NHS Foundation Trust

D

Dorset County Hospital NHS Foundation Trust

The Dudley Group NHS Foundation Trust

E

East and North Herts NHS Trust

East Kent Hospitals University NHS Foundation Trust

F

NHS Frimley Health Foundation Trust

Frimley Park Hospital Trust

G

Gloucestershire Hospitals NHS Foundation Trust

Guy's and St Thomas' NHS Foundation Trust

Gwent Healthcare NHS Trust

H

Hampshire Hospitals NHS Foundation Trust

Harrogate and District NHS Foundation Trust

Hertfordshire Partnership University NHS Foundation Trust

Homerton University Hospital Foundation Trust

Hull and East Yorkshire Hospitals NHS Trust

I

Imperial College Healthcare NHS Trust

Ipswich Hospital NHS Trust

Isle of Man (Nobles Hospital)

L

Lancashire Teaching Hospitals NHS Trust

Leeds Teaching Hospitals NHS Trust

M

Maidstone and Tunbridge Wells NHS Trust

Medway NHS Foundation Trust

Mid Cheshire Hospitals NHS Foundation Trust.

Mid Yorkshire Hospitals NHS Trust

Milton Keynes University Hospital NHS Foundation Trust

University Hospitals of Morecambe Bay NHS Foundation Trust

N

Newcastle upon Tyne Hospitals NHS Foundation Trust

Norfolk and Norwich University Hospitals NHS Foundation Trust

North Bristol NHS Trust

North Cumbria University Hospitals NHS Trust

Northern Health and Social Care NHS Trust

The North Herts NHS Trust

Northern Lincolnshire and Goole NHS Foundation Trust

Northwick Park and St Mark's Hospitals NHS Trust

Nottingham University Hospitals NHS Trust

O

Oxford Health NHS Foundation Trust

P

Pennine Acute Hospitals NHS Trust

Peterborough and Stamford Hospitals NHS Foundation Trust

Plymouth Hospitals Acute Trust

Portsmouth Hospitals NHS trust

R

Rotherham NHS foundation Trust

The Royal Bournemouth and Christchurch Hospitals NHS Trust

Royal Devon & Exeter NHS Foundation Trust

The Royal Free NHS Foundation Trust

Royal Liverpool and Broadgreen University Hospitals NHS Trust

The Royal Marsden NHS Foundation Trust

Royal United Hospitals Bath NHS Foundation Trust.

The Royal Wolverhampton Hospitals NHS Trust

S

Salford Royal NHS Foundation Trust

Sheffield Teaching Hospitals NHS Trust

Shropshire community health NHS Trust

Somerset Partnership NHS Foundation Trust

Surrey and Borders Partnership NHS Trust

Surrey & Sussex NHS Trust

South Devon Healthcare NHS Foundation Trust

South London and Maudsley NHS foundation Trust

Southwark NHS Foundation Trust

St George's Healthcare NHS Foundation Trust

Stockport NHS Foundation Trust

T

NHS Tayside

Torbay and South Devon NHS Foundation Trust

W

Wakefield Council and Mid Yorkshire Hospitals NHS Trust

Wye Valley NHS Trust

NHS West Hampshire CCG

Y

York Teaching Hospital NHS Foundation Trust

Appendix 12 Ethics approval documentation

NHS
Health Research Authority

Dr Liam Bourke
Collegiate Hall, Collegiate Crescent
Collegiate Campus, Sheffield
Hallam University Sheffield
S10 2BP

Email: hra.approval@nhs.net

18 January 2017

Dear Dr Bourke

Letter of HRA Approval

Study title:	**A COMbined progRamme of exercise and dietary ADvice in mEn with castrate resistant prostate cancer - COMRADE trial**
IRAS project ID:	**215735**
Protocol number:	**2**
REC reference:	**16/NE/0382**
Sponsor	**Sheffield Teaching Hospitals NHS FT**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.

- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **215735**. Please quote this on all correspondence. Yours sincerely
Michael Pate
Assessor

Email: hra.approval@nhs.net

Copy to: *Mr Luke Barron - Sheffield Teaching Hospitals NHS FT – Sponsor contact and lead NHS R&D contact*
NIHRN CRN Portfolio Applications Team.

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	1	25 October 2016
Covering letter on headed paper [response to rec]		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sheffield Hallam employer's liability and public liability]	2016-17	29 July 2016
GP/consultant information sheets or letters [GP Letter]	1	25 October 2016
Interview schedules or topic guides for participants [focus group topic guide]	1	14 December 2016
IRAS Application Form [IRAS_Form_19122016]		19 December 2016
Letter from funder [funding award]		
Letters of invitation to participant [participant invitation letter]	1	06 December 2016
Non-validated questionnaire [Screening questionnaire]	1	25 October 2016
Other [healthy eating and dietary guidance]	2	06 December 2016
Other [CCTC approval letter]		
Participant consent form [Participant consent form]	3	18 January 2017
Participant information sheet (PIS) [Participant information sheet]	3	18 January 2017
Referee's report or other scientific critique report [Independent scientific review]		
Research protocol or project proposal [research protocol]	2	14 December 2016
Sample diary card/patient card [3 day diet diary]	1	06 September 2016
Sample diary card/patient card [exercise diary]	2	12 December 2016
Summary CV for Chief Investigator (CI) [CV for CI]		
Summary CV for student [CV for student]		
Summary CV for supervisor (student research) [CV for supervisor]		
Validated questionnaire [FACIT-F]		
Validated questionnaire [FACIT-P]		

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Mr Luke
Barron Tel: 0114
226 5943
Email: Luke.Barron@sth.nhs.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	Following REC favourable opinion, the information sheet and consent form were updated via a non-substantial amendment to bring them in line with HRA assessment standards.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a single site study where that site is also the NHS sponsor; therefore, no agreement is expected.

4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			research study
4.3	Financial arrangements assessed	Yes	The study is funded through an NIHR programme grant for the STAMINA study. It is expected that the research costs of the single site will be covered by this grant.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a single site study where that site is also the NHS Sponsor; therefore, one site type. If this study is subsequently extended to other NHS organisation(s) in England, an amendment should be submitted to the HRA, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
This is a single site study sponsored by the site. The R&D office will confirm to the CI when the study can start.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each *type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).*
A local Principal Investigator should be in place at the single participating site, and this person has been identified. GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
The direct clinical team will identify potential participants; therefore will already hold a contract with the NHS site. For radiographers conducting DXA scans, who do not already hold a contract with the participating site, an Honorary Research Contract would be required. Evidence of enhanced DBS, the appropriate barred list check and occupational health clearance would be expected. Analysis of blood samples will be conducted by staff employed at the participating site, therefore no LOAs or HRCs are required for these staff.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
• The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio. • HRA approval does not extend to research activities at non-NHS organisations.

Health Research Authority

North East - Newcastle & North Tyneside 2 Research Ethics Committee

Jarrow Business Centre Rolling Mill Road

Jarrow NE32 3DT

Telephone: 02071048152

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

06 January 2017

Dr Liam Bourke
Collegiate Hall, Collegiate Crescent
Collegiate Campus, Sheffield Hallam University Shefifeld
S10 2BP

Dear Dr Bourke

Study title: A COMbined progRamme of exercise and dietary ADvice in mEn with castrate resistant prostate cancer - COMRADE trial
REC reference: 16/NE/0382
Protocol number: 1
IRAS project ID: 215735

Thank you for your letter of 20th December 2016, 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 Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish

to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

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.

Conditions of the favourable opinion

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

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

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.
If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

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).

Ethical review of research sites

NHS 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).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

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

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	1	25 October 2016
Covering letter on headed paper [response to rec]		
GP/consultant information sheets or letters [GP Letter]	1	25 October 2016
Interview schedules or topic guides for participants [focus group topic guide]	1	14 December 2016
IRAS Application Form [IRAS_Form_19122016]		19 December 2016
IRAS Application Form XML file [IRAS_Form_19122016]		19 December 2016
IRAS Checklist XML [Checklist_19122016]		19 December 2016
Letter from funder [funding award]		
Letters of invitation to participant [participant invitation letter]	1	06 December 2016
Non-validated questionnaire [Screening questionnaire]	1	25 October 2016
Other [healthy eating and dietary guidance]	2	06 December 2016
Other [CCTC approval letter]		
Participant consent form [participant consent form]	2	14 December 2016
Participant information sheet (PIS) [Participant Information Sheet]	2	14 December 2016
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Summary CV for student [CV for student]		
Summary CV for supervisor (student research) [CV for supervisor]		
Validated questionnaire [FACIT-F]		
Validated questionnaire [FACIT-P]		

Statement of compliance

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

After ethical review

Reporting requirements

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
Notification of serious breaches of the protocol
Progress and safety reports

Notifying the end of the study

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

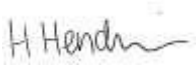
HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/NE/0382	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



pp

Dr Alasdair MacSween Chair

Email:nrescommittee.northeast-newcastleandnorthtyneside2@nhs.net *Enclosures:*
"After ethical review – guidance for researchers" *[SL-AR2] Copy to:*
Mr Luke Barron, Sheffield Teaching Hospitals NHS FT

Appendix 13 Patient invitation letter and information sheet

Collegiate Hall
Collegiate Crescent
Centre for Sport and Exercise Science
Sheffield Hallam University
National Centre for Sport and Exercise Medicine
S10 2BP

Date:

(Participant address)

Dear sir,

I am writing to inform you about a new research study for men with advanced prostate cancer. Scientists from Sheffield are working with clinical consultants from the NHS in Yorkshire to understand the role of exercise training and dietary supplements and how it may improve muscle mass, fitness and overall men's health.

In this feasibility study men will be allocated at random (randomised) to one of two groups. There is equal chance of being in either group. Please find enclosed a patient information sheet, which describes the study in detail and answers the most frequently asked questions.

If you are interested in participating in this study, or wish to discuss it further please contact Rosa Greasley or Dr Bourke using the details below. One of the study researchers will then speak to you and will gladly answer any further questions you may have.

Yours sincerely,

Mr Derek Rosario (Consultant Urologist)

Contact: Rosa Greasley xxx-xxxx-xxxx Dr Liam Bourke 0114 225 4654 (Chief investigator)

Patient Information Sheet

A COMbined progRamme of exercise and dietary ADvice in mEn with castrate resistant prostate cancer (COMRADE trial)

You are being invited to take part in a research study. Before you decide if you want to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. You may also wish to talk to others about the study. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

The aim of this study is to see whether men with advanced prostate cancer might benefit from a supervised programme of exercise and dietary advice over sixteen weeks. We would like to assess the effects of regular exercise and dietary changes on physical fitness, muscle mass and quality of life.

Why have I been invited to participate?

Because according to our information, you satisfy the requirements for our study.

Do I have to take part?

No. It is up to you to decide whether or not to take part in this research. After we have described the study and go through this information sheet, which we will then give to you, we will then ask you to sign a consent form to show you have agreed to take part. If you do decide to take part, you will be free to withdraw at any time and do not have to provide a reason for doing so. This would not affect the standard of care that you receive. You will keep this information sheet.

What will happen to me if I take part?

If you are interested in participating, a member of the study team will speak to you (usually over the telephone) about what the study involves, and take a brief medical history from you to check that you are likely to be eligible to participate.

Your involvement in the study will last for sixteen weeks. During the first week you will undertake two assessment visits. You will then be assigned at random (i.e. there is a 50:50 chance) to an exercise training and dietary advice (intervention) group or a usual care (control) group. If you are in the intervention group, you will receive supervised exercise training three times a week for sixteen weeks and provided with healthy diet and nutrition advice. We will also ask you to take part in some exercise in your own time and give you supplements to take home. The supplements we ask you to taker home are whey protein and creatine, both which have been demonstrated to have

beneficial effects on muscle mass. You will be required to take these supplements daily, the quantity of which will depend on your current weight. If you are in the control group, you will receive no supervised or structured exercise training, dietary advice or supplements. Men allocated to this group will receive usual best care from their treating doctor and also we will give you the Macmillan physical activity pack ("Move more"). At the end of the trial, some men will be asked to do a short group interview about their experiences of the exercise and diet programme. This will only happen once. You can still be part of the main study even if you do not want to consent to taking part in these group interviews.

If you have consented to taking part in the interviews, we will contact you by phone to invite you to Sheffield Hallam University were the interviews will take place. The interviews will be recorded using a digital Dictaphone and later written out as a word processor document (we called this process 'transcribing') which will be anonymised and you will not be individually identified. You can ask for a copy of the transcribed document which you can check and you can inform us of any edits that you feel should be made to your comments. Direct quotes from the interviews, which may be used in publication, will not be identifiable outside of those which were present in the group interview, even whilst you may recognise your own words. Equally, we ask all participants in the group interview to keep all that is said confidential to protect all who participated in the discussion.

If I am assigned to the exercise group, where will my exercise sessions take place?

Supervised exercise will take place at the Centre for Sport and Exercise Science at Sheffield Hallam University.

What will the study assessment visits involve?

Men in Yorkshire will visit a physiology testing laboratory at Sheffield Hallam University (assessment day 1) and the Clinical Research Facility (CRF) at Northern General Hospital (assessment day 2).

Before you attend any assessment visits you will be sent details of these visits via post as well as a three day diet diary via post to log your food and drink intake over the course of three days which we will then ask you to return in day 1 of your first assessment visit.

In day 1 of your assessment visit you will be invited to the physiology testing laboratory at Sheffield Hallam University where you will be met by one of the clinical team to undertake assessments of your muscle function and some blood tests. This will require a blood draw with a needle. This assessment will

be required three times during the course of the trial: at the beginning of the trial, 8 weeks into the trial and at the end of the trial (post 16 weeks).

Day 1 assessment visit (Sheffield Hallam University):

- When you arrive a member of staff will go through the study procedures with you and will answer any questions you may have. If you are still happy to participate you will be asked to sign a consent form and hand over your three day diet diary.
- After you have signed the consent form you will have a blood sample taken.
- A member of staff will then take you through some questionnaires regarding your health and wellbeing and you may be asked questions regarding any other medical conditions you may have and medications you are taking.
- We will ask you to fill in some questionnaires about your exercise and diet habits as well as your overall quality of life.
- You will be asked to perform three muscle strength tests to assess upper and lower body muscle strength overseen by an exercise specialist. These include knee extension, leg press and shoulder press. You will be familiarized with these exercises and shown the proper technique by the exercise specialist.
- You will then be asked to perform a hand-grip test which is a digital pressure device which measures the strength in your hand.
- You will be asked to perform a chair sit to stand test in which we will count the number of times you can rise as fast as possible to a full standing position and then return to a full sitting position in 30 seconds.
- The final test is a six minute walk test in which a member of staff will ask you to walk between two marked points ten meters apart at a comfortable pace and in a straight line for six minutes.

Day 2 of your assessment visit will be held at the Clinical Research Facility (CRF) at Northern General Hospital for a scan, details of which will be sent to you via post. You will be required to undergo this assessment twice during the course of the trial: at the beginning of the trial and at the end of the trial (post 16 weeks). On the morning of the assessment visit you can eat and drink as

normal and should take any medications as usual. The study visit will take place on a weekday and is anticipated to take no longer than 90 minutes

Day 2 assessment visit (Northern general hospital):

- Your height and weight will be measured and you will then be asked to have what is called a DEXA (Dual energy x-ray absorptiometry) scan which will assess your bone density and body composition giving us information on your bone and muscle health. A DEXA scan takes a few minutes. During the DXA scan you will lie on a table. The scan is completely painless and there are no tunnels involved.

What checks take place before I exercise?

All men will be checked for medical suitability to exercise by the research team before they undergo any assessments or partake in any exercise which will include a health screening questionnaire. Following this, a letter will be sent to your GP informing them of your participation in this study, where they will have the opputunity to contact the team regarding any questions or concerns. This information will be treated in the strictest confidence.

What are the benefits of taking part in this study?

Previous studies have shown that exercise training improves fitness, strength, cardiovascular health, quality of life, whilst reducing anxiety, fatigue and helps weight loss. There is some evidence that it can also help slow the progress of cancer. Men randomized to the intervention will undergo an individually tailored exercise programme at no cost for 16 weeks. Studies have also shown that diets low in carbohydrate and high in protein and fibre may confer a benefit for cancer patients. Men taking part in the experimental intervention will also receive dietary advice and guidance. Men will also receive some supplements including whey protein and creatine. Creatine is commonly found in the diet in foods like fish and meat. The whey protein is derived from milk; therefore it is important to notify us if you cannot take whey protein due to dietary restrictions.

Men who are randomised to the control arm of this study will also receive a free bespoke cancer survivorship guide, the Macmillan "Move More" guide.

