Exercise during stem cell transplantation for haematological cancer - exploring the feasibility of embedding exercise within a clinical pathway in multiple myeloma

Orla McCourt

A thesis submitted for the degree of Doctor of Philosophy

University College London

2022
Declaration

I, Orla McCourt confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

October 2022
Acknowledgments

Firstly, huge thanks to my supervisors, their collective support and guidance enabled me to successfully deliver this thesis and thoroughly enjoy my whole PhD experience. I am especially grateful for Professor Kwee Yong for her continued support of survivorship and rehabilitation research for people with myeloma. Her expertise, encouragement and mentorship has hugely influenced my early clinical academic career. I would like to thank Dr Abigail Fisher for her insight and direction in guiding me through the delivery of each of my studies and for her consistent encouragement and feedback. Thank you to Dr Gita Ramdharry for her contribution to this work and her inspiration and guidance as a senior clinical academic physiotherapist, forging a path that I hope to follow.

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Abstract

The benefit of physical activity during and after cancer treatment has been demonstrated. There is a growing evidence base indicating that structured exercise interventions delivered before and during cancer treatment (‘prehabilitation’) can have positive effects on physical and psychological wellbeing before, reduce deterioration during, and increase rate of recovery following treatment. There is emerging evidence for exercise prior to and during stem cell transplantation in haematology/oncology patients. Guidelines recommend prehabilitation and rehabilitation as integral components of the treatment pathway in multiple myeloma, for whom autologous stem cell transplantation (ASCT) is a preferred first line treatment. However, provision of rehabilitation and structured physical activity support is lacking in haematology/oncology clinical services in the United Kingdom.

This thesis aimed to explore the feasibility of embedding exercise within haematology/oncology clinical pathways, with a focus on ASCT in multiple myeloma. It describes multi-methods research that includes: feasibility and outcomes data from a pilot randomised controlled trial of a prehabilitation and rehabilitation intervention embedded within the multiple myeloma ASCT pathway; qualitative interview data on the experiences of myeloma patients who were approached for and declined or took part in exercise research after referral for ASCT; and data from a national survey of haematology health professionals on their beliefs and understanding of exercise during haematology/oncology treatment. Additionally, the impact of the COVID-19 pandemic, the adaptation of the pilot trial and how this allowed for evaluation of feasibility of both face-to-face and remotely delivered exercise support will be described.

The pilot trial recruited 50 of 109 (46%) eligible participants with an attrition rate of 34%, mainly related to failure to undergo ASCT. Loss of follow-up for other reasons was low, with 33 of 39 (85%) participants who underwent ASCT completing an assessment at final timepoint. Secondary outcomes indicate benefit of physiotherapist-led exercise prior to, during and after ASCT with improvements in quality of life, fatigue, functional capacity and PA evident on admission for ASCT and 3 months post-ASCT.

Eighteen people with myeloma (56% male, mean age 62 years) who declined participation in the trial and sixteen who took part in the trial were interviewed for the
qualitative studies. Themes from analysis of the decliners’ study highlighted that travel was the most common reason for declining but it was more than a logistical challenge and that participants welcomed the personalised approach to being asked to participate in research but their recall of research information was variable. Other important findings included the impact of reduced physical activity due to treatment, that there is a lack of support to counteract this and that patients with myeloma may be underreporting common side-effects of treatment to their clinical teams because these are expected despite their impact on engagement in daily activities. Themes from analysis of the pilot trial completers study indicated both altruistic and personal motivations for participating and remaining in the trial but that allocation to control group brought about disappointment and may have led to contamination. There were also disparities in the experience of recovery from ASCT between those who took part in the intervention and those who did not. Participants also recalled the impact of diagnosis and early treatment on physical activity and that they saw exercise as important for preparation and recovery from ASCT.

156 health-professionals completed the survey study. Beliefs of health professionals regarding the role of physical activity during and after treatment for haematological cancer were generally positive. A third (31%) reported knowing relevant guidance related to physical activity for people with cancer and nearly half (47%) reported providing physical activity advice routinely to their patients. Those reporting familiarity with guidance were more likely to give advice. However, misalignment existed between guidelines and advice given by professionals to their patients.

Findings from this thesis suggest that it is feasible to embed a prehabilitation and rehabilitation intervention into the myeloma ASCT pathway, indicating possible benefit and that health professionals and patients are accepting and supportive of greater physical activity support during and after haemato-oncology treatment.
Impact statement

Progress in scientific and medical research has resulted in ever improving survival outcomes for people with the blood cancer multiple myeloma. It is increasingly important that people living with this complex disease are supported following diagnosis, through their treatment and beyond, to live as well as possible. Physical activity plays an important role in enhancing quality of life and function for people living with and beyond cancer. Myeloma affects older people and has unique disease characteristics that cause bone destruction, resulting in high burden of symptoms, persistent pain and disability, yet the role of rehabilitation and exercise is under researched and provision of services to support specialist rehabilitation are scarce.

The work presented in this thesis provides greater understanding of the views and experiences of health professionals and people with myeloma regarding the role of physical activity and exercise during treatment. The pilot study of an exercise intervention delivered before, during and after autologous stem cell transplant (ASCT) has provided important information regarding the feasibility and acceptability of two different approaches to delivery of exercise support during intensive treatment; face-to-face and virtually supervised group based exercise led by a physiotherapist. Results from secondary outcomes provide preliminary indication of benefit in terms of recovery of physical functioning and well-being following ASCT. This feasibility data will be used, in conjunction with patient and public involvement activities, to inform further research to develop and evaluate the efficacy of virtually supervised exercise in haematological cancer.

This doctoral work has supported my clinical and academic development and has already had impact outside of academia, in the real-world clinical setting. Findings from this research have been shared with clinical colleagues locally, nationally and internationally. Data from this thesis has been combined with local clinical information to inform funding applications for a specialist physiotherapy service, with the ambition to translate the intervention tested in this thesis into the ASCT clinical pathway in myeloma locally.

Much of the work included in this thesis has already been disseminated. The pilot trial protocol has been shared in two peer-reviewed papers and its results manuscript has
been invited for inclusion in a special cancer rehabilitation issue of another journal. This study has also been presented, as platform and poster presentations, at two international conferences. An abstract of the trial results was selected for presentation in the first oral abstract session at the annual International Myeloma Society meeting. A paper sharing the results of the health professionals survey has been published, a manuscript detailing the findings from one qualitative study has been submitted for peer-review and another, detailing the second qualitative study, is in preparation for submission.
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Chapter 1  Background

1.1  Haematological cancer: an overview

Haematological cancer includes a number of different neoplasms that arise from the blood, bone marrow and lymph nodes. Haematological cancers belong to one of two types: myeloid or lymphoid, depending on the part of the haematopoietic system, the bodily system involved with the creation of blood cells, that is affected (Brown, 2017). Collectively haematological cancers are the fifth largest group of cancers and are the third largest cause of death related to cancer in the UK. 40,000 people are diagnosed with a haematological cancer each year in the UK and there are thought to be approximately 250,000 people in the UK living with a haematological cancer (Blood Cancer UK, 2018). Despite being one of the leading causes of cancer deaths, survival of haematological malignancies has been increasing faster than that of the most common solid tumour malignancies, such as lung, prostate and breast cancer. 5-year survival in haematological cancer is now approximately 60%. Dramatic increases in survival in multiple myeloma have contributed most to this increase (Blood Cancer UK, 2019).

Management of haematological cancers differ according to the diagnosis but generally involves use of regimens or combinations of systemic anti-cancer chemotherapy agents, radiotherapy and bone marrow or stem cell transplantation (SCT). Many patients having treatment for haematological cancer may require prolonged treatment with different phases of therapy using a combination of different modalities, resulting in an array of morbidity and side-effects perpetuated by toxicities and deconditioning. Fatigue, pain, reduced role functioning and dyspnoea are common physical deficits experienced by patients with haematological cancer (Hall et al., 2013). There is acknowledged variation in symptoms and consequences of treatment experienced by patients with different haematological cancers (Lobb et al., 2009), and between undergoing allogeneic and autologous SCT (Cohen et al., 2012; Persoon et al., 2013). Studies among allogeneic SCT recipients, whereby the patient receives donor stem cells, highlight the intensive nature of the medical intervention and its associated symptom burden and consequences, most notably graft versus host disease (GvHD) and an increased risk of treatment associated mortality (Yin et al., 2018). In contrast, with autologous transplantation, whereby the patients receive their own pre-harvested stem cells, the mortality is considerably lower.
and there is no risk of GvHD, with its attendant risk of infections and short and long term morbidity (Yin et al., 2018).

Patients with cancer are known to have reduced quality of life (QOL) compared to the general population (Quinten et al., 2015), but the effect on QOL may be more marked among haematological cancer patients. A systematic review of 21 studies including 7349 patients demonstrated that having haematological cancer impacted all-over health-related QOL with fatigue, pain and psychological problems among the most prevalent physical symptoms (Allart-Vorelli et al., 2015). Worsening of these symptoms and deterioration in physical functioning effects older patients (Quinten et al., 2015) and those with more advanced stage disease more significantly (Allart-Vorelli et al., 2015). These impairments are associated consequences of haematological cancer treatment, which is considered more debilitating than treatment for more common solid tumour cancers.