By taking part in the study all participants will also receive the benefits of bone and muscle health screening which you would not otherwise receive (DXA scan). Two scans of your bones and muscle will be taken during the study, one at the beginning of the trial and one at the end of the trial after 16 weeks, and reviewed by a clinician. You will also receive benefits from blood tests where we look at specific proteins that will provide us with information on the condition of your muscle and well as tests measuring the strength and function

of your muscles. If there is a problem with your bone or muscle health, we will refer you to appropriate specialists if further tests or treatment are needed.

Currently, there is no evidence which exists that demonstrates either the risks or benefits of this intervention in men like you. But, if this study does demonstrate a benefit for men like you, we hope that the information from this study will help us to plan future studies and help improve the care of prostate cancer patients.

What are the possible disadvantages of taking part in this study?

The procedures that we are using in this research are all well-established techniques which have been used in other patient groups in numerous research studies without any significant side effects being reported. The major drawbacks are that you will have to give up you your free time to attend assessments and possibly exercise classes.

The risks involved in having a DXA scan are very low as the radiation exposure of these scans is minimal, less than that of normal background radiation you are exposed to over the course of a year. There are also small risks from having blood samples taken. For most people, taking a blood sample using a small needle to puncture the skin does not cause serious problems but you may develop a bruise or experience a small amount of bleeding or pain at the needle site. Some people may also feel faint. In very rare cases infection may occur.

The diet supplements we ask you to take are very safe and most side effects which are associated with these supplements occur when taken in excessive amounts. However, you may experience some symptoms such as mild GI discomfort (such as abdominal cramps) at the doses which you will be provided with.

What if there is a problem?

Any complaint about any aspect of the way in which you have been approached or treated during the course of this study will be addressed. If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. You can also contact the study chief investigator Dr Liam Bourke. The normal National Health Service complaints mechanisms are available to you which are not compromised because you have taken part in a research study. Alternately you can use Patient Advisory Liaison Service if you have any concerns regarding the care you have received, or as an initial point of contact if you have a compliant, via telephone on 0114 271 2400 or via email on PST@sth.nhs.uk.

Will my taking part in this study be kept confidential?

Yes. All information you provide will be anonymised and kept confidential. Nothing which could reveal your identity will be disclosed outside of the research study site. Once you have consented to take part in the research study all of your data will be anonymised using a study code including any blood samples which you give.

Involvement of your General/Family doctor (GP)

With your consent, your GP will be informed that you have taken part in this research study and be given the results of your bone scans. Your oncologist or urologist will also be informed. We may also contact your GP if we need to clarify anything in relation to your medical information.

What will happen to the results of this research?

The results of this research may be presented at scientific meetings in the UK and overseas. Results will be written up for publication in scientific journals, will be fed back to patient groups, charities and also be fed back to national bodies. It will not be possible to identify you or your measurements from any of the information that will be presented. We will feed back the results to all participants of the study.

Who is funding the study?

This study has been funded internally by Sheffield Hallam University

Who has reviewed and approved the study?

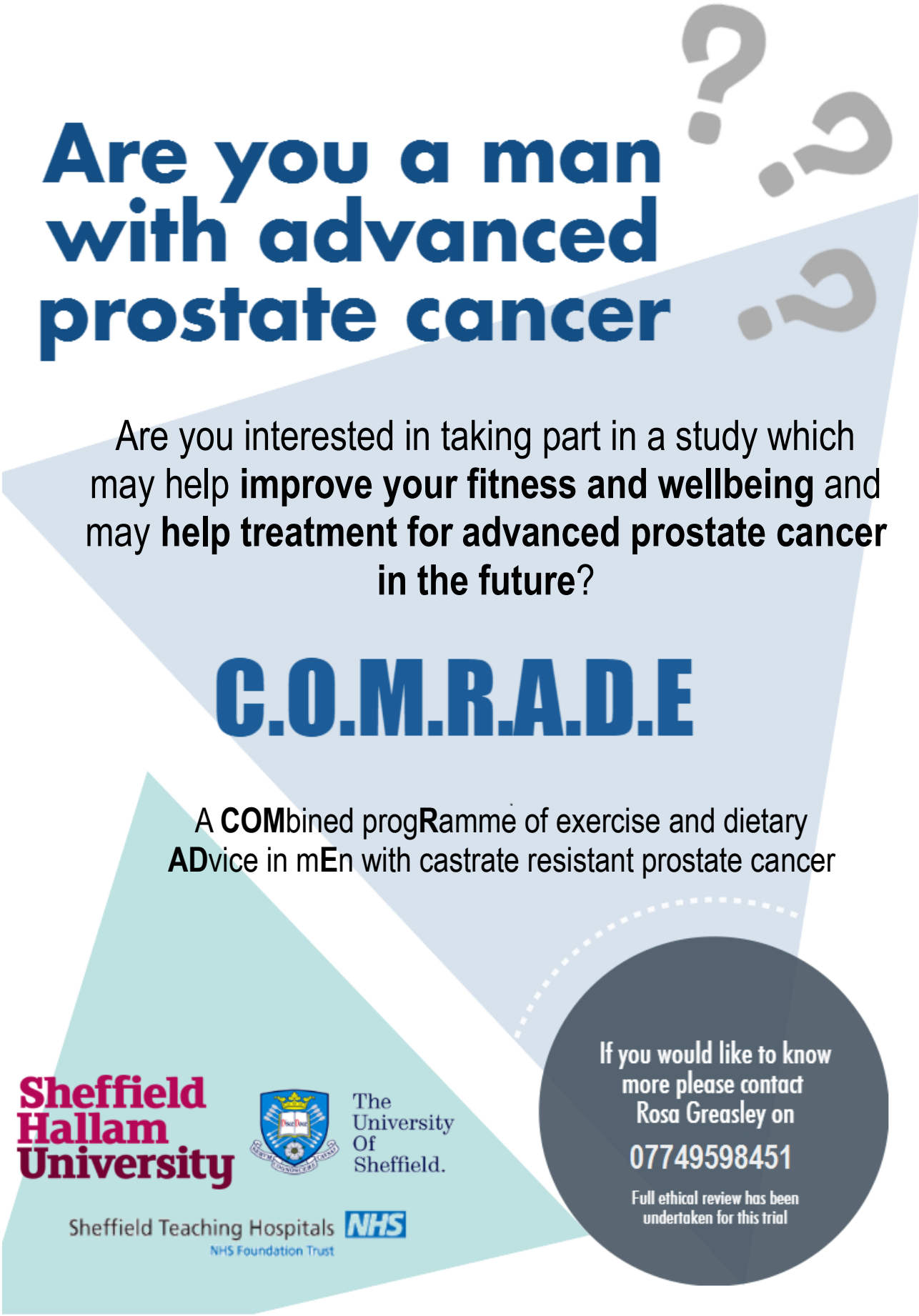
The study will not take place without independent scientific review , ethical, research governance and Health research authority approval.

Contact details

If you would like more information about the study you are invited to contact:

Rosa Greasley Tel: *Insert telephone number*
Dr Liam Bourke Tel: 0114 225 5396
Mr Derek Rosario Tel: 0114 271 3223

Thank you for reading this information sheet and considering taking part in the study.



Appendix 14 Recruitment poster

Appendix 15 Health screening questionnaire

Sheffield Hallam University

COMRADE trial:

Health Screening Questionnaire

Version 1 25.10.2016 IRAS ID 215735

Sheffield Teaching Hospitals NHS Foundation Trust

The University Of Sheffield.

Personal details

Name:

Occupation:

Date of Birth: Age: Ethnicity:

Medical History

a. Please answer the following

Past History			**Family History**			**Present Symptoms**	
Have you ever had ?	**Y**	**N**	***Have any immediate family had?***	**Y**	**N**	***Have you recently had?***	**Y**
High blood pressure	☐	☐	Heart attacks	☐	☐	Chest pain/discomfort	☐
Any heart trouble	☐	☐	High blood pressure	☐	☐	Shortness of breath	☐
Arterial disease	☐	☐	High Cholesterol	☐	☐	Heart palpitations	☐
Lung disease	☐	☐	Stroke	☐	☐	Dizzy spells	☐
Asthma	☐	☐	Diabetes	☐	☐	Frequent headaches	☐
Diabetes	☐	☐	Early death	☐	☐	Frequent colds	☐
Epilepsy	☐	☐	Other family illness	☐	☐	Back pain	☐
Arthritis	☐	☐				Orthopaedic problems	☐
Renal disease	☐	☐					

b. If you answered yes to any of the above, please give brief details:

c. Are you registered disabled? (Please circle) **Yes / No**

d. Other than your prostate cancer, please give details on any medical conditions you have:

e. Do you currently have any form of muscle or joint injury? (Please circle)
Yes/ No

If yes please give brief details:

f. Please give details on all current medications below:

Medication	**Dose and frequency**	**Date started**	**Date stopped (if applicable)**

g. Is there any other issue you are aware of that might prevent you from completing the 16 week trial? (Please circle) **Yes/ No**

If yes, please give details:

Lifestyle

Smoking

a. Do you currently Smoke? (Please circle) **Yes/ No**

If yes, how much per day

b. Are you a previous smoker? (Please circle) **Yes/ No**

If yes, how long is it since you stopped and how much did you smoke?

Drinking

a.i. Do you drink alcohol? (Please circle) **Yes/ No**

If yes, how often? (Please circle)

Daily Weekly Monthly Less than once a month A few times a year Never

a.ii. How many units?

(Examples: A small glass of wine = 1.5 units; a large glass of wine = 3 units; a pint of lager/beer/cider ABV 3.2% = 2 units or ABV 5.2% = 3 units; can of lager/beer/cider = 2 units; single shot of spirits ABV 40% = 1 unit)

1-3 4-8 8-12 More than 12

b. In the last week, how many consecutive days have you drank alcohol? (Example: If you drank Friday and Saturday, this counts as 2 consecutive days)

0 2 3 4 5 6 7

Physical Activity

a. How would you describe your current level of fitness? (Please circle)

Very unfit Unfit Moderately fit Fit Very fit

Examples:

Very unfit: Get in and out of an armchair unaided

Unfit: Leave the house on your own to carry out daily activities

Moderately fit: Climb three flights of stairs unaided without stopping. Walk 100 yards without stopping.

Fit: Walk for 1 mile without stopping. Jog for 100 yards without stopping.

Very Fit: Jog a mile without stopping.

b. How would you describe your occupational activity level? (Please circle)

Sedentary Light Moderate Heavy

c.i Do you currently engage in any physical activity? (Please circle) **Yes/ No**

If yes, what type?

c.ii Are you currently doing more than 90 minutes of moderate intensity exercise per week regularly? Moderate intensity requires a consistent high heart rate, a consistent high breathing rate and for you to work up a sweat. (Please circle) **Yes / No**

c.iii On average:

How often do engage in physical activity? Times / week:

For how long do you engage in physical activity? Time/session:

Is there any other issue you are aware of which might prevent you from completing the trial assessments over 16 weeks? If yes please give details below.

Name of person completing form:

Signature of person completing form:

Date:

Appendix 16 COMRADE Consent form

Sheffield Hallam University

The University Of Sheffield.

PARTICIPANT CONSENT FORM:

Version 3: 18/01/2017

A COMbined progRamme of exercise and dietary ADvice in mEn with castrate resistant prostate cancer (COMRADE trial)

Please initial

1	I confirm that I have read and understood the information sheet (Version 3.0) for the above study, I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without my medical rights or legal rights being affected.	
3	I understand that my medical records and information collected during the study may be looked at by authorised individuals from this NHS Trust or regulatory bodies in order to confirm that the study is being carried out correctly. Responsible representatives of the sponsor may also have access to this information for the purposes of monitoring and auditing. I give permission for these individuals to have access to my records.	
4	I understand that I will be required to give blood samples which will be tested in the local hospital central laboratories and undergo a dual energy x-ray absorptiometry (DEXA) scan at Northern General Hospital.	
5	I give permission for research personnel to retain my personal details only for the purposes of participation in the research study. I understand these details will not be passed on to third parties under any circumstances. I understand that my identifiable data will be kept securely by the study co-ordinating centre (Sheffield Hallam University). I understand my contact details will be retained for up to 6 months after the end of the study.	
6	I agree that my anonymised responses from health questionnaires may be used for research purposes and publication.	
7	I agree to my G.P. being informed of my participation in the study.	
8	I agree that if I take part in a recorded post-intervention focus group, my anonymised responses may be used for research purposes and publication.	
9	I understand if I withdraw from the study, all data taken from my participation in the study will be retained for analysis.	
10	I agree to take part in the COMRADE trial	

Name of participant (PRINT)	Date	Signature
Name of individual taking consent (PRINT)	Date	Signature

Three copies to be kept; original for site file; 1 for participant, 1 to go in medical notes

Appendix 17 COMRADE GP letters

Sheffield Hallam University

The University Of Sheffield.

A COMbined progRamme of exercise and dietary ADvice in mEn with castrate resistant prostate cancer - COMRADE trial

[GP NAME]

[GP ADDRESS]

[DATE]

Dear Dr [NAME]

Re: [NAME, D.O.B, ADDRESS]

Your patient (named above) recently attended the Clinical Research Facility, Northern General Hospital, Sheffield as a participant in a clinical research study entitled:

'A COMbined progRamme of exercise and dietary ADvice in mEn with castrate resistant prostate cancer - COMRADE trial'

As part of this study your patient is required to undertake two dual energy X-ray absorptiometry (DEXA) scans approximately 16 weeks apart. We shall analyse both of these scans at the end of the study and provide you with a formal report.

No action is required from you at this stage.

If you have any queries regarding the study, please do not hesitate to contact me on 0114 271 3223.

Thank you for your help.
Yours sincerely,

Mr Derek Rosario (Consultant Urologist and Principal Investigator)

Appendix 18 Healthy eating and dietary guidance booklet

COMRADE:

HEALTHY EATING AND DIETARY GUIDANCE

Sheffield Hallam University

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

The University Of Sheffield.

ABOUT THIS GUIDANCE

As part of the COMRADE study, we are asking our participants to make positive changes in their diet. This is not only for your own health and wellbeing but also as we feel this will help compliment the effects of the exercise intervention you are taking part in. You may already feel like you have taken some steps toward a healthy diet but please continue to read this information for further guidance as you may still find this helpful.

We understand that whilst receiving treatment for cancer making the best food choices can be very challenging. You may find it easier to make changes to your diet gradually, at a budget you can afford, and when you feel ready. The diet diaries we ask you to fill out are also a good opportunity for you to see what you are currently eating and compare it with this information, to help you decide whether you wish to make healthier choices.

This dietary advice doesn't have to be restricted to just you, getting your spouse, family members and friends on board will help to keep you on track and make it a much more enjoyable experience.

The treatment that you are undergoing can be very trying on your body and therefore on your appetite. A loss of appetite on chemotherapy is a common side effect, in this case you may find it beneficial to eat little and often as opposed to three meals a day. Whilst we may talk about restricting high calorie high sugar foods in this guidance, you must also make sure you are maintaining a sufficient calorie intake. Every individual is different and therefore it is important to follow any information and advice given to you by your healthcare team (like your dietician, GP or specialist nurse) and inform them of any changes to your diet. Additionally, if you have an allergies or intolerances then speaking to your healthcare team before making any changes to your diet will help you to choose suitable and healthy alternatives. Also informing the research team is important; we can also help to offer some advice and

knowing your specific dietary requirements helps us monitor your progress.

Care has been taken in these dietary guidelines to take into account any special dietary requirements and needs, including religious and cultural requirements. This includes both vegetarian and vegan alternatives. In addition, if you should chose to try any of the recipes in this dietary guidance, we encourage you to still source your ingredients from your regular supermarket in compliance with any religious or cultural beliefs. This is to ensure that you are able to continue to follow any required religious or cultural practices without compromise.

If there is anything you are unsure of in these guidelines please speak to a member of the research team who will be more than happy to talk you through any questions you may have.

We are here to help guide you and want to help you make the best choices you can.

PLAN YOUR MEALS AS OFTEN AS POSSIBLE

Some people turn to food when life is stressful, known as comfort eating. For others being busy means that they often turn to convenience food such as microwave meals or take-always. For this reason we ask you to **plan your meals daily**, generating a meal plan often helps. It is not always possible to plan your meals (if you are visiting family members or going on holiday) and sometimes it may not be possible to plan what you are going to eat. But if you make efforts as often as possible you may often find **you will save money in the process and actually spend less time preparing food than you thought**, whilst achieving a healthy diet. For example, a big batch of homemade chilli made on a Sunday can be split into several meals, frozen and defrosted when necessary. Making use of your microwave also means that on those days you are just too tired to cook or don't have time, you have a portion of ready and waiting in the

fridge or freezer; which is much easier than ordering and waiting for a takeaway, and easier on your wallet too.

READ THE LABELS

You may have seen a lot in the news recently about hidden sugars in everyday foods. Some of the worst offenders for this are cereals (including cereal bars), bread, sauces and soups, yogurts, dressings and baked beans. Low fat or “diet” foods can often have added sugars to make the taste more palatable. Nutritionally fats do have higher calorie content, but some fat in the diet is essential. Fats from more nutrient dense foods such as nuts, seeds and fish provide essentially fatty acids (including omega-3). **It is always important to read labels to check for any added sugars.** Additionally, fruit juices and smoothies should be consumed within moderation. They are still high in fruit sugars and nutritionally offer much less fibre than the fruit in its natural form.

WE ARE NOT SAYING YOU CAN’T ENJOY THAT FRIDAY NIGHT TAKE-AWAY

A main point we want to make in this guidance is **moderation**. That means that we are not asking you to give up your Friday night rituals of a take-away or to stop drinking at your local pub with friends. Ultimately you will decide whether you want to eat more healthily not us and the argument we are making here is one we've all heard before that is: Moderation is key! One idea to improve your diet is that you **eat as best and healthy as possible 90% of the time allowing for 2-3 meals each week as "treats"** – meaning meals which don’t necessarily follow the dietary guidance, say for example a meal out with friends and family. This will help you to be more flexible and realistic with your healthy eating

plan, but ensuring you continue to enjoy a healthy lifestyle. The important thing is not to binge eat when you do decide to have a treat. Be mindful, but don't feel guilty if you have that chocolate bar after a week of healthy eating!

ALCOHOL

The government suggests that men **should not regularly drink more than three to four units of alcohol a day**. We consider this to be an **absolute maximum** and ask that you minimise your alcohol intake as much as possible. Good advice seems to be if you are a drinker focus in having some drink free days, again like the diet diary I suggest below recording what you drink and when you drink may help you keep track and control your alcohol consumption. i.e.

How many units of alcohol are in a drink?[1]

- ***A pint of lager, beer or cider contains 2-3 units.***
- ***A 175ml glass of wine contains about 2 units.***
- ***A 25ml measure of 40 per cent single spirit with mixer contains 1 unit***

[1]***Information taken from prostatecanceruk.org/prostateinformation***

SOME SUGGESTIONS

1. **Wholewheat or whole grain foods** rather than the white versions where possible (e.g. breads, cereals, crackers, pastry, pasta and

grains like rice and couscous). If you struggle to have wholegrain and high fibre foods, speak to your dietician for advice on how best to control this whilst maintaining a healthy diet.

2. Aim for **at least 5 portions of fruit and vegetables** each day, they can be fresh, tinned, frozen or dried (check the portion sizes with dried fruit however as you need a lot less than the natural versions). Try to have a range of different colours of fruit and vegetables to give you a variety of vitamins and minerals. Here are a few examples of a portion:

   - ✓ **Fruit juice** counts (150ml or a small glass) but only once a day
   - ✓ Roughly a **handful of veg** is a portion
   - ✓ An **average sized banana or apple** is a portion
   - ✓ One portion is **two or more small fruit**, for example 2 plums, 2 satsumas or 14 cherries.
   - ✓ **Three heaped tablespoons of beans** e.g. baked beans, chickpeas, kidney beans or cannellini beans count as one portion each. Remember, however much you eat, beans and pulses count as a maximum of one portion a day.

3. **Drink plenty of water.** Particularly as your activity level is going to increase you will be losing more fluid as you sweat and it is important to replace this and remain hydrated but avoid high sugar soft drinks. A good test for checking hydration is to maintaining a fairly clear "straw" coloured urine whereas smelly, dark urine usually signifies dehydration. You should aim to drink six to eight glasses of fluid a day to day and more if you are exercising or if it is particularly warm weather (water, lower fat milk and sugar-free drinks including tea and coffee all count). Water is really important for many bodily processes including the removal of toxins, (NB some medicines and water soluble vitamins also affect the colour if our urine).

4. **Regular meal patterns** might work well for helping you maintain a healthy weight some people find that when they miss meals, for

example breakfast, they make up for this later in the day by over-eating as they become so hungry

5. **Keep a food diary**- this seems to help for many people as the diary raises self-awareness over what we are consuming. We give you a three day food diary at the start of this intervention but you may want to continue your own diary to keep track of your healthy eating. Give it a try you may be surprised by the effects!

PROTEIN

As part of the exercise programme you are undergoing we are offering you a whey protein supplement to help you achieve a diet high in protein. Please speak to our research team if you cannot consume dairy/milk products. **A diet high in protein** is also important in helping to enhance the effects of the exercise programme you will be undertaking. We ask that you avoid protein sources such as red meat and processed meat and opt for fish, nuts, legumes, beans and poultry as alternatives. Pulses such as beans, lentils and peas, they are a low fat alternative to meat and a good source of protein as well as being suitable for a vegetarian and vegan diet. Other non-meat high protein sources include: tofu, tempeh, quinoa, amaranth, soy milk and seeds (hemp, chia and pumpkin are best). If you do chose to have a meal with red meat then opt for the leanest cuts and trim any excess fat.

SOME STORE CUPBOARD FAVOURITES

These are a few things we think would be helpful to have in your cupboards regularly. We are not suggesting you go and purchase everything now. But you may find as you are trying new recipes you pick up a few of these products anyway and then they naturally become a regular staple in your cupboards.

BEANS, PULSES, LEGUMES AND GRAINS

- A selection of beans and pulses for example chickpeas, kidney beans, black beans, butter beans
- Brown rice
- Bulgur wheat
- Pearl barley
- Oats
- Couscous (wholegrain)
- Quinoa
- Dried legumes like lentils (green, red, yellow, brown which ever you prefer) and split peas

NUTS, SEEDS AND DRIED FRUITS

A selection of dried fruit and nut (these are great for snacking but avoid too much as they can have a high calorie content, especially dried fruits in comparison to their natural undried versions. As they are much smaller it's a lot easier to get carried away, so be mindful). As a general rule opt for the non-peanut natural variety. Roasted and flavoured versions (like BBQ flavouring) can have added ingredients like sugar or be high in salt so always check the packets. If you can, avoid sweetened dried fruit as these can have added sugars. They can be a bit harder to spot so just make sure you read the labels when you get to the super market.

- Almonds

- Cashews
- Dried cranberries
- Dried apricots
- Brazil nuts
- Anything goes really

OILS ANF FATS

We recommend that you try to grill, steam or poach food where you can but when you do choose to fry foods try to do it in fats which have had minimal processing such as:

- Extra virgin olive oil (this can be quite expensive so you can also opt for regular olive oil)
- Coconut oil
- Sesame oil
- Nut oils (like groundnut and walnut)

TOMATO PRODUCTS

Avoid any products with any added sugar or salt.

- Chopped/plum tomatoes
- Passata
- Tomato puree

DRIED HERBS AND SPICES

Always keep you favourites in to add a little flavour to your vegetables. An even easier way is to add spice mixes to your food but do check there are no hidden sugars. A few more suggestions are given below:

- Bay leaves

- Oregano
- Thyme
- Basil
- Rosemary
- Smoked paprika
- Chilli flakes
- Cayenne pepper
- Chinese five spice
- Cajun spice
- Ground cinnamon
- Garlic granules
- Curry powder

FLOUR

Stick to wholemeal or wholegrain varieties.

- Wholemeal plain and self-raising
- Brown rice flour
- Buckwheat flour
- Spelt
- Gram flour (also known as chickpea flour)

RECIPES

The recipes in this booklet are a few suggestions we have given you to get you started. Feel free to adapt them as you see fit. If there is an ingredient you dislike then feel confident to swap it to something else and seems like it would fit the recipe.

Vegetarian and vegan options are given for all the recipes (excluding the salmon fish cakes and chicken Kiev). All of the recipes can be made gluten free too; swap oats, wholemeal breads and breadcrumbs for their gluten free versions available in major supermarkets.

BREAKFAST .....

MAIN MEALS ..... ERROR! BOOKMARK NOT DEFINED.

HEALTHY SWAPS..... ERROR! BOOKMARK NOT DEFINED.

SNACKS ..... ERROR! BOOKMARK NOT DEFINED.

BREAKFAST

STUFFED BREAKFAST MUSHROOM ON WHOLEMEAL BREAD – SERVES 2

4 Portobello mushrooms

50g of goat's cheese*

1 tbsp of olive oil plus extra for brushing

1 leek finely chopped

3 garlic cloves, finely chopped

100g spinach

½ tsp of nutmeg

A pinch of cayenne pepper

¼ tsp of Dijon mustard

4 slices of wholemeal bread

Preheat the oven to 200°C/ gas mark 6.

Rinse the mushrooms and pat dry with a little kitchen roll.

With a knife, remove the stalks and brush the underside of the mushroom with olive oil. Place the mushrooms on a baking try lightly brushed with olive oil

Heat the olive oil in a pan at a medium heat and add the leek, fry until soft, then add the garlic. Gently fry for a few minutes.

Stir in the spinach, nutmeg, cayenne pepper and heat through until the spinach wilts then stir in the mustard.

Fill each mushroom with the leek filling and crumble over the goats cheese. Bake in the oven for around 25-30 minutes.

Serve immediately on toasted wholemeal bread or rye.

*For a non-dairy version leave out the goats cheese and sprinkle with pumpkin/sunflower seeds.

BANANA PANCAKES – SERVES 2

2 bananas

2 eggs*

50g porridge oats

½ teaspoon baking powder

½ teaspoon of cinnamon

Pinch of salt

Greek yogurt*

Flaked or whole almonds, to serve (optional)

Fresh fruit, to serve

In a food processor add the banana, eggs, oats, baking powder, cinnamon and salt and blend until smooth. If you don't have a food processor, mash the banana thoroughly first with a fork then mix in the whisked eggs, oats, baking powder, cinnamon and salt. If the mixture looks too thick, add a splash of milk to loosen the mixture.

Heat a non-stick frying pan over medium heat. If you are using a regular pan melt a ½ tsp of coconut oil to the pan first and melt.

Fry tablespoons of the batter until golden brown on both sides.

Serve with a dollop of Greek yogurt, fresh fruit of your choice and scatter a handful of flaked or whole almonds over the top.

*For a non-dairy version substitute each egg with 1 tablespoon of ground flax seed with 3 tablespoons of water and substitute out the Greek yogurt for a soy or coconut alternative.

HEALTHY SIMPLE BREAKFAST BOWL – SERVES 2

3 pine nuts

1 ripe avocado, sliced

10 cherry tomatoes, halved

1 large carrot, grated

150g of spinach, washed

200g of smoked salmon*

1 tbsp of whole grain mustard

2 tblsp olive oil

2 eggs*

Toast the pine nuts in a pan on a medium heat until they begin to go golden brown. Take off the heat and set to one side.

Serve the avocado, tomatoes, carrot, spinach and salmon in two bowls.

Combine the mustard and olive oil in a small bowl or mug and stir well.

Poach or soft boil the eggs in a pan then serve immediately over the salad and salmon. Spoon over the mustard dressing and sprinkle the pine nuts.

*For a vegetarian and vegan version substitute the smoked salmon for vegetarian/vegan sausages and omit the eggs for a handful of edamame beans

NUTTY GRANOLA – SERVES 8-10

1 tbsp sunflower or coconut oil

100ml of maple syrup or honey

1 tsp of vanilla extract (plus 1 tsp of almond essence, optional)

250g of porridge oats

50g of whole almonds

50g of seeds (pumpkin, sunflower, poppy all go well)

100g of mixed nuts, whichever you prefer like hazelnuts (without skins), brazil nuts or walnuts

50g of dried fruit (like cranberries, chopped dates, satsumas, apricots)

1 tsp of ground cinnamon

Greek yogurt*

Fresh fruit

Preheat the oven to 150°C/ gas mark 2 and line a relatively deep baking tray with baking parchment.

Heat the oil and maple syrup together on a low heat in a large saucepan. Place the oats in the pan, add the vanilla essence and stir to coat thoroughly.

Spread the oats out in an even layer onto the baking tray and bake for 10 minutes.

Remove from the oven and add all of the nuts, try to distribute them as easily as possible. Place back into the oven and bake for a further 10-15 minutes.

Remove from the oven and add the dried fruit and cinnamon then stir through

Serve with Greek yogurt and fresh fruit like blueberries.

*For a non-dairy version substitute the Greek yogurt for unsweetened soy yogurt or coconut yogurt

Store the remaining in an airtight container; it will keep for a couple of weeks

MAIN MEALS

AVOCADO AND SALMON CAKES – SERVES 4

340g of tinned salmon or tuna

2 eggs

80ml of milk

75g of breadcrumbs

1 shredded courgette or carrot (a cheese grated works well if you don't have a food processor)

2bsp of curry powder or 2tblsp of Thai green curry paste

Avocado

120g Plain Greek yogurt

Juice of one lime

1 tsp of wasabi paste

1 small bag of spinach or mixed salad, washed

Pre-heat the oven to 180°C/gas mark 4 and grease 8 muffin cups of a muffin tray.

Mix by hand or put all the ingredients in a food processor. Once combined, using a spoon scoop out and distribute evenly in the 8 greased muffin cups.

Place in the oven and bake for around 25-30 minutes.

Whilst the salmon cakes are baking, blend a large avocado with the Greek yogurt, lime juice and wasabi until smooth.

Serve on the side with a big portion of spinach.

BAKED SWEET POTATO WITH SMOKY BLACK BEANS AND SPICY AVOCADO QUINOA SALAD– SERVES 2

2 large sweet potatoes, washed

100g of quinoa

250g of tomatoes, washed and roughly chopped

1 large avocado, roughly chopped

2 spring onions, thinly sliced

Juice of one lime

1 small red or green chilli

1 handful of fresh coriander (more if you like)

1 red onion, peeled and chopped

Olive oil

1 tsp of cumin seeds

1 tbsp of chipotle paste (if you can't find this a chilli and paprika paste or alternative Mexican paste is fine)

1 x 400g tin of black beans

2 heaped teaspoons of low fat cottage cheese (optional)

Preheat the oven to 180°C/gas mark 4.

Pierce a cross through the sweet potatoes wrap in a little tin foil and just before you close the top up drizzle a little olive oil and season lightly with salt and pepper.

Roast for 45 minutes to an hour (when they are soft in the middle they are ready).

After about 25 minutes of the sweet potatoes roasting, rinse the quinoa well before cooking to the packet instructions (this removes the slight bitter taste quinoa can get when exposed to air).

Place the tomatoes, avocado and spring onions in a bowl. Finely chop the coriander leaves and the chilli and place in the bowl. Drizzle over the lime juice, give it a quick stir then mix the whole thing together with the quinoa and place to one side.

Put a pan on a medium heat with a teaspoon of olive oil and add the cumin seeds. After about 30 seconds, or when they start to smell a little fragrant, add a splash of water and stir it through the seeds before adding the onion. Cook until softened and then add the chipotle paste and stir through.

Continued…

Add the beans with all of their juice. Reduce the heat and cook for a further 5 minutes until the sauce becomes thick,

add a little more water if necessary. Season with a pinch of salt and pepper.

Divide the beans and quinoa salad evenly between two plates and slice open the sweet potatoes. Add a dollop of cottage cheese to the centre of each sweet potato and serve.

Continued…

SESAME SEED SALMON WITH SUMMER VEG STEW AND WHOLEWHEAT COUSCOUS – SERVES 2

2 fillets of salmon*

4 teaspoons of sesame seeds

1 packet of baby corn, halved

1 tbsp olive oil

2 large carrots, grated

1 red pepper deseeded and roughly chopped

1 celery stick, roughly chopped

1 small red onion, peeled and diced

1 avocado, roughly chopped

The juice of 1 lemon/lime

150g of whole wheat couscous/quinoa/ wild rice

30g basil leaves, torn

4 sundried tomatoes in oil, drained and roughly chopped

Preheat a pan to a medium heat.

Lay out the sesame seeds on a flat surface and gently press the sides salmon lengthways into the seeds (not the skin side). Leave to one side.

Add the olive oil to the pan and throw in the sweetcorn and fry for around 4 minutes. Then add the red pepper, celery and red onion and toss in the pan for a further 4 minutes.

Take off the heat and combine the veg with the avocado and carrot and leave covered to one side.

Turn the heat up and fry the salmon on one side for four minutes or until the seeds go golden brown. Turn the salmon over and cook for a further minute then take off the heat and transfer to plates.