Most studies investigating QOL, symptom burden and consequences of treatment have been conducted among people with haematological cancer in later stages of treatment or among long-term survivors with confirmation of increasing burden with increasing time on treatment, that can remain well into survivorship. However there is a possible deterioration in QOL and functional capacity evident even in newly diagnosed patients with haematological cancer. In a cross-sectional study, newly diagnosed patients yet to commence treatment (n=23) had significantly lower QOL scores, exercise capacity and levels of physical activity compared to healthy controls (n=20) (Celik et al., 2022b). The known cumulative burden of living with and beyond a haematological cancer diagnosis and indications that physical and psychological impairments are evident early after diagnosis, even prior to receiving systemic anti-cancer treatment, suggest a need for early rehabilitation approaches parallel to management of disease.

1.1.1 Multiple myeloma

Multiple myeloma, also referred to as myeloma, is a haematological malignancy, arising from the lymphoid cell line which affects the plasma cells in the bone marrow, with a peak incidence in the seventh decade of life (Brown, 2017; Zhou et al., 2021). Myeloma is a relapsing-remitting cancer: periods of active, symptomatic disease that require intensive treatment, are separated by periods of stable disease or plateau phase where
no, or only maintenance treatment, is required. This repetitive pattern of remission followed by relapse results in depreciating disease prognosis interjected with everchanging management plans (Nicol et al., 2020). Symptoms of haematological malignancies include disruption of normal blood cell production and abnormal blood levels, known as cytopenia (e.g. anaemia, thrombocytopenia, neutropenia), immunosuppression, as well as high levels of calcium in the blood, and renal impairment which are associated with myeloma (Kyle & Rajkumar, 2008; Gozzetti et al., 2014), and can lead to significant physical disability and reduction in QOL. Myeloma survivors can have a high symptom burden and unmet supportive care needs (Gulbrandsen et al., 2004; Allart-Vorelli et al., 2015) and experience comparably more symptoms than those with other haematological cancers (Shapiro et al., 2021). The most frequently reported symptoms among myeloma patients are fatigue, pain, peripheral neuropathy and reduction in physical functioning (Nielsen et al., 2021). Approximately a quarter of myeloma survivors report having unmet supportive care needs. In a UK survey of 132 myeloma patients, significant proportion of participants reported signs of anxiety (27.4%) and depression (25.2%) with one-third (35.9%) experiencing significant pain (Molassiotis et al., 2011). A large observational study examining health-related QOL in 16095 older people with less common cancers included 302 people with multiple myeloma. Those with myeloma were found to have the lowest mean scores for general health, emotional and physical functioning, at levels similar to those with pancreatic cancer diagnoses (Kent et al., 2015). Another observational study of 92 Danish myeloma survivors found that participants had a median of three moderate or severe symptoms or functional problems that were persisting even during stable disease, resulting in lower QOL. Moderate or severe pain and fatigue was evident in half of survivors. The presence of persistent pain and fatigue appear to be interrelated and central to impairment in physical functioning, with presence of myeloma related bone disease further perpetuating impact on QOL (Nielsen et al., 2021). It is recognised that the impact of myeloma on physical function extends further beyond initial treatment (Shapiro et al., 2021). The increased incidence of co-morbidities with age common in this older age group further impacts treatment trajectory and consequences on function and QOL (Moller et al., 2021).
1.1.1.1 Prevalence and increasing survival

Approximately 29.5 per 100,000 people in the UK are affected by multiple myeloma (Haematological Malignancy Research Network, 2022) and it accounts for 10% of all haematological cancers (Gozzetti et al., 2014). There are approximately 4000 new diagnoses of myeloma in the UK each year. Incidence of myeloma increases with age, with a marked increase in incidence from 55 years (Haematological Malignancy Research Network, 2022). Although incurable, improved understanding of the disease mechanisms along with advances in treatments over the last decade has meant that survival in myeloma is increasing at the fastest rate among all cancer types in the UK (Myeloma UK) and contributes most to the increasing survival rates of haematological cancers generally (Blood Cancer UK, 2019). Median estimated survival time for patients with a diagnosis of myeloma has increased six-fold over the last four decades and most recent statistics available indicate that 5-year survival was around 52% in 2017, increasing 9.2 percentage points since 2010 (Blood Cancer UK, 2019; Cancer Research UK, 2019). This increase in survival is particularly seen in younger (under 70 years) patients who are able to undergo autologous stem cell transplantation (ASCT) as part of first line therapy. Survival outcomes following ASCT have been steadily improving and patients with myeloma receiving ASCT have a median survival of 6-7 years (Krejci et al., 2009; Nishimura et al., 2020) and among patients receiving ASCT in more recent years (2014 onwards) 5-year survival is estimated to be as high as 70% (Nishimura et al., 2020).

The management of myeloma as a disease is changing. Once considered an acute, short lived cancer diagnosis, the continual increase in overall survival with increasing periods of progression free time or inactive disease are shifting myeloma towards a pattern more typical of a chronic health condition (Nielsen et al., 2021). Approximately 19,000 people are living with myeloma in UK (Haematological Malignancy Research Network, 2022). With more diagnoses of myeloma expected with population aging and improving overall survival due to medical advances, the proportion of older people living with the disease is ever increasing (Zhou et al., 2021). With this change in disease trajectory and increasing burden of myeloma, more emphasis needs to be placed on ensuring good standards of QOL and living well with myeloma not just between lines of treatment but as a possible long-term health condition (Shapiro et al., 2021). The notion of functional or statistical cure is becoming a possibility in myeloma, with small proportions of ASCT
recipients experiencing longer periods of progression-free survival beyond ten years, however relapse can still occur after many years and longer follow-up data is required (Nishimura et al., 2020). Therefore, the role of rehabilitation and supportive care to maximise participation in daily lives during and after treatment, as well as optimising patients for any future treatment that will be required, warrants further investigation.

1.1.1.2 Myeloma related bone disease

Bone disease is a unique and common feature of multiple myeloma, caused by over stimulation of osteoclast activity (bone reabsorption) that exceeds osteoblast activity (bone formation), leading to unopposed bone resorption. This highly abnormal bone metabolism leads to osteolytic bone lesions, resulting in long bone and vertebral fractures, causing pain, deformity, neurological damage and loss of mobility (Davies et al., 2019). Evidence of osteolytic bone damage is reported in up to 80-90% of patients at diagnosis and 50-60% of myeloma patients are expected to develop a fracture during the disease course (Terpos et al., 2018; Coluzzi et al., 2019; Terpos et al., 2019). Patients with bone involvement are often limited by severe pain and compromised mobility, which can be evident before diagnosis, and can persist long after they complete treatment (Coluzzi et al., 2019). Skeletal disease is associated with increased reporting of moderate to severe deficits in physical functioning (Nielsen et al., 2021). Functional and psychological deficits present at diagnosis are exacerbated by intensive treatment with chemotherapy and ASCT (see Section 1.1.1.3). Evidence that significant ongoing symptoms and impairment related to osteolytic bone disease continues into remission distinguishes myeloma survivors from other cancer survivors and poses a challenge to provision of adequate support following completion of active disease management. With increasing survival of these patients, there is an urgent health, psychosocial and socio-economic need to develop supportive interventions to maximise QOL and physical functioning.

1.1.1.3 Autologous stem cell transplantation in multiple myeloma

ASCT is a therapeutic procedure that enables the use of dose-escalated chemotherapy to consolidate initial (standard dose) chemotherapy in selected patients with myeloma. It is most frequently used as part of the treatment protocol for newly diagnosed patients who are considered ‘fit’ enough for intensive chemotherapy. ASCT and the introduction
of novel treatment agents are thought to be responsible for the increasing prolonged survival and decline in overall disease-related mortality in myeloma (Zhou et al., 2021). It has been shown in multiple randomised controlled trials (RCTs) to prolong progression-free survival, and in some studies, overall survival (Krejci et al., 2009; Gozzetti et al., 2014; Nishimura et al., 2020). The procedure involves the harvesting of the patients’ own stem cells, which are stored, then re-infused into the patient after high dose chemotherapy (NHS Commissioning Board, 2013).

In the UK, the total numbers of ASCTs carried out each year have been increasing on average by 5% year on year (NHS England, 2015), with figures from the British Society of Blood and Marrow Transplant (BSBMT) Registry indicating a 40% increase in transplant numbers between 2001 and 2020. Data from the BSBMT registry shows that myeloma is the most common indication for ASCTs carried out in the UK, totalling 1411 procedures (British Society of Blood and Marrow Transplantation, 2016).

Undergoing ASCT carries a 5% risk of transplant related death and a 5-10% risk of severe infection or organ failure resulting in admission to intensive care. Soon after return of stem cells, patients are likely to suffer with fatigue, moderate-to-severe nausea, diarrhoea and neutropenic fevers, resulting in reduced oral intake, often necessitating intravenous replacement with fluids and blood products (Sanchez et al., 2017). Some patients will suffer these symptoms for several weeks afterwards, and occasionally get readmitted to hospital with infection. A longitudinal study of symptom burden measured using the M. D. Anderson Symptom Inventory (MDASI) among myeloma patients undergoing ASCT reported that global symptom severity increases between pre-ASCT (day -36 to -3) and day of lowest blood counts (nadir) approximately 7-10 days post-ASCT, returning to levels similar to baseline by day 30 post-ASCT. Fatigue, weakness, physical activity and enjoyment for life were individual symptoms that worsened between baseline pre-ASCT and day 0, before reaching highest intensity at nadir and although all improved post-ASCT these symptoms did not improve to baseline scores by day 30 post-ASCT (Campagnaro et al., 2008). Thus procedure-related morbidity of an ASCT may be considerable, and almost all patients suffer with a reduction in functionality and wellbeing for up to six months post-transplantation (Tuchman et al., 2015). In this context, exercise interventions may have much to offer
both in terms of improving fitness before transplant in the form of prehabilitation, and speeding up recovery after transplant through rehabilitation.

1.2 Physical activity and haematological cancer

There is an established need for supportive strategies adjuvant to anti-cancer treatments to assist improvements in treatment responses whilst lowering burden of treatment. Increasing importance is being placed on the availability of effective advice and interventions aimed at improving QOL among cancer patients, including promoting physical activity and structured exercise programmes (Christensen et al., 2018). Physical deconditioning is a common consequence of living with and undergoing treatment for haematological cancer. Despite this there remains a continuing trend to err on the side of caution regarding physical activity or exercise by health professionals, with prevailing advice focussed on avoidance of intense exercise and promotion of rest despite the known negative effects of physical inactivity on the person with cancer (Knips et al., 2019).

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. Exercise, is a subcategory of physical activity aimed at improving or maintaining one or more components of physical fitness through activities that are planned, structured, repetitive, and purposeful (Caspersen et al., 1985). The positive role of physical activity and exercise interventions across the continuum of cancer survivorship has been evidenced in numerous systematic reviews, from diagnosis, through treatment and post-treatment, with reliable effects seen on aerobic fitness and muscle strength (Christensen et al., 2018; Sitlinger et al., 2020), levels of fatigue (Oberoi et al., 2018), psychological outcomes and QOL (Speck et al., 2010; Mishra et al., 2012b; Patel et al., 2019). Positive effects on these outcomes are more evident with moderate or vigorous intensity exercise compared to mild intensity activities (Mishra et al., 2012b). Despite this, physical activity levels among cancer patients during and after treatment are known to be below recommended levels (Jones et al., 2004b; Walsh et al., 2011; Tonosaki & Ishikawa, 2013).

Specifically, in haematological cancer, a Cochrane review and meta-analysis of aerobic exercise in adult haematological cancer patients included 14 RCTs and found evidence
of positive effects on fatigue (n= 826; SMD 0.31; 95% CI 0.13 to 0.48) and depression (n=445; SMD 0.19; 95% CI 0.0 to 0.38). Despite eight of the included studies reporting significant benefits in physical performance such as cardiovascular fitness or aerobic capacity in their intervention arms, however, variation in outcomes and measures used by studies limited pooling for meta-analysis. The included studies mostly involved walking based interventions and were often small and inadequately powered (Knips et al., 2019). Among SCT recipients, a systematic review and meta-analysis of eleven studies by van Haren et al. (2013) concluded exercise interventions are safe and well tolerated during SCT, and may improve QOL, physical function and reduce fatigue. Differences were seen particularly among allogeneic SCT recipients at discharge from hospital when exercise was introduced before or during admission (van Haren et al., 2013). A more recent review and meta-analyses of outcomes following exercise interventions among people treated with SCT included 24 RCTs and 3 non-randomised trials (n=2432) and also found clinically relevant improvements in a range of physical and psychosocial health outcomes, including clinically relevant increases in functional capacity, health-related QOL and fatigue (Abo et al., 2021a). The authors also found greater benefit among allogeneic SCT recipients and it is not known why these differences may occur between subgroups. Generally, all the aforementioned reviews reached similar conclusions, and although the size, quality and heterogeneity of the included studies and their intervention components do warrant careful interpretation of findings, exercising and being physically active is safe, feasible and beneficial for haematological cancer patients receiving intensive systemic treatment (Wolin et al., 2010; Persoon et al., 2013; van Haren et al., 2013; Abo et al., 2021a).

1.2.1 Physical activity and exercise in multiple myeloma

Variations in clinical features support the need to study rehabilitation interventions in uniform blood cancer patient populations. The complex, perpetual nature of myeloma as a relapsing-remitting disease, the variations in disease and co-morbid state at diagnosis, consequences and trajectory of disease management and impact on QOL and function indicates a need for distinct studies of rehabilitation interventions for people living with myeloma (Nielsen et al., 2021). As discussed, studies have suggested that physical domains of QOL are most affected in people with haematological cancer (Allart-Vorelli et al., 2015). QOL related to physical functioning has been reported to be most
problematic for myeloma patients, including inability to do strenuous activities or take long walks, with many of these impairments persisting for years following diagnosis, particularly in older patients (Gulbrandsen et al., 2004; Molassiotis et al., 2011). While it may be expected that exercise could have benefits on physiological variables, it must also be noted that physiological and psychological parameters are often associated and evidence indicates the positive role of exercise on both for people with myeloma (Shapiro et al., 2021).

More physically active myeloma survivors have improved QOL, reduced treatment related side-effects and lower fatigue compared to those who are less active (Jones et al., 2004b; Groeneveldt et al., 2013; Servadio et al., 2019). A matched-pair cohort study of physically active and inactive multiple myeloma patients undergoing ASCT found active patients had less co-morbidities and treatment-related symptoms as well as better tolerance and lower frequency of dose reductions during induction chemotherapy prior to ASCT (Moller et al., 2021). Patients in this study were deemed ‘active’ by meeting physical activity guidelines of 150 minutes of moderate aerobic exercise and two sessions of resistance or strength training per week through participation in a clinical exercise programme rather than via self-report or objective measurement of physical activity. A limitation of this study is its observational design, and its use of real-world data from a clinical service indicates that patients who are functionally better may be more likely to participate in a programme such as this. Indeed, the authors reported higher incidence of myeloma related bone disease and higher levels of baseline fatigue and depression in those who did not participate in the programme (Moller et al., 2021), further indicating the need for prospective, randomised trials of exercise interventions in this group. Levels of physical activity among myeloma patients are known to be low (Jones et al., 2004b; Shapiro et al., 2021). One study based on self-reported physical activity found approximately 7% of myeloma patients on treatment and 20% of those off treatment were meeting recommended levels of physical activity (Jones et al., 2004b). Another self-report study reported similar levels of physical activity post-diagnosis and demonstrated that levels of physical activity dropped significantly from pre-diagnosis with the number achieving recommended levels of physical activity following diagnosis reducing by half (Craike et al., 2013a). Another recent study also found the proportion of survivors off treatment meeting
recommended levels of physical activity, according to self-report measure, to be approximately 17% (Nicol et al., 2020). However, self-report physical activity measurement is prone to recall bias and over-estimation by participants (Sallis & Saelens, 2000; Downs et al., 2014). A UK based trial of an exercise intervention for myeloma survivors, conducted at our centre, used accelerometry to assess objective levels of physical activity and found that between 14-16% of participants were meeting physical activity guidelines of 150 minutes/week of moderate to vigorous physical activity at baseline (Koutoukidis et al., 2020). This evidence of low levels of physical activity indicates a need for developing interventions to support improvement and maintenance of physical activity in this population given the probable benefits it may induce during the fluctuating myeloma disease course.

Whilst a number of exercise interventions have been tested in people with myeloma, the quality of the evidence to date is insufficient to determine efficacy due to heterogeneous, selective inclusion criteria and underpowered trial designs. There is indication, however, that exercise is safe with some evidence for positive effects on physical, psychological and QOL outcomes (Smith et al., 2015; Gan et al., 2016). A single arm pilot study of a physiotherapist-led, tailored, exercise intervention delivered to myeloma survivors post-treatment has been conducted at our centre. It demonstrated that exercise was associated with improvements in QOL, cancer-related fatigue and muscle strength, and was safe and extremely well received by patients (Groeneveldt et al., 2013). A subsequent larger RCT of 133 myeloma survivors testing a similar intervention, which included partly-supervised aerobic and resistance exercise with incorporated behaviour change components, further demonstrated improvements in strength and cardiovascular fitness (Koutoukidis et al., 2020). This trial, for which I was a physiotherapist delivering the intervention, was powered to detect change in cancer-related fatigue as its primary outcome but overall no effect on fatigue was evident. This finding was due to the good performance status of participants and low levels of fatigue at baseline but additional analysis of participants did indicate an effect among those who had clinical levels of fatigue at baseline. Qualitative exploration related to this study highlighted that participants, most of whom had undergone ASCT prior to the trial, would have preferred to receive the exercise intervention earlier in their treatment, perhaps when levels of fatigue were more evident (Land et al., 2022).
Prior to this thesis only two small trials had explored the use of a pre-transplant exercise in a myeloma only population undergoing ASCT, with mixed results (Coleman et al., 2003; Coleman et al., 2008; Coleman et al., 2012). The first, a feasibility study of 24 participants showed a significant increase in lean muscle mass in the exercise group (Coleman et al., 2003). The second study of 166 patients reported a decline in aerobic capacity and increased fatigue in both the experimental and control group, with no difference between groups after ASCT. This study, reported in two papers, was also testing the effect of prophylactic epotin alfa (EPO) therapy, a medical product that raises haemoglobin levels, alongside exercise and was therefore not solely assessing the efficacy of the prescribed exercise (Coleman et al., 2008; Coleman et al., 2012). Additional limitations to these studies include provision of an unsupervised home-based exercise intervention and that the control groups were also advised to walk 20 minutes daily (Coleman et al., 2003; Coleman et al., 2008), which may have diluted the effect size. These studies, however, have demonstrated that it is safe for myeloma patients to exercise whilst undergoing ASCT.