Add the basil and sundried tomatoes to the cooked couscous and stir through. Serve the couscous and veg alongside the salmon and drizzle with a little lemon juice.

*For a vegetarian and vegan version substitute firm tofu for salmon and try coating cubes in sesame seeds and follow the instructions as normal.

FIERY PRAWN STEW- SERVES 4

450g peeled prawns *

4 tbsp olive oil

1 tsp smoked paprika

3 garlic cloves

1 – 1 ½ tsp chilli flakes

1 bay leaf

400g chopped tomatoes

2 x 410g cannellini beans, drained

1 tbsp tomato puree

240ml of chicken or vegetable stock (low salt variety)

2 tbsp fresh parsley or 1 ½ tsp of dried

Pinch of salt

4 large wholemeal flat bread

Greek yogurt (optional)

Toss the prawns with 1 tbsp of olive oil and the paprika then transfer to a heated pan and cook for 2 minutes.

Add half of the garlic and cook for 30 seconds then set the prawns aside in a bowl.

Return the pan to the heat and add a further 2 tbsp of olive oil, the chilli flakes, the bay leaf and the remaining garlic.

Cook until the garlic is lightly golden and then add the chopped tomatoes.

Continue to simmer until most of the liquid evaporates and then add the tomato puree, beans and stock.

Simmer for 10 minutes. Stir in the prawns and parsley and season with a pinch of salt and pepper.

Serve in bowls alongside warm flat breads. Add a dollop of Greek yogurt too if desired.

* For a vegetarian and vegan version roast some roughly chopped butternut squash in the oven until just soft (but not too mushy) and follow the same steps you would for the prawns.

HARISSA BAKED AUBERGINE WITH MOROCCAN QUINOA – SERVES 2

2 tsp harissa

Olive oil

1 large aubergine

1 cup quinoa, rinsed *

¼ cup raisins

2 cups boiling vegetable stock (low salt variety)

3 tablespoons extra virgin olive oil

2 tablespoons lemon juice

1 clove garlic, finely chopped

1 teaspoon ground cumin

1 teaspoon ground coriander

½ teaspoon ground ginger

1 teaspoon salt

1 carrot, grated

1 red pepper, diced

1 red onion, diced

1 cup canned chickpeas, rinsed and drained

2 tablespoons finely chopped flat-leaf parsley

Greek Yogurt (optional)

Pre heat the oven to 180°/ gas mark 4.

Half the aubergine lengthways and crisscross the flesh.

Put the harissa in a bowl and lengthen with a splash of olive oil, mix well. Brush the harissa mix onto the aubergine and place on the baking tray.

Bake for around 20-30 minutes or until it becomes soft in the middle. If the top begins to brown too quickly cover with a little foil and place back in the oven.

Meanwhile, cook the quinoa according to packet instructions in the vegetable stock.

Mix the oil lemon juice and spices in a bowl. Fluff the quinoa with a fork to separate the grains and add the raisins, carrot red pepper, onion, chickpeas and parsley and stir through.

Add the olive oil and spice mix, stir through and serve the quinoa with the aubergine placed on top.

Add a dollop of Greek yogurt if desired.

*If you don't like quinoa then this recipe can be done with wholewheat couscous, just cook to packet instructions and add the rest of the ingredients as normal.

HEALTHY SWAPS

Take everyday comfort food and make it more nutritious with simple swaps

BANGERS AND MASH- SERVES 2

4 Lean sausages like venison or turkey (or vegetarian/vegan ones)

2 sweet potatoes (or try 1 sweet potato and 1 large carrot), peeled and roughly chopped

2 tsp of dried rosemary

A pinch of salt

2 tsp of butter/olive oil

A splash of milk

1 leek thinly sliced

1 tbsp of olive oil (or 2 tsp of butter)

100g of kale (washed)

60g of toasted pine nuts

Pre heat the grill on a medium heat.

Add a splash of oil to a large pan and sauté the sweet potatoes for around 3 minutes before adding water to just cover the potatoes and a little salt.

Bring to the boil and then turn it down to a simmer for around 20 minutes or until soft. You can take it off the heat but keep the lid on to keep it warm.

Add the olive oil to another saucepan on a medium heat and throw in the sliced leek. Sweat the sliced leek for about 20 minutes.

Add the kale and stir through then leave for another 5- 10 minutes, keep it covered if you take it off the heat.

In the meantime grill the sausages according to the packet instructions, usually around 8-10 minutes.

Drain the potatoes and mash with a potato masher or hand blender (if you prefer it smoother) and stir through the butter and rosemary.

Serve up the sausages over the mash and top with the leek kale mix. Sprinkle with the toasted pine nuts.

TURMERIC CHICKEN PITTAS (THINK HEALTHY KEBAB) – SERVES 2

2 sprigs of fresh oregano or 2 tsp of dried

1 level tsp of turmeric

2 tbsp olive oil

2 large skinless chicken breasts *

200g of baby spinach/Swiss chard/kale

2 large wholewheat pitta breads

1 lemon

1 aubergine sliced into half centre meter thick pieces.

1 sliced avocado (optional)

2 heaped tbsp of low fat hummus

Salt and pepper

Your favourite chilli sauce (optional)

Pre heat the oven to 200°C /gas mark 6.

Take a large bowl and add the oregano, turmeric and olive oil and mix to make the marinade.

Toss the chicken in the marinade and coat evenly then leave to one side.

Lay the aubergine flat on a baking tray and drizzle with a little olive oil. Season the aubergine with a pinch of salt and pepper and place in the oven.

After ten minutes turn the slices of aubergine over and place them back in the oven for another 10-15 minutes or until they are tender.

Once done, take the aubergine out of the oven and leave to one side.

In the meantime, blanch the greens until just tender and drain well (if you are using spinach you can eat it raw or just place them in a colander and pour over a kettle of boiled water).

Heat some olive oil in a frying pan on a high heat and cook the chicken for 4 minutes on each side or until cooked through.

Reheat the greens if needed and serve up the chicken, aubergine, greens and hummus on warm pitta bread with the avocado and a lemon wedge on the side. Drizzle over some hot chilli sauce if desired.

*For a vegetarian/vegan version you can sub the chicken for Quorn/Frys (vegan) pieces or cubes of firm tofu.

SIMPLE THAI RED CURRY – SERVES 4

2 tblsp olive oil

1 red onion peeled and chopped

900g skinless chicken breast sliced *

1 tblsp of Thai red curry paste

400ml of light coconut milk (if this is too heavy try half coconut milk and half low salt chicken or vegetable stock)

3-4 dried lime leaves

340g spinach

handful of fresh coriander (optional)

4 portions of cooked brown rice according to packet instructions

Heat the olive oil in a large non-stick pan and sweat the onion for 3-5 minutes.

Add the chicken to the pan and cook, stirring for 5 minutes.

Stir in the curry paste and cook for a further minute before adding the coconut milk (and stock if using) and reduce the heat.

Add the lime leaves and simmer for 7 minutes.

Add the spinach and stir through, leave for a further minute then serve with the cooked rice in bowls and sprinkle with the fresh coriander

.

*You can also try a fish version. Any white fillet fish works best and cook until flaky although times may differ slightly between fish. Prawns also work great too. For a vegetarian /vegan version use firm tofu or Quorn/Frys chicken pieces instead.

SMOKEY BAKED BEANS ON RYE- SERVES 2 (WITH 4 SERVING OF BEANS LEFT OVER TO FREEZE)

6 tins of cannellini beans, drained and rinsed

2 bay leaves

1 tbsp of olive oil

2 onions, diced

4 garlic cloves, finely chopped

2 tsp of chipotle paste (if you can't find this a chilli and paprika paste or alternative Mexican paste is fine)

1 ½ tsp dried oregano

1 ½ tsp dried thyme

2 tbsp of tomato puree

2 tins of tomatoes

1-2 tbsp of maple syrup

1 litre of vegetable stock (low salt variety)

2 eggs (optional)

2 slices of good quality rye bread or a wholemeal alternative

In a large pan, heat the olive oil on a medium heat and fry the onion for 10 minutes or until soft.

Add the bay leaf, celery, garlic, chipotle paste and herbs.

Stir and cook for a further five minutes. Add the tomato puree, tined tomatoes, maple syrup and veg stock and cook at a medium simmer for 20 minutes.

Add the cannellini beans and simmer for a further 30 minutes.

Remove the lid of the pan if necessary to allow the excess water to evaporate and get a thicker consistency towards the end.

Butter the rye bread and serve with the beans on top.

Poach the eggs and serve immediately on top of the beans and rye bread.

CHICKEN KIEV WITH SPRING VEG- SERVES

For the garlic butter:

3 garlic cloves, crushed or diced

50g of butter

1 handful of fresh parsley finely chopped

1 tsp of lemon juice

For the kiev:

100g bread crumbs

½ tsp of cayenne pepper or smoked paprika

1 egg

2 skinless boneless chicken breasts

Salt and pepper

For the spring veg:

1 bunch of asparagus

100g frozen broad beans

100g of frozen peas

1 bunch of mint, chopped

Olive oil

Continued…

Pre heat the oven to 200°C/ gas mark 6 and line a baking tray with baking parchment.

Mix all the ingredients for the garlic butter together using a fork and season with pepper to taste.

Roll in baking parchment or cling film into a sausage shape about 2cm in diameter. Leave in the freezer for 30 minutes.

Put the breadcrumbs into a bowl with the cayenne pepper/paprika with a pinch of salt and pepper. *Tip: you can make your own breadcrumbs with stale bread blitzed in a food processor.*

Beat the egg in a separate bowl.

Push a sharp knife into the fat end of the chicken breast to create a pocket.

Half the garlic butter and place one half inside each of the breast. Seal the pocket closed with your hands.

Dip the chicken breasts in egg first then roll around in the breadcrumbs.

Pat down and place on the prepared baking tray. Bake for 25-30 minutes.

In the meantime heat a pan on a high heat and half fill it with boiling water.

Trim the woody ends off the asparagus then slice the stalks to 1cm think pieces. Leave the tips whole.

Continued…

Feta cheese

1 Lemon

2 slices of rye bread (or a wholemeal alternative), optional

Cook in the water with the beans and peas for just 3 minutes.

Drain and place back in the pan drizzle over some olive oil, toss in the mint and serve alongside the chicken.

Crumble over the feta cheese and a squeeze of lemon.

Serve with warm rye or wholemeal bread.

SNACKS

There are lots of healthy options out there to help you through the day between meals. Although we don't like to encourage snacking *too* often, it is important to have some healthy options when you need it between meals to help you through the day. The exception to this is if you are struggling with your appetite due to treatment or have concerns about too much weight loss. It is always important to consult your treating clinician or dietician first. However, you may still find these suggestions for small snacks helpful if not just for ideas.

Some options for snacks are listed below:

- A portion of fruit
- A handful of nuts
- A slice of rye bread or two rice cakes with nut butter
- Low calorie popcorn (be mindful of sugars)
- A boiled egg
- Raw sliced veg like carrots, cucumber, celery, peppers with hummus or tzatziki
- A fruit and nut bar with no added sugar

We have also given you a couple of recipes for further inspiration.

OAT-Y NUT COOKIES

4 medium bananas

5 heaped tbsp of nut butter (chose varieties with no added sugar)

1½ tbsp of coconut oil or sunflower oil, plus extra for greasing

4 tbsp of honey or maple syrup

1 tsp of mixed spice or cinnamon

1 tsp of vanilla essence

200g of porridge oats

Preheat the oven to 200°C/ gas mark 6 and grease a baking tray lightly with coconut or sunflower oil.

Peel and place the bananas in a food processor and blitz until smooth. If you down have a food processor place in a large mixing bowl and mash with a fork.

Add the nut butter, oil, honey/maple syrup, spice, vanilla essence and oats to the banana and thoroughly mix.

Scoop out heaped tablespoons of the sticky mixture spaced evenly on to the baking tray. Press them out into a thin cookie shape.

Place the tray in the oven and bake for 15 – 20 minutes until they begin to turn golden brown.

Remove the cookies and allow to cool on a wire rack. Store in an airtight container.

SPICY CHICKPEAS

1 tbsp of olive oil

2 cans of chickpeas, drained and rinsed

2 tbsp of lemon juice

1 tsp of maple syrup

1 tsp of soy sauce/ tamari (gluten free)

1 tsp of harissa spice (dry version) If you can't find this try another Mexican spice mix.

Preheat the oven at 220°C/ gas mark 7 and line a baking tray with baking paper.

Heat the oil in a wok at a medium-high heat and add the chickpeas. Fry for around 3-5 minutes.

In the meantime add the lemon juice maple syrup, soy and harissa spice to a mug and mix throrougly.

Pour in the mix and over the chickpeas and coat evenly.

Spread the chickpeas out evenly on the baking tray and place in the oven for 30-35 minutes or until crispy.

Remove and allow to cool for 5-10 minutes before enjoying.

Store in an airtight container.

Appendix 19 COMRADE protocol

Standard Operating Procedure (SOP)

SOP Title	COMRADE Intervention SOP
Version Number	1.0

Author	Rosa Greasley Name	PhD Researcher Position
Reviewed by	Liam Bourke Name	Chief Investigator Position

Approved by	Name	Position
	Signature	Date

Version	Date Approved	Reason for Change	Author
1.0	25/04/2017		RG

Abbreviations

SOP	Standard operating procedure
HRM	Heart rate monitor
LBM	Lean body mass
OS	Overall survival
QoL	Quality of life
CV	Cardiovascular
RPE	Rate of perceived exertion
RM	Rep max
CRF	Case report form
AE/SAE	Adverse event/ serious adverse event

Glossary (add as necessary)

Case Report Form
A printed, optical or electronic document designed to record all of the protocol required information.

1. Objective

This SOP describes the intervention for the clinical trial, which consists of exercise training and dietary guidance. This will be undertaken by participants for 16 weeks, combining supervised resistance exercise session, dietary guidance and supplementation, and encouragement to do independent aerobic exercise. It covers procedures that should be in place to ensure participants perform resistance exercise and independent exercise in a safe and effective manner as well as encouragement to maintain a high protein healthy diet.

2. Scope

This SOP applies to the trial exercise specialist who will be guiding the participants through the complex intervention.

3. Background

Cancer patients of lower performance status and a reduced LBM have repeatedly been shown to have more dose limiting toxicity, a poorer chemotherapy completion rate, a higher risk of neutropenia and poorer OS. The metabolic benefits in LBM gain associated with exercise is thought to be the key determinant in risk reduction of

numerous chronic diseases such as cardiovascular disease, cancer, neurological conditions and diabetes (1).

The beneficial effects of exercise training for improving LBM are also well established (2). Studies investigating the effectiveness of resistance training and cancer have shown positive effects demonstrating an increase in chemotherapy completion rate (3-6). There is also level one evidence specific to improving outcomes in men with prostate cancer from a 2015 systematic review and meta-analysis of randomised controlled trials supporting exercise interventions. Interventions involving a combination of aerobic and resistance exercise can improve fitness, physical function, exercise capacity, cancer specific fatigue and prostate cancer specific QoL (7).

In general cancer, multiple pre-clinical and clinical studies, including observational cohort studies, have demonstrated anti-tumour effects of a low carbohydrate and high protein diet (8-12).

Resistance exercise will be prescribed and monitored throughout the study along with dietary intake using 3 day diet diaries. As with any intervention it is essential that it is conducted in a safe and effective manner in line with GCP standards.

4. Individual responsibilities

The exercise specialist is responsible for delivering the exercise and dietary guidance intervention throughout the study. It is their responsibility to protect the rights, safety, and welfare of subjects under their care during a clinical trial.

5. Procedure

5.1 Exercise intervention

5.1.1 Program overview

Resistance exercise training will be undertaken every week for 16 weeks, combining supervised and independent aerobic exercise training. Participants randomised to the exercise group will be asked to attend up to three (at least two) group based supervised exercise sessions per week, a total of 32-48 sessions. These sessions will ideally be booked in advance with each participant either via a telephone call or during their previous exercise session. They will take place at dedicated exercise rehabilitation suites (A205) at Sheffield Hallam University. Supervised sessions will take place during the daytime and evenings and will be flexible to work around participant's commitments. Participants will also be expected to undertake at least one self-directed aerobic exercise episode of at least 30 minutes per week.

5.2 Session contents

5.2.1 Supervised Exercise

Preceding any exercise sessions, men will attend a one to one consultation (1 hr) with the exercise specialist for a tailored exercise induction. Supervised exercise sessions will comprise of up to 45-60 minutes of a warm up, a resistance exercise main session and a cool down. The cardiovascular (CV) component of the warm up and cool down will include aerobic exercise, using standard ergometers e.g. stationary cycles, rowing ergometers, treadmills and cross-trainers. Participants will be monitored using Polar heart rate monitors (HRM) during the session.

In each session, participants will perform 3-4 sets of 6-12 repetitions of 6 resistance exercises at 60% 3 RM initially. Free weights, body weight and cable machine exercises will form the resistance exercise component of each session. Exercises will be regressed or progressed dependant on the participant's abilities under the supervision of the exercise specialist. Exercises will also be tailored to participant's comorbidities and alternative offered or exercises omitted where necessary. Sessions will be conducted in a group format where possible. Participants will be asked to undertake and log (in a record book provided) at least one independent 30 minute aerobic activity at home during this period. The activity chosen will be based on that most convenient for the participant (such as walking or making use of community exercise facilities). In the record book participants will be asked to record the time of activity, duration and exercise intensity based on the Borg rating of perceived exertion scale, details of which will be provided in the booklet (12). The participant logged activity will be documented when participants attend supervised exercise sessions and further encouraged to undertake aerobic exercise through goal setting and self-regulation.

A heart rate monitor chest strap will need to be worn by the participants with the middle of the strap being aligned with the bottom of the patient's sternum. HRM will be cleaned at the end of each session to adhere with local health and safety procedures. Heart rate & RPE will be monitored by the exercise specialist throughout the supervised sessions, if the exercise intensity falls outside of safe parameters, then it will be altered accordingly.

5.2.2 Session guidance and documentation

All supervised exercise sessions will be guided by the study exercise specialist. During the supervised sessions the exercise specialist will provide ongoing feedback on exercise technique and intensity guidance. The following information will need to be written on the exercise CRF: Trial ID number, medications, co-morbidities, date & time of session and resting/maximum heart rate. The type of exercise and HR will be recorded by the exercise specialist and will be monitored during the exercise sessions. If an adverse event or serious adverse event occurs, it will be noted on the exercise

CRF and the corresponding appropriate AE/SAE form will be completed by the exercise specialist according to the trial protocol. The exercise CRF will be stored in the secure trail filing cabinet in the co-ordinating centre (Sheffield Hallam University).

5.2.3 Self-directed exercise

In addition to the supervised sessions, men are required to undertake at least one self-directed exercise episode of at least 30 minutes per week, recorded in an exercise log book. Independent exercise sessions are purposefully designed to be flexible in terms of where and when they are undertaken by intervention participants. These can be undertaken at home, in local council facilities, local sports clubs, parks etc. The participants will be expected to record type of exercise, duration and average RPE on their exercise log book. Once the study has been completed, the exercise log book will be stored in the trial master file at the co-ordinating centre.

5.3 Dietary guidance

5.3.1 Dietary guidance

Participants randomised to the intervention arm will also be offered dietary advice in the form of a short seminar in a small group format on healthy eating and an information booklet with weekly meal plans and recipes. A dietary guidance information booklet will encourage participants to adopt a diet rich in nutrient dense whole foods, fruit and vegetables and discourage processed foods and those high in refined carbohydrates and saturated fats. Participants will also be asked to limit alcohol intake. Recipes provided will encourage high protein, moderate fat, high fibre and low carbohydrate meals.

5.3.1 Dietary supplementation

Whey protein: To promote muscle protein synthesis, participants will be required to increase protein consumption via whey protein supplementation provided. Participants will be provided with whey protein post-supervised exercise sessions and to take home where they will be advised to consume with 300-500ml of fat-free milk or water (13). The recommended dosage of protein will be bodyweight (kg-1)* 1.2 g/day as previously described (14).

Creatine: Studies have shown that a combination of whey protein and creatine promote increases in LBM (14). The intervention group in our trial will be asked to take 0.25 g·kg-1 of LBM a day of creatine during the acute loading phase (the first 5 days of creatine supplementation) and thereafter a maintenance dose of 5 grams per day. Adverse effects associated with doses are likely to be minimal.

5.4 Non attendance

Patients who do not attend scheduled visits will be contacted by phone to re-schedule.

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A COMbined progRamme of exercise and dietary ADvice in mEn with castrate resistant prostate cancer - COMRADE trial

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Study sites

Recruitment, laboratories and/or technical departments: Sheffield Teaching Hospitals (STH); Royal Hallamshire hospital Sheffield, Northern General Hospital, Sheffield, Collegiate Hall, Sheffield Hallam University, Sheffield..

Sponsors: Sheffield Teaching hospitals

Version 2.0 date: 05/12/2016

Trial summary

Methodology: Feasibility randomised controlled trial

Research sites: Sheffield Hallam University (SHU), Sheffield Teaching Hospitals (STH)

Aim: To determine the feasibility of a 16 week programme of exercise training and dietary advice in men with castrate resistant prostate cancer (CRPC).

Objectives:

1. To investigate the feasibility of a 16 week combined programme of exercise training and dietary advice in CRPC patients.
2. To investigate the changes in physical function, fitness, body composition, including lean body mass (LBM) and fat mass (FM), serum markers, quality of life (QoL) and fatigue in men with CRPC as a result of a combined programme of exercise training and dietary advice.

Number of participants/patients: 50

Main inclusion criteria:

Men with CRPC.

Statistical methodology and analysis:

Feasibility outcomes will be assessed using standard methods for rates and proportions. Changes in secondary outcomes will be assessed using an analysis of co-variance with adjustment for baseline variants.

Proposed start date: 01/01/16

Proposed end date: 01/06/18

Study duration: 18 Months

1. Introduction

Since Huggins and Hodges demonstrated that hormone manipulation was effective in treating prostate cancer more than 70 years ago, androgen deprivation therapy (ADT) has been the cornerstone of prostate cancer treatment (Huggins, Stevens et al. 1941). However, patients with metastatic prostate cancer eventually relapse despite castrate levels of serum androgens and at this stage the disease is considered castrate resistant prostate cancer (CRPC). Until 2010, docetaxel was the only agent which had demonstrated an overall survival (OS) benefit in CRPC (Petrylak, Tangen et al. 2004, Berthold, Pond et al. 2008). Since, then the introduction of five other therapeutic options have shown a survival benefit in phase III trials: carbazitaxel, sipuleucel-T, radium-223, abiraterone and enzalutamide,(Kantoff, Higano et al. 2010, de Bono, Logothetis et al. 2011, Oudard 2011, Scher, Fizazi et al. 2012, Parker, Nilsson et al. 2013). However, CRPC is still the terminal phase of the disease and those with metastatic disease (mCRPC) are expected to live <19 months (Heidenreich, Pfister et al. 2013). Regardless of this ever expanding era of therapeutic options for CRPC, therapies are not curative and therefore essentially palliative for these men.

Improvements in survival of men with the use of cytotoxic chemotherapy at earlier stages of PCa have been demonstrated in the recent STAMPEDE and CHAARTED studies (James, Sydes et al. 2012, James, Spears et al. 2015, Sweeney, Chen et al. 2015). Consequentially, changes in clinical practice have followed and an increasing number of men receive chemotherapy earlier in their treatment pathway. With this change in treatment paradigm for PCa, patients as well as urologists and oncologists are presented with new set of challenges concerning adverse effects of cytotoxic agents, the impact on QoL, sequencing and adherence to subsequent treatment regimens.

Given the earlier introduction of chemotherapy in the standard care pathway for advanced prostate cancer, fitness for such treatment has become of increasing importance in order to achieve best possible outcomes. Cancer patients of a poorer performance status and a reduced lean body mass have repeatedly been shown to have more dose limiting toxicity, subsequently affecting survival (Antoun, Baracos et al. 2010, Massicotte, Borget et al. 2013, Timilshina, Breunis et al. 2014, Tan, Brammer et al. 2015). Further, retrospective data has positively associated better overall survival in men with metastatic prostate cancer receiving docetaxel with skeletal muscle mass (Wu, Liu et al. 2015).

There is sound theoretical rationale and increasing evidence demonstrating that exercise may represent a useful stand alone or combination therapy for the treatment of cancer, improving physiological and psychosocial outcomes (14-19). The beneficial effects of exercise training for improving lean body mass (LBM) are also well

established (13). Studies investigating the effectiveness of resistance training and cancer have shown positive effects demonstrating an increase in chemotherapy completion rate and improvements in fatigue and quality of life (QoL)(14-17).

There is level 1 evidence supporting the improvement of health-related outcomes in men with prostate cancer from a 2015 systematic review and meta-analysis of randomised controlled trials (RCT) supporting exercise interventions. Interventions involving a combination of aerobic and resistance exercise can improve fitness, physical function, exercise capacity, cancer specific fatigue and prostate cancer specific quality of life (Bourke, Smith et al. 2015). Furthermore, observational data and early pilot trials have consistently linked exercise behaviour after diagnosis to favourable disease progression and cancer specific mortality outcomes in men with prostate cancer (Ornish, Weidner et al. 2005, Frattaroli, Weidner et al. 2008, Kenfield, Stampfer et al. 2011, Richman, Kenfield et al. 2011, Magbanua, Richman et al. 2014).

However, to date there has been limited investigation of the effects of exercise training in men with castrate resistant prostate cancer (CRPC). Furthermore, no study has attempted to investigate the impact of both an exercise and dietary intervention with regard to physical fitness and the effect upon LBM of CRPC patients. Therefore the aim of this study is to investigate the feasibility of a 16 week combined programme of exercise training and dietary advice in CRPC patients.

2. Trial objectives

Hypothesis:
1) Exercise therapy in men with CRPC will be feasible in terms of recruitment rate and willingness of the participants to be randomized, intervention adherence, compliance to the exercise prescription, attrition due to the intervention, and reporting on secondary outcome standard deviations (variance in the data) to assist in sample size estimates for a larger-scale trial.
2) Secondary outcomes including physical function, body composition, fitness, fatigue and quality of life will favour the intervention group, following the combined exercise and dietary intervention

Primary objectives

1. To determine the rate of recruitment
2. To determine the eligibility of men among those screened to take part in the trial
3. To measure intervention adherence
4. To measure study completion rate
5. To measure adverse events
6. Assess objectives 1-5 using standard methods for rates and proportions
7. Use objectives 1-6 to inform the design of a definitive RCT.

Secondary objectives

1. To investigate changes in physical function and fitness.
2. To quantify changes in muscle hypertrophy, lean body mass (LBM), fat mass (FM) and bone mineral density (BMD) assessed by dual energy x-ray absorptiometry (DXA) scanning and anthropometric measurements.
3. To assess changes in prostate specific quality of life and fatigue perception.
4. To assess changes in serum biomarkers, including sex hormone binding globulin (SHBG), testosterone, prostate specific antigen (PSA) and lactate dehydrogenase.
5. To assess changes in the dietary and nutritional status using 3-day diet diaries.

3. Methodology

Study design: The study is a two arm feasibility RCT (randomisation ratio 1:1) comparing a resistance exercise training intervention plus dietary advice and usual care to usual care plus exercise advice. Purposive sampling of men identified as having CRPC and under the care of STH will be used to identify the study cohort.

Inclusion criteria:

Men with CRPC

Men with histologically confirmed PCa on long-term ADT with either

- PSA>2ng/ml above nadir or PSA level that has risen serially on at least two occasions (each at least 4 weeks apart) in the presence of castrate levels of testosterone or;
- Evidence of symptomatic disease progression whilst undergoing first line androgen deprivation therapy (ADT) in the presence of castrate levels of testosterone or;
- Radiographic disease progression whilst undergoing first line ADT in the presence of castrate levels of testosterone

Exclusion criteria:

- Participation in other trials which might bias the evaluation of the primary objectives of the present study.
- Current participation in regular physical activity (defined as purposeful physical activity of a moderate intensity for 90 minutes per week for at least six months).
- Unstable angina, uncontrolled hypertension, recent myocardial infarction, pacemakers.
- Uncontrolled painful or unstable bony metastatic lesions.
- Within two months of invasive surgical treatment (transurethral surgery allowed).

- Any physical, neurological or psychiatric impairment or disease or other condition that would limit the ability to understand and complete the study assessments and complete the required questionnaires, recall and record of dietary information would be excluded.

Recruitment: Men will be recruited from routine urology/oncology clinics at Sheffield Teaching Hospitals (STH). Men will be recruited in one of the following ways:

1. Identify men in Urology outpatient clinics who are attending as part of ADT follow-up clinics. First approach will be done by the clinical team.

2. Identified during routine clinical follow-up as part of 2nd line treatment for prostate cancer. First approach will be done by the clinical team.

3. Identify men as part of oncology treatment and follow-up clinics at Weston Park Hospital. First approach will be done by the clinical team.

4. If a man is identified but is not due for a clinical follow-up visit for some time, a study pack (participant invitation letter, participant information sheet and informed consent form) will be sent to his home address for consideration. First approach will be the participant invitation letter, signed by the PI.

5. In addition, posters in treatment clinics will advertise the study and invite men to contact the study team for more details about how to participate.

4. Outcome measures

The primary outcome will be the feasibility of the intervention including recruitment rate, adherence and attrition due to the intervention, loss to follow-up and adverse event rate (Arain, Campbell et al. 2010). These will be assessed by extracting data from screening and recruitment logs, attendance at supervised exercise training sessions and independent exercise log book records and a review of adverse events. Blinded assessors will perform the outcome testing. Feasibility outcomes will be assessed using standard methods for rates and proportions.

Secondary outcomes will be assessed at baseline, 8 and at 16 weeks (apart from DEXA scans which will only take place at baseline and 16 weeks). Where possible, patient visits will be harmonised with participant routine clinic visits. The assessments will include:

- Physical function assessment: Chair sit to stand, 6 minute walk test and grip strength test.

- DEXA scan (Smith, Finkelstein et al. 2002): appendicular LBM (kg), FM (kg) and BMD.
- Muscle hypertrophy assessment: anthropometric measurements of muscle circumference.
- Muscle Strength assessment: 1RM testing
- Performance status scoring: ECOG (Oken, Creech et al. 1982) and Karnofsky (Yates, Chalmer et al. 1980).
- Biochemical assessment: Lactate dehydrogenase, SHBG, testosterone and PSA
- Quality of life assessed by the FACT-P (The Functional Assessment of Cancer Therapy-Prostate) (Esper, Mo et al. 1997) and FACT-F (The Functional Assessment of Cancer Therapy-Fatigue) (Yellen, Cella et al. 1997) questionnaire.
- Diet and nutrition assessment: 3 day diet diaries analysed using the dietary analysis software package Nutritics.
- Anthropometrics and demographics including height, weight, age, stage of disease, current and previous treatment for disease, co-morbidities and ethnicity.

5. Study procedures

Hospital recruitment and screening: Potential participants will be screened against the study inclusion criteria. Men who meet the criteria will either be approached in clinic by the clinical team during routine follow-up visits or have study details (participant invitation letter, participant information sheet and informed consent form) sent via the post to their home address, on behalf of the treating clinician. A follow-up phone call will be made to men who have details sent via post, to ensure contact address is up to date. Men who are interested in taking part in the study will be invited to contact the research team via phone or email. The men are then screened against the study exclusion criteria (described in section 3). Men who are not excluded, and are still interested, will be asked to provide informed consent to participate in the trial which will be conducted before their trial study assessments.

A log of all patients screened for the study, excluding those who then enter into the study will be kept in the STH urology research office.

Informed Consent Procedures: All men will be provided with the participant information sheet to consider for a minimum of 24 hours before informed consent is obtained for participation.

Randomisation procedures: Patients will be randomised at an allocation ratio of 1:1 to either the exercise and dietary intervention arm plus usual care (intervention arm) or the exercise guidance advice plus usual care (control arm). A computer algorithm randomisation tool will administer the randomisation allocation procedure.

Usual care: All men will continue to be followed up in clinic as normal by their oncology/urology team.

Specimens to be collected outside of routine care: At baseline, 8 and 16 weeks, fasting blood samples, for the assessment of lactate dehydrogenase, SHBG, testosterone and PSA will be collected by a trained member of the research team. Men will have approximately 20ml of venous blood drawn. Serum samples will be analysed according to local hospital laboratory standard operating procedures. Blood serum lactate dehydrogenase is a regulatory enzyme involved in anaerobic glycolysis activity is correlated to muscle fatigue and tissue damage (Machado, Koch et al. 2011, Washington, Healey et al. 2014) as well as prostate cancer progression in advanced disease (Naruse, Yamada et al. 2007).

SHBG is a glycoprotein with a high affinity binding for hormones such as testosterone and oestradiol and its use in combination with total testosterone will provide us with information regarding the proportion of protein bound and free testosterone (Selby 1990).

PSA is a protein secreted by the epithelial cells of the prostate gland and will be monitored to monitor any biochemical disease changes.