Limited published literature exists regarding physical activity or exercise interventions in patients undergoing SCT originating in the UK. A single-arm feasibility study of exercise before ASCT among people with myeloma has been conducted in a centre in Sheffield (Keen et al., 2018). The single-arm pre-post study design recruited 23 participants and reported high attendance to scheduled exercise sessions (mean attendance 75% of scheduled sessions; median attendance 5 sessions pre-ASCT) but the study had high attrition with only 57% of participants attending follow-up assessment (Mawson et al., 2021). In addition to small numbers of participants completing follow-up, the study design alternated use of patient reported outcome measures between participants resulting in even smaller numbers reported for some outcomes. This study indicated that exercise pre-ASCT was feasible in terms of recruitment to the study, acceptable in terms of adherence of exercise sessions at a UK centre and showed meaningful improvement in six minute walk test distance (n=13; mean difference +104.9 meters; 95% CI 61.8, 148.1) (Mawson et al., 2021).
1.3 Summary

Exercise interventions can improve QOL and ameliorate many of the consequences of cancer and its treatment. Survival is increasing fastest amongst haematological cancers compared to most solid tumour types and this increase is largely driven by the improvement in survival in myeloma. The current literature in exercise during haematological cancer treatment is limited by small studies, in mostly heterogeneous samples and there is an identified need for testing of interventions in defined patient populations. The exponential increase in survival and ever-extending progression-free survival in myeloma, the added complexity of its associated bone disease and high symptom burden, coupled with the small number of exercise studies conducted in myeloma, highlight it as an ideal index group. Multiple myeloma is the most common indication for undergoing ASCT and the generally consistent clinical pathway of ASCT in myeloma provides an excellent established clinical pathway in which to explore the feasibility of exercise as a component part of haematological cancer treatment.
Chapter 2  Research Aims

2.1  Aims of this thesis

Current research evidence (summarised in Chapter 1) indicates potential benefit in being physically active and engaging in structured exercise during and after a haematological cancer diagnosis. Feasibility of conducting research studies of exercise interventions during and after haematological cancer treatment has been demonstrated although mostly in small studies with heterogenous study samples. Another important factor regarding existing literature is that most included exercise interventions delivered in research settings, not as part of clinical services. In order for research to translate and result in exercise rehabilitation as an established part of the management of haematological cancer, further feasibility and efficacy testing of interventions delivered in real-world settings is required. Therefore, the overall aim of this thesis was to explore the feasibility of embedding exercise within haemato-oncology clinical pathways, using a more homogeneous approach, focusing on the autologous stem cell transplant pathway (ASCT) in myeloma. This doctoral work was conducted in three parts to address specific aims as follows:

2.1.1  Aim 1. To carry out a pilot randomised controlled trial of an exercise intervention as prehabilitation for myeloma patients undergoing autologous stem cell transplantation, to assess feasibility

The PERCEPT pilot randomised controlled trial (RCT) aimed to investigate the feasibility of introducing an exercise intervention to an existing treatment pathway and preliminarily investigated the benefits of this intervention as an integral part of the ASCT pathway for patients with myeloma. It was hypothesised that this physiotherapist-led tailored exercise intervention delivered prior to, during and after ASCT treatment for myeloma would be feasible in terms of recruitment rate and willingness of the participants to be randomised, intervention adherence, compliance to the exercise prescription, attrition due to the intervention, and collection of secondary outcomes to inform development of a future larger-scale trial.
2.1.2 **Aim 2. To explore the experiences of myeloma patients approached for, declining and taking part in exercise related research activities**

Alongside the quantitative data collection of the pilot RCT, two separate qualitative studies were conducted with separate samples to understand factors that influence recruitment to and involvement in interventions aligned with a clinical pathway. The first study sought to answer the following research questions: what influences the decision making of potential research participants who are approached to take part in exercise research during treatment; do potential participants recall the details of the study adequately and understand what was involved in taking part in the study; and why do potential participants choose not to take part in the pilot RCT? The second study explored: what are the experiences of participants who take part in exercise related research during treatment in relation to assessment and intervention processes; what are their views on being randomly allocated between usual care or intervention; and general experiences of undergoing ASCT for myeloma.

2.1.3 **Aim 3. To explore the views of haematology health professionals regarding physical activity for patients with haematological cancer**

Research questions explored included: what are haematology health professionals beliefs and understanding surrounding evidence for physical activity among their patients, what proportion of health professionals provide advice about physical activity already and what advice do they provide and is it based on recommended guidelines? There was no published research in this area focussed on health professionals working with haematological cancer patients and it was hypothesised that their levels of knowledge and provision of advice may be similar to that of health professionals working in oncological settings, which has been published (Williams *et al.*, 2015; Keogh *et al.*, 2017; Pugh *et al.*, 2017; Cantwell *et al.*, 2018; Koutoukidis *et al.*, 2018).
Chapter 3  Methods for the PERCEPT trial: a pilot randomised controlled trial of exercise during autologous stem cell transplantation\textsuperscript{1,2}

3.1 Introduction

As covered in the Chapter 1, there exists a small number published studies assessing the feasibility of conducting exercise interventions among people with haematological cancer, deeming it to be safe and acceptable. There is a large gap in this evidence base in terms of studies conducted among the UK population and more specifically among myeloma patients before or during stem cell transplantation. Importantly, there is a dearth of literature that describes how or if these interventions were conducted alongside or integral to the clinical pathway which the study samples are also experiencing. Therefore, it was felt appropriate and proportionate to conduct a pilot RCT of the intended intervention, focussing on the feasibility of conducting the exercise intervention and research evaluation in a UK sample, as well as the practicalities of introducing such an intervention within the existing clinical pathway. This chapter will outline the methods for the PERCEPT trial, a pilot randomised controlled trial (RCT) of an exercise prehabilitation and rehabilitation intervention, led by a physiotherapist, carried out across the continuum of autologous stem cell transplantation (ASCT) treatment among people with myeloma.

This trial was designed with the clinical pathway at the centre of delivery so that the intervention could be embedded within it. The Medical Research Council (MRC) guidance for developing and evaluation complex interventions describes a complex intervention as one that contains several interacting components, that involve behaviours required by both those delivering and receiving the intervention, a number of outcomes and variability of those outcomes, and elements of flexibility or tailoring

\textsuperscript{1}The original protocol for the trial has been published (Appendix A), McCourt O, Fisher A, Ramdharry G, Roberts AL, Land J, Rabin N & Yong K (2020). PERCEPT myeloma: a protocol for a pilot randomised controlled trial of exercise prehabilitation before and during autologous stem cell transplantation in patients with multiple myeloma. \textit{BMJ Open}, 10(1), e033176.

Figure 3.1 Mapping of existing myeloma autologous stem cell transplant clinical pathway in relation of study recruitment and assessment timeline
required of such intervention (Craig et al., 2008). The pilot RCT and associated qualitative studies were developed to address key elements of the MRC framework—principally ‘feasibility/piloting’ and ‘evaluation’. Use of this framework and more recent consensus based literature building on the framework underpinned study design and evaluations (O’Cathain et al., 2019). Central to developing the study design was mapping the existing clinical pathway and determining how the intervention and evaluation could best fit into the structures and constraints already established by the clinical pathway. This mapping informed decision making on recruitment procedures, study assessment time points as well as choice of outcome measures. Figure 3.1 shows a graphical timeline of the ASCT clinical pathway, mapped through input from the consultant lead for the myeloma transplant service at University College London Hospitals NHS Foundation Trust (UCLH), alongside the final study timeline.

As a pilot trial, feasibility measures were the primary outcomes. In order to identify a primary endpoint for a future powdered trial, a selection of secondary outcomes were assessed. Secondary outcomes were chosen based on those evaluated in previous exercise oncology research studies and measures were selected based on their validity, reliability and practical application within the clinical environment.

### 3.1.1 Study design changes due to the novel coronavirus (COVID-19) pandemic

During the restrictions introduced by Government and the NHS in March 2020, study recruitment was temporarily paused and no new participants were recruited between March and July. ASCT clinical services were paused for approximately three months. From late June 2020, ASCT clinical activity recommenced with an adjusted clinical pathway in response to the clinical and logistical restrictions in place to mitigate risks still imposed by the ongoing threat from the COVID-19 pandemic. Changes to the pre-COVID-19 clinical pathway meant that major amendments to the study were required in order to continue to target recruitment, using a virtual approach for ongoing recruitment and intervention delivery. The virtual approach was incorporated to reduce unnecessary travel, contact and use of hospital sites as per trust and clinical team policies and allowed assessment of feasibility of both a face-to-face and virtual approach to prehabilitation delivery as part of myeloma ASCT care. Where changes to the original
trial procedures were made in response to the pandemic they will be detailed as a subsection within the relevant sections of this methods chapter.

3.2 Study design

The PERCEPT myeloma study was a pilot RCT with two arms; an intervention arm and a usual care control arm of participants with a diagnosis of myeloma, undergoing treatment with ASCT at UCLH. Originally it was proposed that that approximately 60-75 patients would be recruited over a 15-18 month period, with completion of final (T3) follow-ups within 18-21 months. This recruitment target was conservatively estimated based on the approximate number of myeloma patients referred for ASCT at UCLH each year. No formal sample size calculation was undertaken. The trial was prospectively registered on the ISRCTN registry (ISRCTN15875290).

The trial protocol also included two embedded qualitative interview studies: a decliners study exploring approached participants’ reasons for declining to take part in the trial; and a completers study exploring the experiences of participants from both trial arms who participated in the trial. The qualitative methods utilised have been described in detail in Chapter 4.

3.3 Ethical approval

Full Health Research Authority approval for the original study protocol was provided by London – Camden & Kings Cross Research Ethics Committee (REC) (reference 19/LO/0204) and confirmation of capability and capacity to commence recruitment to the study was obtained in June 2019. In response to the COVID-19 pandemic in March 2020 a non-substantial amendment to pause recruitment and proceed with postal follow-up procedures was approved by the sponsor. Further changes were made to continue the study with virtual enrolment and consent processes, assessment procedures and delivery of a partly supervised intervention delivered via an online platform Zoom. These changes required a substantial amendment, which was given favourable opinion from the REC in August 2020 (reference 18/0552 Amendment SA1). Study approval letters are included in Appendix C and D.
3.4 Participants

All patients with a diagnosis of myeloma referred to UCLH for consideration for ASCT were identified through discussion with the clinical multidisciplinary team (MDT) responsible for coordinating treatment for patients with myeloma, and the team included the medical team and clinical nurse specialists (CNSs). Potential participants were receiving chemotherapy treatment under the care of UCLH or their local haematology team as either first line, induction therapy following diagnosis or as a subsequent line of therapy following relapse and were referred for consideration for their first or second transplant. Some participants identified were awaiting a tandem ASCT, where they had already received a recent ASCT and were to undergo a second ASCT, usually between 3 and 6 months following their initial one, as management of high-risk myeloma. Potential participants were screened using the following inclusion and exclusion criteria.

3.4.1 Inclusion criteria:

- Adult patients referred to the UCLH transplant MDT and awaiting ASCT as treatment for myeloma.
- Clinically able to carry out an exercise training programme on a regular basis.
- Patients must have a good command of written and spoken English.
- Patients must have access to and ability to use internet based video conferencing platform, or a family member who can facilitate access.  
- Willing and able to provide written informed consent.

3.4.2 Exclusion criteria:

- Patients with known spinal instability, spinal cord compression or neurological deficits.
- Those who have had recent (within six weeks) spinal surgery or other surgery for pathological fractures.
- Abnormal resting echocardiogram and/or unstable angina.
- Those deemed unsuitable to partake by the MDT.

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3 This additional criteria was added for amendment to virtual protocol.
• Unable or unwilling to undertake a virtual exercise programme on a regular basis.
• Unable or un-willing to provide informed consent.

Additionally, participants were excluded from the virtual protocol if they already had a date for admission for ASCT within four weeks of being approached.

3.5 Recruitment, randomisation and concealment

All patients with a new referral to the ASCT team coming into a clinic appointment that week, were contacted ahead of their appointment by OM. During an initial telephone call to introduce the study, patients who were interested provided an email address to receive the participant information sheet (PIS) and OM arranged to follow up with them in person during their clinic visit that week. This allowed participants at least 24 hours between approach and follow-up approach to consider participation. If participants were agreeable to take part, then study consent and baseline assessment was conducted during the clinic visit or subsequent UCLH hospital appointment visit. Written, informed consent was obtained from participants, in person after completion of study screening tool by OM, the research physiotherapist or a delegated member of the research team in line with Good Clinical Practice.

All participants who provided written informed consent and had undergone a baseline assessment were randomised. Participant randomisation was undertaken centrally at UCL by a colleague independent of the study using minimisation, with age and gender as the stratification factors, via the free, open source computer software program MinimPy. Group allocation of participants was communicated with the study physiotherapists by the UCL colleague undertaking randomisation. The study physiotherapist then contacted the participants to notify them of their allocation and arrange for the intervention group participants to attend their first exercise gym session at UCLH. This process allowed blinding of OM in line with the original study protocol.

3.5.1 Protocol amendments for virtual study: recruitment

Due to substantial changes to the ASCT clinical pathway related to the COVID-19 pandemic, patients were mostly receiving telephone appointments with the medical
team and were listed for ASCT admissions based on clinical priorities. Therefore, following approval of the study amendment and recommencement of the ASCT programme, potential participants were identified from a database of patients listed and waiting for ASCT admission and contacted in no particular order, rather than approaching patients consecutively on referral each week. Following a telephone call to introduce the study, provision of the PIS by email and after adequate time, participants who agreed to take part were posted consent forms and study assessments.

Randomisation continued using MinimPy software however, the software was not accessible remotely and due to rules limiting non-essential travel into workplaces a person independent of the study could not carry out the randomisation and it was conducted by OM. This meant that blinding of allocation from OM was no longer possible.

3.6 Study assessment procedures

Study assessments took place at four timepoints mapped to the typical ASCT clinical pathway at UCLH: on enrolment at a routine clinic visit approximately eight weeks prior to scheduled ASCT admission (T0); on admission to UCH for ASCT (T1); the day before or day of discharge from hospital following ASCT (T2); and finally 3 months after ASCT during a routine clinic visit (T3) (see Figure 3.1). The schedule of study assessments for the original protocol is presented in Table 3.1.

3.7 Outcome Measures

3.7.1 Demographics and clinical history

Following confirmation of informed consent and enrolment into the study participants’ were asked to self-complete a questionnaire related to demographics. Information on gender, ethnicity, social situation (marital status, living arrangements), education, and employment was sought. Disease activity history, comorbidities and concomitant medications were accessed from electronic hospital medical records and discussed with the participants for confirmation of accuracy. Comorbidities information was used to complete the Charlson Comorbidity Index, the Katz Index of Activities of Daily Living (ADL) and Lawton Instrumental ADL scales were self-completed by participants (Lawton,
1988), and combined with age, these measures allowed categorisation of participants as ‘frail, intermediate-fit or fit’ using the International Myeloma Working Group (IMWG) Frailty Score (Palumbo et al., 2015).

### 3.7.2 Primary outcomes - feasibility

#### 3.7.2.1 Recruitment rate and uptake

Recruitment rate was calculated using the number of potential participants screened as eligible to approach and the number of those who consented to take part and were randomised. The number of potential participants identified and screened for eligibility was also recorded. A target recruitment rate of >50% of potential participants screened as eligible and approached was decided a priori as a primary indication of feasibility (McCourt et al., 2020).

#### 3.7.2.2 Attrition

Attrition rate was derived by dividing the number of withdrawn participants (calculated as the number of people retained in the study subtracted from the total number randomised) by the number originally randomised. Attrition is presented as number and proportion of participants lost from the study between T0 and T1, and between T0 and T3.