All participants will have blood samples sent to STH central laboratories for analysis. Anonymised blood results will be made available for research staff by central laboratories according to local policy. Results will be manually entered directly onto the secure research database according to participant trial number by the study team.

Radiographic assessment outside of routine care: At baseline and 16 weeks a DEXA scan will collect data on via a full body scan to determine post-cranial appendicular whole body LM, whole body fat free mass (FFM) and whole body FM. Bone health assessed by BMD assessment at the lumbar spine, total hip and whole body. Areas of previous fracture or where known bone metastasis exist will be excluded from the region of interest to calculate BMD. Scans will be performed using the Hologic densitometer, at the clinical Research Facility, Northern General Hospital and analysed by the scan technician using the standard DXA software. Participants will be asked to lie flat in the centre of the scan table and remain still for the duration of the scan. Participants found to be osteoporotic on baseline scanning (i.e. high risk of fracture and requiring osteoporosis treatment) will be referred to the metabolic bone centre in Sheffield for further assessment and treatment.

Muscle function measures outside of routine care:

Muscle Strength assessment

One-repetition maximum (1 RM) strength tests will be carried out on knee extension, leg press and chest press at baseline and 16 weeks using resistance machines in physiology testing suites at Sheffield Hallam University. The 1 RM test was defined as the maximal load that could be moved through the full range of motion with proper form for one repetition(Delmonico, Kostek et al. 2005, Hanson, Sheaff et al. 2013). Participants will undergo at least one familiarization session preceding the testing session in which they will complete the exercise with little or no resistance and instructed on proper warm-up, stretching, and exercise techniques to help prevent injuries and reduce muscle soreness after the strength testing assessment. The same blinded investigator will be present conducting the strength tests for each subject both at baseline and 16 weeks using standardized procedures with consistency of seat adjustment, body position, and level of vocal encouragement. The 1 RM will be achieved by gradually increasing the resistance from an estimated submaximal load after each successful exercise repetition until the maximal load was obtained.

Physical performance assessment outside of routine care:

Physical function assessment

Chair-sit to stand, hand grip strength and 6 minute walk test (shuttle walk test) to be performed in Sheffield Hallam physiology suits alongside muscle strength assessment under guidance of the blinded investigator at baseline, 8 and at 16 weeks. Even small changes in muscle mass can have significant effects on physical function testing (Argilés, López-Soriano et al. 2011). The grip strength, 6 minute walk test and chair sit to stand are markers of disability, high dependency, nutritional status, survival in elderly people and short and long-term mortality and morbidity (Ling, Taekema et al. 2010, De Feo, Tramarin et al. 2011, Norman, Stobäus et al. 2011, Kim, Yabushita et al. 2012).

Chair-sit to stand: Participants will be seated in a hard-backed chair, arms folded across their chest, and instructed to rise as fast as possible to a full standing position and then return to a full sitting position as many times as they can within 30s. (Galvão and Taaffe 2005, Galvao, Nosaka et al. 2006). Their number of repetitions will be recorded (Bourke, Doll et al. 2011).

Grip strength test: Measurements will be made using a digital hand dynamometer. Participants are asked to grip the dynamometer for five seconds and the results are recorded, repeated on each hand three times. The maximal grip strength will be used for analysis.

6 minute walk test (shuttle test): The participant will walk along a marked ten meter course at their normal pace with the number of steps and time recorded to the nearest second for six minutes. The test will be repeated three times and the average time calculated.

Performance status outcomes

Performance status will be assessed by the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status (KPS) assessment tools at baseline, 8 and at 16 weeks.(Yates, Chalmer et al. 1980, Oken, Creech et al. 1982)

Questionnaires and diet diaries: Participants will be asked to complete quality of life assessed by the FACT-P and FACT-F questionnaires at baseline and at 16 weeks.(Esper, Mo et al. 1997, Yellen, Cella et al. 1997, Cella, Nichol et al. 2009) At baseline and 16 weeks participants will be asked to complete and return three day diet diaries. Individual feedback will be given on diet diaries with the aim of facilitating optimal nutritional intake. A dietary analysis software package (Nutritics) will be used to assess nutritional intake.

End of Study Definition: Once all participants have completed 16 week follow-up, study feasibility analysis and fidelity measures are completed, the research ethics committee will be informed of study end.

Post intervention participants will be invited to attend a focus group to share their experiences of the exercise intervention. The experiences and views of participants in this pilot study will be used to inform the strategy for the design and running of a subsequent larger study.

Current medications and comorbidity: Current medications will be recorded during study assessments as well as any other known co-morbidities.

Criteria for discontinuation/withdrawal: exit criteria would be patient choice. Data from participants who have withdrawn from the study (see Criteria for discontinuation/withdrawal above) will be retained up until the point of withdrawal on the study database and will be included in the overall study analysis.

Subject withdrawal: (including data collection / retention for withdrawn participants): Data from participants who have withdrawn from the study (see Criteria for discontinuation/withdrawal above) will be retained up until the point of withdrawal on the study database and will be included in the overall study analysis.

Procedure for collecting data: hard copies of case report forms will be used during study assessments and then stored in Collegiate Hall (Sheffield Hallam University), in a locked cabinet which only the trial team have access to.

Participant evaluation of the intervention: post intervention, participants will be invited to attend a respective focus group to share their experiences of the exercise intervention, dietary supplements and overall participation in the trial. The experiences

and views of participants in this study will be used to inform the strategy for the design of a definitive phase III/IV trial.

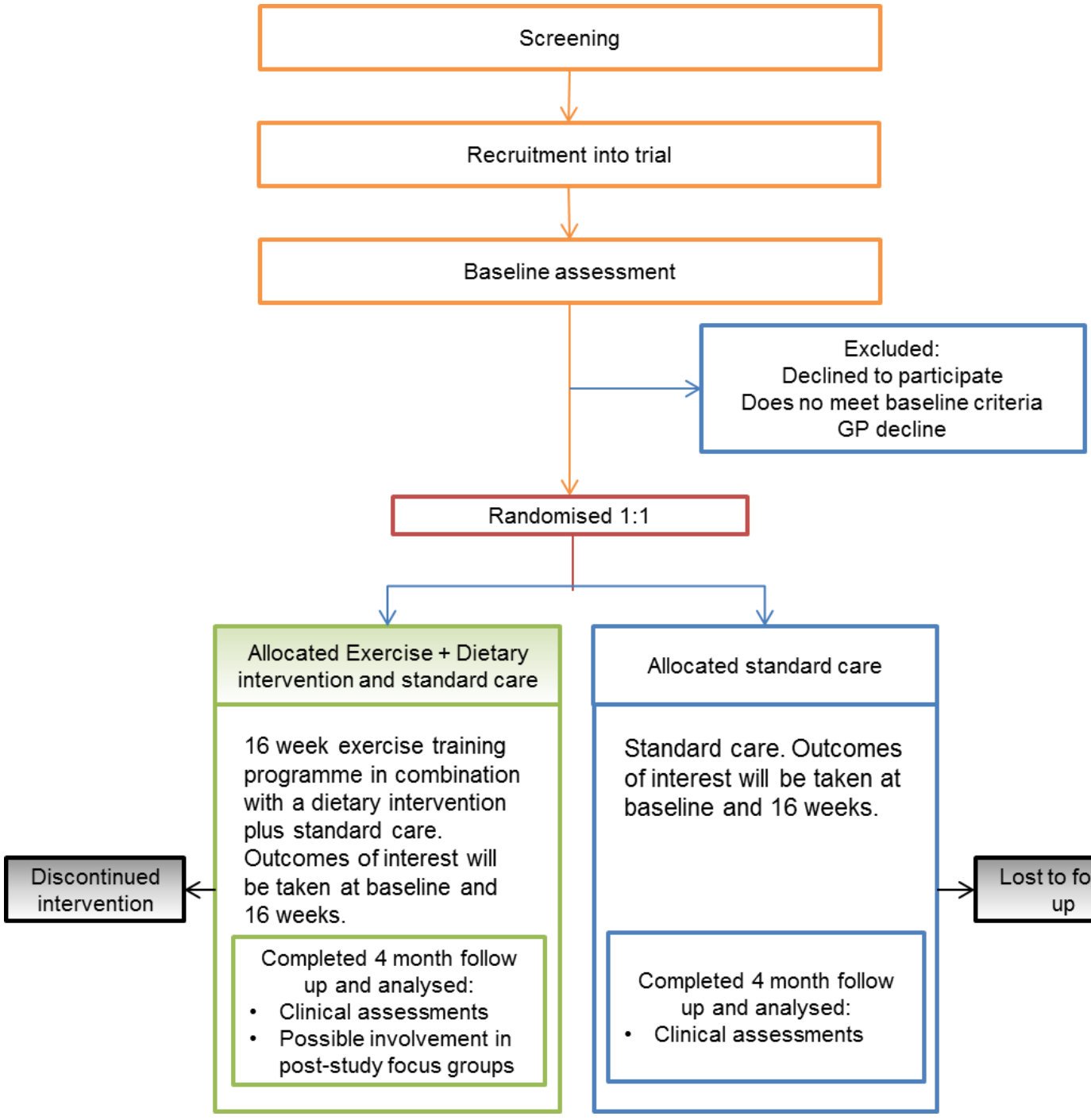

Figure 1: Study schematic

6. The Intervention and control group.

Exercise and dietary intervention arm:

Exercise sessions will take place at The Centre for Sport and Exercise Science at Sheffield Hallam University in a dedicated exercise facility with an experienced exercise specialist.

Structure and content of supervised exercise and dietary intervention

Men randomised to the exercise intervention arm will undergo a 16 week programme of exercise involving three supervised exercise sessions a week and encouragement to undertake home-based independent exercise. Preceding any exercise sessions, men will attend a one to one consultation (1 hr) with the exercise specialist for a tailored exercise induction.

In each session, participants will perform 3-4 sets of 6-12 repetitions of 6 resistance exercises. Sessions will be conducted in a group format where possible. Participants will be asked to undertake and log (in a record book provided) at least one independent 30 minute aerobic activity at home during this period. The activity chosen will be based on that most convenient for the participant (such as walking or making use of community exercise facilities). In the record book participants will be asked to record the time of activity, duration and exercise intensity based on the Borg rating of perceived exertion scale, details of which will be provided in the booklet (Borg 1982). The participant logged activity will be documented when participants attend supervised exercise sessions and further encouraged to undertake aerobic exercise through goal setting and self-regulation.

Dietary advice

Participants randomised to the intervention arm will also be offered dietary advice in the form of a short seminar in a small group format on healthy eating and an information booklet with weekly meal plans and recipes. Multiple pre-clinical and clinical studies, including observational cohort studies, have demonstrated anti-tumour effects of a low carbohydrate and high protein diet (Slattery, Benson et al. 1997, Terry, Jain et al. 2003, Fung, Hu et al. 2011, Ho, Leung et al. 2011, Fokidis, Yieng Chin et al. 2015). In addition, a high fibre diet has been associated with chemoprotective effects, lowering the risk of colorectal cancer (Bingham, Day et al. 2003, Peters, Sinha et al. 2003). Dietary advice will encourage participants to adopt a diet rich in nutrient dense whole foods, fruit and vegetables and discourage processed foods and those high in refined carbohydrates and saturated fats. Participants will also be asked to limit alcohol intake. Recipes provided will encourage high protein, moderate fat, high fibre and low carbohydrate meals.

Dietary supplementation

Whey protein: To promote muscle protein synthesis, participants will be required to increase protein consumption via whey protein supplementation provided. Whey protein is rapidly digested and has a high leucine content which appears more efficient at muscle protein synthesis than other protein alternatives (e.g. soya protein) post-resistance exercise (Wilkinson, Tarnopolsky et al. 2007). Participants will be provided with whey protein post-supervised exercise sessions and to take home where they will be advised to consume with 300-500ml of fat-free milk or water (Hartman, Tang et al. 2007). The recommended dosage of protein will be bodyweight (kg-1)* 1.2 g/day as previously described (Burke, Chilibeck et al. 2001).

Creatine: Studies have shown that a combination of whey protein and creatine promote increases in LBM (Burke, Chilibeck et al. 2001). Additionally, there is a body of evidence to indicate that creatine supplementation during resistance training is more effective at increasing muscle strength and weightlifting performance than resistance training alone (Rawson and Volek 2003) including its use in older adults (Brose, Parise et al. 2003). Participants will require a dosage of 0.25 g·kg-1 of LBM a day of creatine during the acute loading phase (the first 5 days of creatine supplementation) and thereafter a maintenance dose of 5 grams per day (Burke, Chilibeck et al. 2003).

Control arm: Men randomised to this arm of the trial will receive usual care from their oncology/urology team, will be provided with Macmillan exercise advice guidelines and signposted to local exercise programmes for cancer patients (e.g. Move more Sheffield).

7. Statistical considerations

Sample size and power calculation: A target recruitment figure of 50 patients can provide estimates of feasibility measures and of variability in secondary outcomes for use in power calculations with reference to the design of a subsequent larger-scale RCT (Lancaster, Dodd et al. 2004, Bourke, Doll et al. 2011). In addition a sample size of 50 men is sufficient to detect preliminary improvements in physical performance (chair sit to-stand test) similar to those reported in an earlier feasibility trial of men with advanced prostate cancer undergoing androgen deprivation therapy. Assuming an improvement of 4 reps in the performance test, and a standard deviation of 4 reps (providing an effect size of 1.0) at an alpha level of 0.05 and with 80% power, this would require 19 men per arm, allowing for a 20% drop-out rate over 16 weeks, (Bourke, Doll et al. 2011)

Analysis: Feasibility outcomes will be assessed using standard methods for rates and proportions. Secondary outcomes will also be compared at each follow-up point using ANCOVA procedures, with baseline values being used as the covariate. Asscoaitions between physical activity dose and other outcome variables will be analysed using

bivariate correlation and regression analysis. Statistical significance will be set at $p < 0.05$. Data will be analysed using the SPSS statistical package (SPSS U.K. Ltd, Woking U.K.). The data will be analysed on an intention to treat basis.

A Mann-Whitney U test will be used for non-normally distributed data. Statistical considerations will be made for potential effects of medications or comorbidities on blood serum markers if necessary.

A thematic 'framework' approach will be used for the analysis of post-intervention focus groups.(Bourke, Sohanpal et al. 2012)

8. Ethics

Full local ethical and research governance approval will be obtained before study recruitment begins. All men will be provided with the participant information sheet to consider for a minimum of 24 hours before written informed consent is obtained for participation.

9. Safety

All recruited men will continue to be under the care of their treating cancer clinician who will be aware of their participation in the trial and will follow current best practice standard of care. A formal risk assessment has been carried out (see Appendix 1)

Study adverse events will be recorded and addressed according to the criteria below. Any new pain (e.g. bone pain) will be discussed with the participant's cancer clinician and referred to the patient's GP or individuals own oncologist as advised by clinician. Any other medical complication e.g. cardiovascular, will be referred directly to the study participants GP. Immediate life support facilities will be available in the exercise suite.

The risks of the exercise programme will be fully apparent at the end of the trial, but are likely to be minimal.

Adverse Events (AE)

Notification and reporting Adverse Events or Reactions

Non-serious adverse events: the AE is recorded in the study file and the participant will be followed up by the research team. The AE is documented in the participants' medical notes (where appropriate).

Serious incidents/ serious untoward incidents (SI/SUI)

A SI/SUI defined as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) is otherwise considered medically significant by the investigator.

A SI/SUI occurring to a research participant will be reported to the study REC where in the opinion of the Chief Investigator the event was:

• Related – that is, it resulted from administration of any of the research procedures, and

• Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

SI/SUIs that are considered to be 'related' and 'unexpected' will be reported within 7 working days of learning of the event.

10. Data handling and record keeping

All data will be stored according to the 1998 Data protection Act. Participant data will be anonymised before entered into a password protected study database. Participant identifiable data collected during screening assessments and contact details will be retained in the study co-ordinating centre (Collegiate Hall, Sheffield Hallam University and Royal Hallamshire hospital) in restircted access research offices in locked filing cabinets. Data from paper case report forms will be entered by the coordinating centre (Sheffield Hallam University, SHU), onto a secure, password protected, encrypted hard drives. Copies of paper CRFs received at the coordinating centre will be stored in the Trial Master File (TMF) for source data verification purposes, in a locked cabinet which is protected by security code doors which only authorised personnel can gain entry to.

11. Laboratories

Exercise intervention and physical function assessments

- The physiology research facilities at Sheffield Hallam University will be used to carry out the exercise intervention, the muscle function measures and physical performance assessments.