#### 3.7.2.3 Adherence and acceptability of the intervention

Attendance of supervised exercise sessions and telephone-based support sessions are presented using median, interquartile range and range. The number and proportion of participants randomised to the intervention group who attended at least one supervised session or telephone contact with the physiotherapist is also reported. The number of weeks available to receive the prehabilitation intervention (pre-ASCT phase) was calculated as the number of weeks between randomisation and admission for ASCT for each participant.
<table>
<thead>
<tr>
<th>Visit No:</th>
<th>Screening</th>
<th>Baseline Assessment (T0)</th>
<th>Follow up 1 (T1)</th>
<th>Follow up 2 (T2)</th>
<th>Follow up 3 (T3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>On referral to UCLH ASCT MDT</td>
<td>On day of first transplant clinic appointment</td>
<td>Day of transplant</td>
<td>Day of discharge from hospital</td>
<td>Post-transplant follow-up clinic at 3 months</td>
</tr>
</tbody>
</table>

Table 3.1 Study schedule of assessments (original protocol)

- **Qualitative Interview (~20 patients who decline study)**: X
- **Window of flexibility for timing of visits**: +/- 2 days 0+/- 1 day 0+/- 1 day +/- 5 days
- **Screening eligibility**: X
- **Informed Consent**: X
- **Demographics & Clinical History**: X
- **Fatigue: FACT-F**: X X X X
- **QOL: EORTC QLQ C-30-MY20**: X X X X
- **QOL: FACT-BMT**: X X X X
- **Exercise Behaviour: IPAQ-SF**: X X X X
- **Exercise Self-efficacy Scale**: X X X X
- **Functional Capacity: 6MWT**: X X X X
- **Functional Capacity: 30s STS**: X X X X
- **Functional Capacity: hand held dynamometry**: X X X X
- **Resting BP and HR**: X X X X
- **Height and weight**: X X X X
- **Accelerometery (3-7 days)**: X X X X
- **Qualitative Interview (20 participants)**: X
- **Health and Social Care Service Use: CRSI**: X
- **Blood Counts**: X X X X
- **Levels of Immune Function (blood)**: X X X X

Table abbreviations: UCLH, University College London Hospitals NHS Foundation Trust. ASCT, autologous stem cell transplant. MDT, multidisciplinary team. FACT-F, Functional Assessment of Chronic Illness Therapy Fatigue questionnaire. EORTC QLQ C-30-MY20, European Organisation for Research and Treatment of Cancer QOL Questionnaire and myeloma specific module. FACT-BMT, Functional Assessment of Cancer Therapy Bone Marrow Transplantation scale. IPAQ-SF, International Physical Activity Questionnaire short form. 6MWT, six minute walk test. STS, sit to stand. BP, blood pressure. HR, heart rate. CRSI, Client Service Receipt Inventory.
3.7.2.4  Completion of study assessments

In order to assess the acceptability of undergoing physical assessments of functional capacity the numbers of participants who declined or were unable to complete such assessments has been reported for the original face-to-face protocol. For the amended virtual study protocol the number of postal assessment packs sent out and the number returned has been reported, as well as the number of participants who provided a self-completed sit to stand test score.

3.7.3  Secondary outcomes - measures of functional capacity

3.7.3.1  Timed sit to stand test

In the original protocol a 30 second timed sit to stand (STS) test protocol was used and n=35 participants were assessed at baseline using this. Of these, twenty-five completed the study and 10/25 (40%) completed a 30 second timed STS test at all timepoints (Control: n= 6; Intervention: n=4). Following amendment of the study to virtual delivery, a 1 minute timed STS protocol was used with baseline test supervised by OM via video call and follow-up assessment scores were self-assessed by participants and provided on follow-up postal questionnaires. During the supervised baseline 1 minute STS tests the number of repetitions carried out at 30 seconds was also recorded. N=14 participants were assessed using the 1 minute protocol. Follow up assessments for the virtual participants was self-assessed and scores returned on postal questionnaires. Of the fourteen participants with a supervised 1 minute STS test at baseline, eight completed the study but only two (25%) provided follow-up scores at all timepoints both intervention participants.

As good agreement between the two testing protocols has been reported (Morita et al., 2018), a correlation analysis was conducted using number of repetitions completed at 30 seconds and 1 minute from participants who underwent a supervised 1 minute STS protocol at baseline (n=14). The model showed the two variables to be highly correlated (r=1, 95% CI 0.99,1.0, p<.001) and provided an equation to extrapolate a ‘calculated 1 minute STS score’ for participants who were tested using the 30 second STS protocol:
\[ Y = -0.6597 + 2.096 \times X, \]
where \( Y = \) ‘Calculated 1 minute STS score’ and \( X = \) ‘30 second STS repetitions’

Population based reference values for the 1 minute STS test suggest repetitions before the 25\textsuperscript{th} centile for age and sex indicate a below average value, with scores below the 2.5\textsuperscript{th} centile indicative of severely impaired lower body muscular strength and endurance (Strassmann \textit{et al.}, 2013). The 1 minute STS test has been found to be an effective measure in COPD patients undergoing pulmonary rehabilitation with an MID of 3 repetitions (Vaidya \textit{et al.}, 2016; Crook \textit{et al.}, 2017). Another value for minimal detectable change of 4 has been suggested among people undergoing haemodialysis (Segura-Orti & Martinez-Olmos, 2011).

3.7.3.2 \textit{Six minute walk test}

The six minute walk test (6MWT) is a pragmatic, submaximal walking test that measures functional exercise capacity. Designed originally to assess patients with respiratory and cardiac morbidity (Guyatt \textit{et al.}, 1985; Giannitsi \textit{et al.}, 2019), it has been validated in multiple patient populations (Singh \textit{et al.}, 2014) as well as healthy middle-age and elderly populations (Steffen \textit{et al.}, 2002; Camarri \textit{et al.}, 2006; Albright \textit{et al.}, 2014). It has also found to be valid and reliable in cancer patients with distance walked correlating strongly with measures of maximal exercise capacity and measures of physical functioning (Schmidt \textit{et al.}, 2013). 6MWT is the most commonly used measure of functional exercise capacity in exercise intervention studies among stem cell transplant recipients (Abo \textit{et al.}, 2021a).

6MWT was assessed at each timepoint in the original study protocol using procedures as outlined in the guidelines by the American Thoracic Association (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). The tests were carried out after at least 15 minutes seated rest using a 30 metre track marked out in the outpatient clinic area and/or on the haematology wards. Participants were instructed to walk the track and were informed that the object of the test is to walk as far as possible in six minutes. On completion of the time or if the participant stopped before the time elapsed, the total distance walked by the participant was recorded. Participants were asked to provide a rating of perceived exertion using the BORG Rating of Perceived Exertion scale (Borg, 1982) pre- and post-testing. A difference or change of
30.5 meters is considered a minimal clinically important difference (MCID) for the 6MWT across multiple patient populations (Bohannon & Crouch, 2017).

A reference equation for predicting expected 6MWT distance based on age and gender was used to calculate predictive scores for all participants who were tested at T0 (Gibbons et al., 2001).

\[
\text{Predicted 6MWT (meters)} = 868.8 - (age \times 2.99) - (74.7 \times \text{gender})
\]

where gender is “women = 1” and “men = 0”

This reference equation has previously been used to predict 6MWT values in samples of haematological cancer patients (Celik et al., 2022a) including myeloma patients following ASCT (Tuchman et al., 2015). Participant 6MWT scores were also calculated as a percentage of their predicted score. A score less than 80% of predicted 6MWT has been considered abnormal in haematological populations indicating reduced functional capacity (White et al., 2005).

### 3.7.3.3 Hand grip strength

Hand grip strength was assessed using a Jamar dynamometer. Testing was conducted in sitting and three measurements were recorded per hand with adequate rest period between each attempt. The mean of three measurements was used for each hand. Participants self-reported hand dominance during baseline assessment.

Reference equations for predicting expected hand grip strength based on age, gender, height and weight were used to calculate predictive scores for all participants who were tested at T0 (Wang et al., 2018).

\[
\text{Expected hand grip strength for dominant hand (males)} = -29.959 - 3.095 \times 10^{-5} \times \text{age}^3 + 38.719 \times \text{height (meters)} + 0.113 \times \text{weight (kg)}
\]

\[
\text{Expected hand grip strength for dominant hand (females)} = -22.717 - 1.920 \times 10^{-5} \times \text{age}^3 + 30.360 \times \text{height (meters)} + 0.048 \times \text{weight (kg)}
\]

Participant hand grip strength values were also calculated as a percentage of these predicted values. A score <80% of predicted hand grip strength has been considered...
abnormal in haematological populations indicating impaired muscle functionality (White et al., 2005; Smith & Madden, 2016). Changes in hand grip strength of 5-6.5kg indicate a possible MCID (Bohannon, 2019a).

3.7.3.4 Self-reported physical activity and sedentary behaviour – International physical activity questionnaire - short form (IPAQ-SF)

Self-reported physical activity was measured using the IPAQ-SF. Scoring of this instrument was carried out according to IPAQ-SF scoring guidance, including rules for data cleaning and use of truncation to limit of 180 minutes for high values of reported time for each level of activity (IPAQ, 2005). Where a participant selected ‘Don’t know’ answers were coded as missing and excluded for that activity/intensity only. Where ‘0’ was reported for days, then ‘0’ minutes was calculated for that activity/intensity. Total physical activity was calculated as the sum of vigorous, moderate and walking activities and presented as metabolic equivalent time (MET) minutes per week.

The proportion of participants who reported sufficient physical activity to meet recommended levels according to guidelines was computed using syntax. Those meeting guidelines was defined as participants who reported greater than 150 minutes moderate or vigorous activity per week or greater than 30 minutes moderate or vigorous activity on at least five days per week (United Kingdom’s Chief Medical Officers, 2019).

3.7.3.5 Objectively measured physical activity and sedentary behaviour – accelerometry

Objective physical activity was measured using an activPAL accelerometer (PAL technologies, Glasgow, UK). The activPAL is a small device that was fitted with a waterproof dressing to the anterior thigh of the participant at the end of each functional assessment. Participants were instructed to wear the device continuously for seven days. They were requested to keep a record of the time they rose from and went to bed each day on a paper log sheet. Participants were provided with a freepost return envelope in which to return the device and log sheet after removal. Adaptation of study assessment protocols due to the COVID-19 pandemic resulted in objective physical activity data from smaller than planned numbers per group, particularly at follow-up timepoints when accelerometers where not provided following study amendment. In
the virtual protocol participants were sent a preprogramed device with their consent forms and baseline questionnaires, they were assisted to fit the device virtually during the video call with OM. Accelerometers were not sent with follow-up postal assessments.

Data was processed according to published recommendations (Edwardson et al., 2017). Data was considered valid if devices returned with a minimum of three days valid wear time, including at least one weekend day. Data was processed through activPAL analysis software (version 8.11.6.70, PAL Technologies, Glasgow, UK) using proprietary algorithms for defining non-wear time and classification of activity (CREA, v1.3). Average summary outcomes of step count, time spent stepping, time spent sitting, number of sit to stand transitions and total sedentary time were extracted. More sophisticated analysis using raw data from accelerometers was not undertaken therefore calculation of time spent in moderate to vigorous physical activity was not possible.

3.7.3.6 Self-efficacy for exercise

Self-efficacy for exercise was assessed using the 9 item Exercise Self-Efficacy Scale (ESES) (Resnick & Jenkins, 2000). A summary score was calculated if at least three items were completed, scores for all items were summed and divided by number of items answered.

3.7.4 Secondary outcomes – patient reported outcome measures (PROMs)

3.7.4.1 Fatigue

Fatigue was assessed using the Functional Assessment of Cancer Therapy - Fatigue (FACT-F) questionnaire (Yellen et al., 1997). This questionnaire is a 13 item FACT subscale with 5-point response scales for each item. Total FACT-F score ranges between 0 and 52. Higher scores indicate lower levels of fatigue (Webster et al., 2003). Minimally important difference (MID) for the FACT-F have been defined as a change in score of 3-4 (Cella et al., 2002b; Nordin et al., 2016).

3.7.4.2 Quality of life

Quality of life (QOL) was assessed using a number of different outcomes measures. Generic health related QOL was also measured using the EuroQOL EQ-5D-5L
questionnaire. Two questionnaires from the Functional Assessment of Cancer Therapy (FACT) measurement system; the FACT-G general QOL base questionnaire and the FACT-BMT transplant-related QOL subscale. The FACT-G and FACT-BMT, together with the European Organisation for Research and Treatment of Cancer (EORTC) core QOL questionnaire measured multiple domains and provide global and summary scores for cancer-related QOL.

**EuroQol EQ-5D-5L Questionnaire**

The EQ-5D-5L is a generic health-related QOL instrument incorporating five dimensions of health status; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five response levels (‘no problem’, ‘slight problems’, ‘moderate problems’, ‘severe problems’ and ‘unable or extreme problems’). The EQ-5D-5L also incorporates a visual analogue scale (VAS) of overall health state and the instrument can be summarised by a utility or index score calculated from a population-based value set. The EQ-5D-5L VAS of overall current health provides scores ranging from 0-100 where 0 equals ‘worst health you can imagine’ and 100 equals ‘best health you can imagine’, which provides a quantifiable measure of an individual’s perception of their overall health. MID for the EQ-5D-5L VAS scores have been estimated using anchoring against performance status ratings with a change between 8-12 considered important (Pickard et al., 2007).

**Functional assessment of cancer therapy – general questionnaire**

The FACT-G is a validated, reliable QOL questionnaire commonly used in cancer studies (Cella et al., 1993). The FACT-G base questionnaire consists of 27 items with 5-point response scales for each item (‘Not at all’, ‘A little bit’, ‘Somewhat’, ‘Quite a bit’ and ‘Very much’). Within the FACT-G there are four subscales measuring different domains of QOL; physical, social/family, emotional and functional well-being. The sum of the four subscales provides a summary total FACT-G score. FACT-G total score range is 0-108 with higher score indicating better QOL. A change in FACT-G total score of 5-7 points has been described as MID (Cella et al., 2002a).
When combined with the FACT-G general base questionnaire, the FACT-BMT symptom subscale provides a specific measure of QOL that has been recommended for use in transplantation related clinical trials (McQuellon et al., 1997). Version 4 of the FACT-BMT subscale used in this study consists of 23 items with the same 5-point response as the FACT-G. Although it is recommended to administer the complete FACT-BMT subscale questionnaire, only ten items are used to provide a summary score of the subscale. The FACT-BMT subscale score ranges from 0-40 and is combined with the FACT-G subscale to provide an overall summary score of QOL (FACT-BMT total score) and a separate trial outcome index (TOI) score.

The FACT-BMT total score is the sum of the domains of the FACT-G (physical, social/family, emotional, and functional well-being) plus the ten item transplant symptom subscale. The FACT-BMT total score ranges from 0-148, with higher score indicating better QOL. A mean difference of 2-3 on the FACT-BMT subscale is associated with a one point change in performance rating and therefore considered a MID. When combined with the MID of 5-7 for the FACT-G then a mean change in the range of 7-10 would be considered meaningful for the FACT-BMT total score (McQuellon et al., 1997; Cella et al., 2002a).

The FACT-BMT TOI score is the sum of two domains from the FACT-G (physical and functional well-being) plus the FACT-BMT symptom subscale, which results in scores ranging from 0 to 96. It is considered a precise and sensitive measure of transplant treatment effects recommended for use as a summary QOL measure in clinical trials (McQuellon et al., 1997). Literature review failed to identify any published MID for the FACT-BMT TOI. In the situation where there is no reported MID for a health related QOL instrument, then MID for QOL instruments can be defined as half of the population standard deviation (Norman et al., 2003) and this approach has been used previously to define MID in FACT-BMT TOI (Pidala et al., 2011; Kurosawa et al., 2017). The FACT-BMT TOI standard deviation for the whole study sample at T0 was 14.1, therefore MID was defined as 7 and equals the value used by a BMT trial also using this approach for defining MID (Pidala et al., 2011).
EORTC QLQ-C30 is a generic QOL instrument designed for people with cancer, which includes five functional scales (physical, role, emotional, cognitive and social functioning), nine symptom specific scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and a global QOL scale (Aaronson et al., 1993). The EORTC consists of 28 items with a 4-point response scale for each of the functional and symptom items (‘Not at all’, ‘A little’, ‘Quite a bit’ and ‘Very much’) and two additional items for global QOL with 7-point numeric scale ranging from 1-7. Scores for the scales range from 0-100 with higher score indicating higher levels of QOL or higher levels of symptomatology. The MID for the EORTC global QOL scale suggested for people with myeloma is a change between 8-12 points (Kvam et al., 2010; Kvam et al., 2011).

A EORTC QLQ-C30 summary score can be calculated from the mean of 13 of the 15 QLQ-C30 scales, excluding the global QOL scale and the financial impact scale (EORTC, n.k.). The summary score is considered to be a more reliable, meaningful and robust measure of QOL and more sensitive to detecting group differences in QOL over time than the global QOL scale alone (Giesinger et al., 2016; Pompili et al., 2018; Kasper, 2020). As no published MID for EORTC-QLQ-C30 summary score was found during literature search, the method for defining MID as 0.5 of standard deviation of the study population has been used and MID is defined as a change in score greater than 8.6.

### 3.8 Exercise intervention and control group

This trial compared a group of patients who received an exercise intervention and a control group that received the current usual hospital care among people with myeloma before ASCT.

#### 3.8.1 Intervention Group

The exercise intervention included aerobic and resistance exercises across 3 phases of ASCT treatment.

In phase 1, for an estimated 8 weeks (or longer) prior to admission to UCLH for ASCT (8 supervised sessions approximately) participants were asked to exercise three times per
week. One session supervised by a physiotherapist in a hospital gym and two other sessions carried out at home independently. Participants were provided with resistance exercise bands and intervention booklets which included log sheets (Appendix E) and asked to record what exercise they undertook. The intervention exercise programme was first introduced to the participants in the initial gym session by the physiotherapist. The participants were familiarised with the gym environment and equipment and made aware of safety considerations when exercising, including when to cease exercise. Each element of exercise was individually tailored by the physiotherapist to the participants considering baseline fitness, exercise experience and adapted in response to any symptoms or impairments.

In phase 2, during hospital admission, immediately after their stem cell transplant, the exercise participants received telephone contact from the physiotherapist. It was anticipated that participants would be symptomatic from the effects of their ASCT, which may include thrombocytopenia (low blood count levels), nausea, gastrointestinal complaints and fatigue, therefore the exercise intervention was highly individualised and tailored according to each participant’s capacity to carry out exercise. The study physiotherapist would consult the haematology medical team ward regarding the status of a participant. Participant medical notes and clinical observation chart was reviewed prior to exercise. Precautions and contraindications related to blood count for commencing the supervised exercise sessions on the hospital ward are detailed in Table 3.2.