Radiographical imaging (DXA scans)

- DXA scans will be performed in the Clinical Research Facility (CRF), Northern General Hospital, Herries Road, Sheffield S5 7AU.

Data Preparation and Collection

- Samples will be labelled with participant identification numbers, time & date collected and analysis to be carried out (PSA etc).
- Samples will be sent to local hospitals central laboratories for analysis and results will be uploaded to the NHS STH Integrated Clinical Environment (ICE) system.

12. Dissemination and research findings

The study results will be published and broadcasted via papers, conference, feedback to patients and charities. Trial feasibility analysis will be written up for publication in scientific peer-reviewed journals.

Appendix

Safety and risk assessment

Radiation dose: The effective radiation dose from DEXA scans is 32μSV less than one year's radiation dose and considered "low risk". Public Health England describe a radiation exposure equivalent to a few years average natural background radiation as 'Low Risk', with between 1:10,000 and 1:1,000 lifetime additional risk of cancer.

Venepuncture: Blood samples will be taken by an appropriately trained trial staff member. Consent to use and store the samples will be obtained according to the Human Tissue Act 2004. Risks include a small amount of bruising, bleeding or pain at the needle site. Some may feel faint and on very rare occasion infection can occur.

Exercise intervention: Exercise in men for prostate cancer has been demonstrated to be of low risk in a recent meta-analysis of 16 RCTs. Minor musculo-skeletal issues such as cramps and or low grade strains can occur but are very infrequent. Serious averse events such as MI, are very seldom indeed and there is no difference in the rate of cardiac serious adverse events in men undertaking exercise interventions compared with comparison control groups.

Supplementation guidelines

Whey protein: Participants will be provided with whey protein post-supervised exercise sessions within the sports labs and to take home where they will be advised to consume with 300-500ml of fat-free milk or water. The recommended dosage of protein is bodyweight (kg-1)* 1.2 g/day. Participants will be asked to take 4.5 scoops of whey protein a day, amounting to 90g of protein, and asked to make up the rest with diet. Dietary guidelines will be provided to aid in the required protein consumption. Participants will be provided with protein shakers.

Creatine: Participants will require a dosage of 0.25 g·kg-1 of LBM a day of creatine during the acute loading phase (the first 5 days of creatine supplementation) and

thereafter a maintenance dose of 5 grams per day. One and a half scoops equates to 5g. Participants will be encouraged to take the creatine supplement alongside the whey supplement.

Sheffield Hallam University

Sheffield Teaching Hospitals NHS Foundation Trust

The University Of Sheffield.

COMRADE trial

16 week **supervised** exercise case report form

Participant: Date:

Phase one DAY ONE			WEEK 1 Session 1			WEEK 1 Session 2			WEEK 2 Session 1			WEEK 3 Session 1		
Warm-up			*Date*			*Date*			*Date*			*Date*		
<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**														
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Body weight squat	R - Chair placed behind client/ swiss ball P - Goblet squat	**Reps** **Weight**												
Seated cable row	R – Standing cable row/ reduce weight P- increase weight/ bent over row	**Reps** **Weight**												
Bench press	R - Reduce weight/ single arm press (floor) P - Increase weight	**Reps** **Weight**												
Body weight lunge (single leg)	R - Reduce repetitions/ chair assisted P - Weighted lunge	**Reps** **Weight**												
Lat raise	R – Seated lat raise/ single arm/ reduce ROM (bend elbows) P – increase weight	**Reps** **Weight**												
Dumbbell side bends	R - Reduce weight/ reps P – Increase weight/ Pallof press (cable)	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase one DAY ONE			WEEK 3 Session 2			WEEK 4 Session 1			WEEK 5 Session 1			WEEK 5 Session 2		
Warm-up			*Date*			*Date*			*Date*			*Date*		
<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**														
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Body weight squat	R - Chair placed behind client/ swiss ball P - Goblet squat	**Reps** **Weight**												
Seated cable row	R – Standing cable row/ reduce weight P- increase weight/ bent over row	**Reps** **Weight**												
Bench press	R - Reduce weight/ single arm press (floor) P - Increase weight	**Reps** **Weight**												
Body weight lunge (single leg)	R - Reduce repetitions/ chair assisted P - Weighted lunge	**Reps** **Weight**												
Lat raise	R – Seated lat raise/ single arm/ reduce ROM (bend elbows) P – increase weight	**Reps** **Weight**												
Dumbbell side bends	R - Reduce weight/ reps P – Increase weight/ Pallof press (cable)	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase one	WEEK 1	WEEK 2	WEEK 2	WEEK 3

DAY TWO			Session 1			Session 1			Session 2			Session 1		
Warm-up			*Date*			*Date*			*Date*			*Date*		
<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**														
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Body weight squat	R - Chair placed behind client/ swiss ball P - Goblet squat	**Reps** **Weight**												
Push ups	R – Wall/bench/bent knees push ups P –	**Reps** **Weight**												
Glute bridge hold	R - P – Barbell weighted/ feet on bench	**Reps** **Weight**												
Single arm bent over row	R – Standing cable row/ resistance band P- increase weight	**Reps** **Weight**												
Farmer carries	R – reduce weight/distance P –increase weight	**Reps** **Weight**												
1-arm kneeling lat pulldown	R – resistance band P – increase weight	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase one	WEEK 4	WEEK 4	WEEK 5

DAY TWO			Session 1			Session 2			Session 1		
Warm-up			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**											
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Body weight squat	R - Chair placed behind client/ swiss ball P - Goblet squat	**Reps** **Weight**									
Push ups	R – Wall/bench/bent knees push ups P –	**Reps** **Weight**									
Glute bridge hold	R - P – Barbell weighted/ feet on bench	**Reps** **Weight**									
Single arm bent over row	R – Standing cable row/ resistance band P- increase weight	**Reps** **Weight**									
Farmer carries	R – reduce weight/distance P –increase weight	**Reps** **Weight**									
1-arm kneeling lat pulldown	R – resistance band P – increase weight	**Reps** **Weight**									
Cool down			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**											
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])											

Phase two DAY ONE	WEEK 1 Session 1	WEEK 1 Session 2	WEEK 2 Session 1	WEEK 3 Session 1

Warm-up			Date			Date			Date			Date		
CV machine: Tread/XT/Bike (10-15m) Intensity (incline/speed/resistance)														
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Body weight sumo squat	R - Chair placed behind client/ swiss ball P - weighted sumo squat	**Reps** **Weight**												
Dumbbell Deadlift	R – Resistance band deadlift/ hip hinge P – Barbell Romanian deadlift	**Reps** **Weight**												
Leg raise (bench)	R – Floor based bent knee leg raise P - Floor based V-snap	**Reps** **Weight**												
Upright row (dumbbell/barbell)	R – seated row/resistance band P- increase weight	**Reps** **Weight**												
Dumbbell shoulder press	R – Seated/ single arm press P - Increase weight	**Reps** **Weight**												
Tall plank	R – reduce angle with bench or bosu P – Low plank	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
CV machine: Tread/ XT/ bike Intensity (incline/speed/resistance)														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase two **DAY ONE**	**WEEK 3** **Session 2**	**WEEK 4** **Session 1**	**WEEK 5** **Session 1**	**WEEK 5** **Session 1**
Warm-up	*Date*	*Date*	*Date*	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**															
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Body weight sumo squat	R - Chair placed behind client/ swiss ball P - weighted sumo squat	**Reps** **Weight**												
Dumbbell Deadlift	R – Resistance band deadlift/ hip hinge P – Barbell Romanian deadlift	**Reps** **Weight**												
Leg raise (bench)	R – Floor based bent knee leg raise P - Floor based V-snap	**Reps** **Weight**												
Upright row (dumbbell/barbell)	R – seated row/resistance band P- increase weight	**Reps** **Weight**												
Dumbbell shoulder press	R – Seated/ single arm press P - Increase weight	**Reps** **Weight**												
Tall plank	R – reduce angle with bench or bosu P – Low plank	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase two **DAY TWO**	**WEEK 1** **Session 1**	**WEEK 2** **Session 1**	**WEEK 2** **Session 2**	**WEEK 3** **Session 1**
Warm-up	*Date*	*Date*	*Date*	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**																
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Knee extension	R – reduce weight P – increase weight	**Reps** **Weight**												
Back extension	R – Seated lat raise/ single arm P – increase weight	**Reps** **Weight**												
Standing bicep curl (low pulley)	R - Reduce weight P – Dumbbell/barbell standing bicep curl	**Reps** **Weight**												
Leg press	R - Reduce weight P – Increase weight	**Reps** **Weight**												
Standing tricep pulldown	R – Reduce weight P- increase weight/ seated tricep extension	**Reps** **Weight**												
Sit-ups	R – Reduce reps/ leg raises (bench) P – Hands above head	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase two **DAY TWO**	**WEEK 4** **Session 1**	**WEEK 4** **Session 2**	**WEEK 5** **Session 1**
Warm-up	*Date*	*Date*	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**											
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Knee extension	R – reduce weight P – increase weight	**Reps** **Weight**									
Back extension	R – Seated lat raise/ single arm P – increase weight	**Reps** **Weight**									
Standing bicep curl (low pulley)	R - Reduce weight P – Dumbbell/barbell standing bicep curl	**Reps** **Weight**									
Leg press	R - Reduce weight P – Increase weight	**Reps** **Weight**									
Standing tricep pulldown	R – Reduce weight P- increase weight/ seated tricep extension	**Reps** **Weight**									
Sit-ups	R – Reduce reps/ leg raises (bench) P – Hands above head	**Reps** **Weight**									
Cool down			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**											
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])											

Phase three **DAY ONE**	**WEEK 1** **Session 1**	**WEEK 1** **Session 2**	**WEEK 2** **Session 1**	**WEEK 3** **Session 1**
Warm-up	*Date*	*Date*	*Date*	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**															
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Body weight squat	R - Chair placed behind client/ swiss ball P - weighted sumo squat	**Reps** **Weight**												
Leg press	R – reduce weight P – increase weight	**Reps** **Weight**												
Cable row	R – reduce weight P – increase weight	**Reps** **Weight**												
Bicep curl	R – reduce weight P – increase weight	**Reps** **Weight**												
Cable tricep pull down	R – underarm tricep P - Increase weight	**Reps** **Weight**												
Tall plank	R – reduce angle with bench or bosu P – Low plank	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase three **DAY ONE**	**WEEK 3** **Session 2**	**WEEK 4** **Session 1**	**WEEK 5** **Session 1**	**WEEK 5** **Session 1**
Warm-up	*Date*	*Date*	*Date*	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**															
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Body weight squat	R - Chair placed behind client/ swiss ball P - weighted sumo squat	**Reps** **Weight**												
Leg press	R – reduce weight P – increase weight	**Reps** **Weight**												
Cable row	R – reduce weight P – increase weight	**Reps** **Weight**												
Bicep curl	R – reduce weight P – increase weight	**Reps** **Weight**												
Cable tricep pulldown	R – underarm tricep P - Increase weight	**Reps** **Weight**												
Tall plank	R – reduce angle with bench or bosu P – Low plank	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase three **DAY ONE**	**FINAL WEEK 6** **Session 1**
Warm-up	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**					
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**
Body weight squat	R - Chair placed behind client/ swiss ball P - weighted sumo squat	**Reps** **Weight**			
Leg press	R – reduce weight P – increase weight	**Reps** **Weight**			
Cable row	R – reduce weight P – increase weight	**Reps** **Weight**			
Bicep curl	R – reduce weight P – increase weight	**Reps** **Weight**			
Cable tricep pulldown	R – underarm tricep P - Increase weight	**Reps** **Weight**			
Tall plank	R – reduce angle with bench or bosu P – Low plank	**Reps** **Weight**			
Cool down			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**					

Phase three **DAY TWO**	**WEEK 1** **Session 1**	**WEEK 2** **Session 1**	**WEEK 2** **Session 2**	**WEEK 3** **Session 1**
Warm-up	*Date*	*Date*	*Date*	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**															
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Bench press	R – reduce weight/reduce angle P – increase weight	**Reps** **Weight**												
Deadlift	R – Resistance band deadlift/ hip hinge P – Barbell Romanian deadlift	**Reps** **Weight**												
Hip abbductor	R – reduce weight P – increase weight	**Reps** **Weight**												
Lateral cable hold	R – reduce weight P – increase weight	**Reps** **Weight**												
kick backs	R – reduce weight P – increase weight	**Reps** **Weight**												
Dead bug	R – reduce angle with bench P – walking plank	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase three **DAY TWO**	**WEEK 4** **Session 1**	**WEEK 4** **Session 2**	**WEEK 5** **Session 1**	**FINAL WEEK 6** **Session 1**
Warm-up	*Date*	*Date*	*Date*	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**															
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**	**Set 1**	**Set 2**	**Set 3**
Bench Press	R – reduce weight/reduce angle P – increase weight	**Reps** **Weight**												
Deadlift	R – Resistance band deadlift/ hip hinge P – Barbell Romanian deadlift	**Reps** **Weight**												
Hip abbductor	R – reduce weight P – increase weight	**Reps** **Weight**												
Lateral cable hold	R – reduce weight P – increase weight	**Reps** **Weight**												
kick backs	R – reduce weight P – increase weight	**Reps** **Weight**												
Dead bug	R – reduce angle with bench P – walking plank	**Reps** **Weight**												
Cool down			*Notes*			*Notes*			*Notes*			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**														
Additional notes on session (e.g regressions, fatigue, difficulty with completing sets, AE/SAE [must also fill out AE/SAE form])														

Phase three **DAY TWO**	**FINAL WEEK 6** **Session 2**
Warm-up	*Date*

<u>CV machine:</u> Tread/XT/Bike (10-15m) **Intensity (incline/speed/resistance)**					
Main session	**Regressions and progressions**		**Set 1**	**Set 2**	**Set 3**
Bench press	R – reduce weight/reduce angle P – increase weight	**Reps** **Weight**			
Deadlift	R – Resistance band deadlift/ hip hinge P – Barbell Romanian deadlift	**Reps** **Weight**			
Hip abbductor	R – reduce weight P – increase weight	**Reps** **Weight**			
Lateral cable hold	R – reduce weight P – increase weight	**Reps** **Weight**			
kick backs	R – reduce weight P – increase weight	**Reps** **Weight**			
Dead bug	R – reduce angle with bench P – walking plank	**Reps** **Weight**			
Cool down			*Notes*		
<u>CV machine:</u> Tread/ XT/ bike **Intensity (incline/speed/resistance)**					

Sheffield Hallam University

Sheffield Teaching Hospitals NHS Foundation Trust

The University Of Sheffield.

COMRADE trial

16 week exercise diary

Participant: Date:

Before conducting any exercise please read the following information

You should not partake in any exercise or immediately cease any exercise if you experience any of the following:

- **Chest pain or pressure**
- **Reoccurring leg pain or cramp**
- **A sudden shortness of breath**
- **A sudden onset of nausea**
- **Blurred vision, dizziness or feeling faint**
- **Disorientation or confusion**
- **Irregular heart rate or palpitations**

You must **contact the research team** if at any point you experience these symptoms whilst exercising.

Do not undertake any exercise if you have experienced any diarrhoea or vomiting in the past 24 hours.

About this diary

During your participation in the COMRADE trial, we ask that you undertake some independent exercise (i.e. not under the supervision of the research team) every week during the trial period (16 weeks).

We would like you to record any activity you have undertaken that week in this diary.

Independent exercise can include activities like a brisk walk, a bike ride, swimming, tennis or football.

Any activity which raises your heart rate can be included in this diary.

You should bring this diary to at least one exercise session a week so the research team can monitor your progress, even if you haven't managed to do any additional exercise that week.

How to fill out this diary

Example:

Week 1		
Session 1		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Bike ride	16	00:35:00
Session 2		
Brisk walk	15	00:20:00

See the next page for details on how to rate the intensity of your exercise

The BORG scale

Use this scoring system to describe the **intensity** of your activity. A few examples are given to help you decide how you would rate your exertion.

How you might describe your exertion	Borg rating of your exertion	Examples
None	6	Reading a book, watching television
Very, very light	7 to 8	Tying shoes
Very light	9 to 10	Chores like folding clothes that seem to take little effort
Fairly light	11 to 12	Walking through the grocery store or other activities that require some effort but not enough to speed up your breathing
Somewhat hard	13 to 14	Brisk walking or other activities that require moderate effort and speed your heart rate and breathing but don't make you out of breath
Hard	15 to 16	Bicycling, swimming, or other activities that take vigorous effort and get the heart pounding and make breathing very fast
Very hard	17 to 18	The highest level of activity you can sustain
Very, very hard	19 to 20	A finishing kick in a race or other burst of activity that you can't maintain for long

Week 1			Week 2		
Session 1			*Session 1*		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)	Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Session 2			*Session 2*		

Week 3			Week 4		
Session 1			*Session 1*		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)	Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Session 2			*Session 2*		

Week 5			Week 6		
Session 1			*Session 1*		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)	Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Session 2			*Session 2*		

Week 7			Week 8		
Session 1			*Session 1*		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)	Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Session 2			*Session 2*		

Week 9			Week 10		
Session 1			*Session 1*		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)	Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Session 2			*Session 2*		

Week 11			Week 12		
Session 1			*Session 1*		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)	Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Session 2			*Session 2*		

Week 13			Week 14		
Session 1			*Session 1*		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)	Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Session 2			*Session 2*		

Week 15			Week 16		
Session 1			*Session 1*		
Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)	Type of exercise	Intensity (BORG scale)	Duration (hr:min:sec)
Session 2			*Session 2*		

Appendix 22 ECOG and Karnofsky performance scoring

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Severly disabled. Hospitalisation indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

Appendix 23 FACT-F questionnaire and FACT-F scoring

COMRADE FACIT Fatigue Scale (Version 4) 25/10/2016 STH19598

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4

An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACIT-Fatigue Subscale Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. **The higher the score, the better the QOL.**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
	An3	4	-	_____	=_____
Score range: 0-52	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____=**Fatigue Subscale score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

Appendix 24 FACT-P and FACT-P scoring

COMRADE FACT-P version 1 25/10/2016 STH19598

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GE 1	I feel sad	0	1	2	3	4
GE 2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE 3	I am losing hope in the fight against my illness	0	1	2	3	4
GE 4	I feel nervous	0	1	2	3	4
GE 5	I worry about dying	0	1	2	3	4
GE 6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**

GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4

P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

FACT-P Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the

number of items answered. This produces the subscale score.

4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-P).

5. **The higher the score, the better the QOL.**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____

	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____**=SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 6: _____

Divide by number of items answered: _____**=EWB subscale score**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
	GF5	0	+	_____	=_____
Score range: 0-28	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**FWB subscale score**

FACT-P Scoring Guidelines (Version 4) – Page 2

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
PROSTATE	C2	4	-	_____	=_____
CANCER	C6	0	+	_____	=_____
SUBSCALE	P1	4	-	_____	=_____
(PCS)	P2	4	-	_____	=_____
Score range: 0-48	P3	4	-	_____	=_____
	P4	0	+	_____	=_____
	P5	0	+	_____	=_____
	P6	4	-	_____	=_____
	P7	4	-	_____	=_____
	BL2	4	-	_____	=_____
	P8	4	-	_____	=_____
	BL5	0	+	_____	=_____

Sum individual item scores:_____

Multiply by 12: _____

Divide by number of items answered: _____**=PC Subscale score**

To derive a FACT-P Trial Outcome Index (TOI):
Score range: 0-104

_____ + _____ + _____ =_____=**FACT-P TOI**

(**PWB** score) (**FWB** score) (**PCS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-P total score:
Score range: 0-156

_____ + _____ + _____ + _____ + _____ =_____=**FACT-P Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**PCS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org

Appendix 25 COMRADE Three Day Diet Diary

Sheffield Hallam University

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

COMRADE trial

3-Day diet diary

Participant: Date:

How to fill out this diary

As part of your participation in the **COMRADE** trial, we ask you to fill out two 3-Day diet diary's, **one when you first start the trial and one when you finish**.

When you have completed your food diary we ask you to return it to the research team for analysis.

It is important to be as accurate as possible when completing the diary to ensure we get all the correct data on you as a valued participant in the trial. We ask you to be as specific as possible when recording what time you ate/drank and how much (a handful, a cup or however many grams/ml). We also ask that you specify any branded foods you have eaten as this will help us to accurately analyse your diary. An example of how to fill out the diary is given on the next page.

Example

DAY ONE Date: 06/09/2016		Time	What you ate and drank
	Breakfast	8:30am	Bowl of muesli with semi-skimmed milk 1 cup of tea with semi-skimmed milk 1 banana
	Lunch	12:30pm	1 portion of beef chilli with ½ cup cooked brown rice ½ avocado 1 cup of tea with semi-skimmed milk 1 glass of water
	Dinner	6pm	1 portion of shepherds pie with 1 cup of steamed broccoli and green beans 1 Cadbury milk chocolate mousse 1 large glass of water
	Snacks & other drinks		1 flapjack 1 Muller strawberry fruit corner yogurt 1 handful of grapes 2 cups of tea with semi-skimmed milk 1 large glass of water

DAY ONE Date:		Time	What you ate and drank
	Breakfast		
	Lunch		
	Dinner		
	Snacks & other drinks		

DAY TWO Date:		Time	What you ate and drank
	Breakfast		
	Lunch		
	Dinner		
	Snacks & other drinks		

DAY THREE Date:		Time	What you ate and drank
	Breakfast		
	Lunch		
	Dinner		
	Snacks & other drinks		

Appendix 26 The COMRADE participant focus group interview schedule

Version 2: Patient focus group questions

Questions

- Have any of you previously taken part in any other research trials?

[PROBE]

- Yes: Which ones?
- Yes: Were any of these exercise trials?

Motivations and apprehension before taking part in the trial

- Why did you chose to participate in the COMRADE trial what particularly attracted you?

[PROBE]

- Did you receive any support in choosing to participate in the study?
- Did your clinician ever speak to you about exercise, or encourage you to participate?
- Family/ spouse/ peers?

- Did any of you speak to your GP/consultant about the study?

[PROBE]

- Yes: what did they say?
- Yes: Did this affect your participation in the study?

- What was your perception of your clinical team's involvement in the study?

[PROBE]

- Do you have any view or experience of your clinical team liaising with the research team on COMRADE?
- Did you differentiate between the clinical team and the research team?
- Did your clinical team discuss the trial with you, or your progress?

- What expectations did you have of the study?

- What benefits did you think you might get from participation in the study, if any?
- Were you apprehensive about any aspects of the trial before starting?

[PROBE]

  - Yes: what were you apprehensive about?

- Did you feel there might be any barriers to you taking part in the study / signing up for the study?

Previous experience of exercise

- Throughout life, did you consider yourself physically active?

[PROBE]

  - What activities did you do?
  - Did anything change (post-diagnosis)?

- Did your GP/consultant previously recommend exercise to you prior to hearing about the trial?

[PROBE]

  - Yes: Did you take their advice? Why/why not?
  - Yes: what did they say? Did this affect your participation in the study?
  -

Evaluation and acceptability of the general trial procedures

- How did it feel when you were allocated the (control/intervention) arm?
- How did you find the trial assessments?
  - Duration/content
- How did you find the overall duration of the study?
  - What would have been your preferred duration of the study?

- Was the location of the study convenient for you? Did you have any issues with the location/parking?

[PROBE]

  - Yes: Did this ever affect your attendance?

- Did you feel there was any changes to your health during the study?

Exercise Arm Participant Questions

Acceptability of the exercise intervention

- Did you enjoy the experience?

[PROBE]

  - Yes: What did you like about it most of all?

- How did you feel about the structure of the exercise sessions?
- Was the intensity of the sessions OK for you?
  - Duration and frequency
- Did you have any physical limitations (side effects of treatments/prostate cancer) that meant you needed to change/adapt the exercises?

[PROBE]

  - Yes: did you feel the exercises were sufficiently adapted to suit your needs?

- What encouraged you to attend the sessions each week?
- Did anything stop any of you from attending the sessions?
  - Prostate cancer/ treatments/ comorbidity/ fitness/ age

[PROBE]

  - Yes: Do you feel anything could have been done to help with these barriers either by the research team or by someone else?

- Did you ever feel you did not want to attend?

[PROBE]

- Yes: What stopped you or what made you decide to still go?

- Was there anything else that would have helped you to attend the sessions?
- Do you feel you had or have experienced any physical benefits from taking part in the exercise sessions?
    - Activities of daily living (e.g. walking further/upstairs/ less out of breath playing with grandkids); feeling stronger/ fitter
- Were there any other mental wellbeing benefits?
    - Feeling more positive, getting out of the house, distraction, confidence

- How did you find exercising as a group (for those that did)?

[PROBE]

- Is it useful to exercise with others?
- Do you prefer to exercise in a group or alone?

- Did you have any negative experiences whilst on the trial?
    - Fatigue, was too intense, wasn't aware how hard it would be, did not like the environment/setting, did not like the supplements/dietary guidance, did not like seeing younger/fitter men OR older/more advanced men, should have had more experienced staff (physiotherapist)

[PROBE]

- Did these improve at all during the trial?
- Do you feel you received adequate support/ information from the research staff for this?

- Did you experience any adverse effects as a result of the trial?
    - Fatigue, stiff muscles/joints

[PROBE]

- Did these improve at all during the trial?
- Do you feel you received adequate support/ information from the research staff for this?

Exercise Arm Participant Questions

Engaging with the dietary advice and supplements

- Was the information given to you on the dietary guidance and supplementation enough and clear?
    - No: what could be done to improve it?
- What was your experience with the dietary guidance given? Were you able to adhere to the guidance?
    - No: why? What would help you adhere?
- What was your experience with the supplements given?

[PROBE]

- Do you think they helped, if so why?
- Did you experience any adverse effects?
- Did any of you have to reduce the dose of supplements? If you did why, and by how much?

Support

- Do you feel you were adequately supported by the research team during the trial?

[PROBE]

- No: What could the staff have done to better support you?
- Yes: What did they do specifically to support your needs?

- Did you feel you had sufficient contact with the research team?
- Did you develop good rapport with the research team?
- **[Intervention participants]** Over time do you think you needed less help from the research team?

- **[Intervention participants]** How is it useful to have a staff member always there?
    - reassurance, company, motivation, safety, adaptations
- Do you think if you were asked to exercise at home - that would work for you?

  [**PROBE]**

    - Yes: Do you feel that is because you have become more confident to exercise independently since the trial? Do you feel it could be as effective as exercising in a supervised format?
    - No: What do you feel may help you to exercise independently?

Present experience of exercise

- Would you say you are physically active now?
- Who of you have continued with exercise since completing the trial?/ Do you feel like you can continue with exercise since the trial?
- Have any of you had previous experience within a gym environment? (before or after the trial)

[PROBE]

- **[intervention participants]** Yes: How do you feel COMRADE compares to your previous experience with gyms?
- No: How do you feel now with using a commercial gym since completing the intervention? Has anything changed?

- How comfortable would you feel participating in exercise unsupervised or exercising with supervision? Do you have a preference?

Other Comments

- Do any of you have any recommendations for the design of future exercise studies?
- Is there anything else that you have not had chance to discuss relating to the trial that any of you would like to tell me about?

Thank you for your time

Appendix 27 Focus groups initial codes

Look for: | Search In | Nodes | Find Now | Clear | Advanced Find

Nodes

Name	Sources	References
Attitudes and experience of exercise and physical activity outside the trial	0	0
Barriers to exercise	0	0
Age	2	5
Body image	2	5
Boring	2	3
Clinician advice	1	5
Cost	1	1
CV comorbidity	1	1
Disease progression	1	5
Fatigue or lack of energy	3	8
Holidays	1	1
Lack of information tailored to individual	1	3
Lack of support from clinician	1	3
Mobility	2	4
Motivation	3	17
MSK comorbidity	1	2
Not knowing what to do when alone	2	2
Treatment adverse effects	1	4
Experience of exercise outside the trial	0	0
Activity post trial	3	17
Activity prior to study participation	2	4
Physical activity levels throughout life	2	9
Commercial gym experience	3	8
Previous participation in research trial	3	5
Facilitators to exercise	1	7
Encouragement of peers	1	1
Exercise equipment	1	1
Motivation	2	4
Sessions targeted at PCa	1	1
Supervised exercise	2	7
Support for exercise behaviour from clinical team	3	15
Asking advice	2	2
Percieved benefits of exercise	2	4
Experience and opinions of the trial	0	0
Suggested improvements in a future trial	2	11
Acceptability of trial procedures	0	0
Diet and supplementation	0	0
3 day diet diary	2	3
Barriers to diet change	1	1
Control - changes to diet post intervention	1	3
Dietary guidance	1	6
Duration of study	2	3
DXA scan	1	1
Experience with researchers and trainers	0	0
Experience of trial assessments	3	5
Perception of research team role	3	6
Qualified exercise trainers	1	1
Rapport with trainer	3	5
Trial explanation overall	2	4
Length of trial	2	3
Overall experience of the trial	0	0
intervention	2	2

Problems during the trial	1	5
Adverse events whilst on COMRADE	2	9
Equipment which was busy	1	1
Exercises too difficult	1	5
Group exercise format	1	4
The need for more trainers	1	5
Intensity not enough	1	1
Lack of showers	1	1
One on one exercise format	1	1
Reasons for cessation or non-attendance to sessions	2	2
Family illness or death	1	1
Illness	1	2
Weather	1	2
Travel and parking	2	4
Questionnaires	1	5
Randomisation procedures	0	0
Allocated control	2	4
Allocated intervention	2	3
Contamination	1	1
Structure of trial	1	1
Adaptability of the exercise sessions	2	6
Intervention effects	0	0
Activities of daily living	1	2
Camaraderie	1	4
Cost	1	1
Fatigue	1	1
Fitness	1	4
Improvements	2	3
Increased muscle tone	1	1
Inspiration to others	1	2
Muscle strength	2	9
Progression with exercises	2	5
Psychological benefits	2	3
Reduced pain	2	3
Stopped the decline	1	2
Wellbeing	2	5
Whey protein	1	1
Motivations and expectations	0	0
Apprehension in taking part in the trial	2	4
Reasons for taking part in the trial	0	0
Be a part of research trial	2	4
Bone health	1	1
Clinician encouragement	2	4
Doing it for oneself	1	3
Encouragement from family or friends	2	6
Favourable changes in body composition	1	1
Fitness	3	10
Gain greater knowledge of disease	1	1
Get moving or back into exercise	2	6
Prostate cancer	2	15
Psychological	2	2
Routine	1	1
Sleep quality	1	2
Supervision	1	1
Reasons to come to sessions	1	1
Attendance	2	4
Living with CRPC	0	0
Physical health	0	0
Adverse effects of disease	1	3
Psychological effects	1	1
Fitness	0	0
Decline in fitness	3	19
Perceptions of fitness	2	3
Health post trial	1	2
Disease progression	1	1
Other comorbidity	1	1
Pain	1	1
Treatments	0	0
Additional treatments	0	0
Chemotherapy	0	0
Chemotherapy adverse effects	1	1
Enzalutamide	3	9
RTx adverse effects	1	1
Steroids	2	4
Adverse effects	1	3
Standard ADT	2	5
Psychological health	1	1
Lack of motivation for AODL	1	2
Resentment for disease	1	2

Appendix 28 Charting for the focus group analysis

Sources	Motivations and expectations for the trial	Problems and suggested improvements for a future study	Barriers to exercise
Focus group 1: CONTROL	**Reasons to participate - Fitness (1). To be on a trial that could help others with prostate cancer (2)** "M1: I was looking forward, well, I thought if you can find anything out and it'll do someone else some good." **psychological** "M3:. I think my motivations for having exercise to some extent was I can't sleep very well at all. I'll have a couple of hours and then I wake up and then I start thinking about things, nothing desperate or life-changing or anything like that. I'm not a particular worrier about things. I just start thinking about something I'm wanting to do or whatever. And I think having regular exercise, if I could only get myself into the routine of doing it would certainly help me to do that. So if I can get myself sorted out again I'm going to try that because it's depressing not being able to sleep and your day just goes upside down if you're not careful. So I have to get up to take drugs at seven o'clock and then at eight o'clock and then, well, just before that I have my breakfast, then I go back to bed. And then I end up probably staying in bed until 11 o'clock because I can! And it's not good really and so my day is topsy-turvy and it would be far better if I was not to do that and maybe I would sleep better at night, but I just feel shattered." **because of the supervised aspect** "M4:..but at the back of my mind I thought it would be nice if there's somebody there who knows what you should be doing and possibly not be doing and what the best thing is for you. Because we can all, body withstanding, go and get on machines and knock yourself out, but is it really doing you any good? You read so much, don't you? "	**AE: during DXA. It was suggested that a better explanation behind filling out questionnaires would help to know how to fill things out.**	**Age (2). Body Image (3)** "M1: I don't go in swimming pool now; it's embarrassing a bit isn't it? M4: Well I mean as I say, I have got quite, when I take my kit off I've got. M3: Enough detail, go on. M4: No, I've got quite