In phase 3, for 3 months after discharge from hospital the participants were asked to continue exercising at home three times per week independently and received one call per week from the physiotherapist. They were instructed to continue the exercise programme, tailored to their fitness on discharge, independently at home. They received contact from the physiotherapist to provide support and guidance with returning to regular exercise during their recovery and to assist them in overcoming barriers to exercise and to progress the exercise. The participants were encouraged to aim towards engaging in sufficient physical activity to meet recommended guidance (United Kingdom’s Chief Medical Officers, 2019) and requested to record any exercise undertaken in their intervention booklet.
Table 3.2 Precautions and contraindications for exercise during hospital admission (adapted from Santa Mina et al (2018))

<table>
<thead>
<tr>
<th>Clinical Measure</th>
<th>Reference range</th>
<th>Consideration &amp; actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets*</td>
<td>150-400x10^9/L</td>
<td>Platelet count will drop following ASCT. Count 20-150x10^9/L exercise as tolerated, monitor for bruising and bleeding. Count &lt;20x10^9/L – doctor’s clearance, functional mobility exercises, monitor for bruising and bleeding. *any patient with a documented platelet target in their medical records must have a platelet count above target range to exercise.</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Men 140-180 g/L; Women 120-160 g/L</td>
<td>Level &lt;80 g/L is a relative contraindication to exercise, low to moderate intensity exercise only, with doctor’s clearance. Monitor for signs of fatigue and exertion, adjusting exercise accordingly.</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2.0-7.5x10^9/L</td>
<td>Count &lt;1.0x10^9/L (neutropenia) or fever (oral temperature &gt;38°C) relative contraindications to exercise, low to moderate intensity exercise only. High risk of infection. All equipment must be sanitised before use and importance of handwashing reinforced to participants</td>
</tr>
</tbody>
</table>

3.8.1.1 Aerobic exercise

Aerobic exercise comprised of walking, stationary cycling or using a cross-training machine in the gym setting. In the home setting participants were encouraged to use walking as their aerobic exercise, or a stationary bike or cross-training machine if they had access to one. Participants were given a tailored and progressive exercise prescription taking into consideration the phase of ASCT treatment and participants’ individualised symptoms.

Aerobic exercise intensity was determined using percentage of heart rate reserve calculated using the Karvonen formula.

\[
\text{Target Heart Rate} = [(\text{max HR} - \text{resting HR}) \times \% \text{ intensity}] + \text{resting HR},
\]

where maximum heart rate = 220-age (Karvonen et al., 1957)

Duration started at 15 minutes and progressed by 5 minutes per week to achieve a minimum of 30 minutes by week 3. This was further progressed to 40 minutes by week
5. Participants were instructed to carry out a five-minute warm up, followed by a bout of aerobic exercise according to the week of the intervention.

Table 3.3 Aerobic exercise intensity and duration per week

<table>
<thead>
<tr>
<th>Week</th>
<th>Target heart rate</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60-80%</td>
<td>15 minutes</td>
</tr>
<tr>
<td>2</td>
<td>60-80%</td>
<td>20 minutes</td>
</tr>
<tr>
<td>3-4</td>
<td>60-80%</td>
<td>30 minutes</td>
</tr>
<tr>
<td>5-8</td>
<td>60-80%</td>
<td>40 minutes</td>
</tr>
</tbody>
</table>

Heart rate was monitored throughout using heart rate belts linked to a wrist worn monitor. To support monitoring of correct exercise intensity at home, patients were instructed on how to report their rating of perceived exertion (RPE) using the Rating of Perceived Exertion Scale (Borg, 1982). This scale describes levels of exertion. The participants were given a scale in the intervention booklet, instructed in its use, and advised to work to levels of exertion as determined under supervision. Participants were encouraged to reach the target duration in one bout but in the presence of discomfort or wish to change exercise machine/activity then participants were required to complete the target duration in bouts of 15 minutes or more.

3.8.1.2 Resistance exercise

The resistance exercise programme included upper and lower body multi-joint, functional exercises with resistance bands and/or free weights. Both aspects of the intervention were individually tailored to each participant’s ability and progressed to a suitable intensity using Borg RPE Scale and/or heart rate monitoring. Aerobic exercise with resistance exercise has been demonstrated to have a positive effect on people with haematological cancer during and after treatment, but there is no clear consensus on what intensity or duration of exercise is most effective (Bergenthal et al., 2014), therefore the intervention in this study was adapted from the intervention used in a survivorship trial at UCLH, which was acceptable to myeloma patients in plateau phase of their disease, following treatment (Groeneveldt et al., 2013; Koutoukidis et al., 2020).

A number of the exercises was prescribed to target all major muscle groups (depending on individual health and contraindications). Elastic resistance bands of various strengths
were supplied to participants at the start of the study to allow convenient home-based resistance training. Starting resistance and repetitions of the exercises was informed by a 10-repetition maximum assessment carried out by the study physiotherapist during the first supervised session. Gradual progression in resistance training was prescribed as deemed appropriate at each exercise session by the study physiotherapist. Progression was achieved by increasing the weight/resistance/strength of band and/or the number of repetitions performed on each exercise. Again, all exercise prescriptions were prescribed and tailored on an individual basis for each patient to ensure suitability and to promote adherence to the program.

3.8.1.3 Behaviour change techniques

An existing theoretical framework for informing effective behaviour change through interventions has informed the development of this component of the intervention. The behaviour change wheel (Michie, 2014) and associated 93-item behaviour change taxonomy (Michie et al., 2013) was used to understand and describe the key components of the intervention delivery in this work. Previous systematic reviews and meta-analyses have shown the behaviour change techniques (BCTs) that are associated with improved adherence to exercise by cancer survivors include ‘goal setting (behaviour)’, setting ‘graded tasks’, and ‘instruction of how to perform behaviour’ (Bourke et al., 2013; Turner et al., 2018), practice and self-monitoring and encouraging participants to attempt to generalise exercise behaviours learnt in supervised exercise environments to other, non-supervised contexts (Hobbs et al., 2013).

Elements that are associated with improved adherence to exercise by cancer survivors include as goal setting, prompting practise, self-monitoring and encouraging participants to attempt to generalise behaviours learned in supervised exercise environments to other, non-supervised contexts. Repetition of behaviour in a consistent context increases the likelihood of it becoming ‘automatic’, requiring minimal willpower or effort to continue engagement. Facilitating formation of a regular exercise routine with specific times and days and environments may increase the automaticity of exercise, increasing the chance of long-term maintenance (Bourke et al., 2013; Hobbs et al., 2013; Turner et al., 2018).
To complement the individualised exercise intervention and enhance likelihood of long-term maintenance, the intervention programme and sources were developed and coded according to the BCT Taxonomy v1. Strategies to promote adherence to the intervention and promote change in exercise behaviour were mainly incorporated into delivery through input from the physiotherapist and provision of resources. Behaviour change techniques incorporated into the intervention delivery include use of goal setting, problem solving and self-monitoring through use of intervention booklets, as well as behavioural practice, habit formation and generalisation of behaviour. See Table 3.4 for incorporated BCTs and examples of how they have been mapped to related components of the intervention. Use of the taxonomy for mapping specific components of the intervention has been described in the published protocol (McCourt et al., 2020) (see Appendix A).

Physiotherapists who delivered the intervention received training, clinical supervision and were provided with a standard operating procedure to carry out the intervention and support the participants to exercise and incorporate BCTs into intervention delivery. The physiotherapists supported participants to plan how they would exercise more independently before their transplant and during their recovery post-discharge from hospital following transplant.

3.8.2 Control group (usual care)

Participants randomised to usual care received the usual advice provided by haematology clinical nurse specialists. Participants who specifically asked for exercise advice from members of the research team were directed to generic physical activity advice offered for people undergoing cancer treatment on the Macmillan Cancer support website or support service within UCLH.

During hospital admission, patients undergoing SCT are routinely screened by a hospital therapists and receive input for any functional or mobility related deficits that may prevent or delay hospital discharge. All participants within the study who were referred for physiotherapy or occupational therapy during their hospital admission received input as per clinical delivery. The indication for and details of input required was recorded in the study file for enrolled participants who received additional therapy input.
<table>
<thead>
<tr>
<th>BCT Label</th>
<th>BCT No. (BCTT v1)</th>
<th>Component of Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal setting (behaviour)</td>
<td>1.1</td>
<td>Overarching goal of exercise programme for all participants is to exercise 3 times per week. Participants also supported to define own personal sub-goals, which are recorded in log book.</td>
</tr>
<tr>
<td>Problem Solving</td>
<td>1.2</td>
<td>Enablers, barriers and solutions to barriers completed with physiotherapist and recorded in log book. Problem solving with physiotherapist if discrepancy between current behaviour and goal is identified.</td>
</tr>
<tr>
<td>Action Planning</td>
<td>1.4</td>
<td>Attendance at supervised exercise session in gym planned for specific day each week. Participants are also supported to plan independent exercise sessions (e.g. time/day of the week) with physiotherapist. These plans are recorded in log book prior to planned execution.</td>
</tr>
<tr>
<td>Review Behaviour Goal</td>
<td>1.5</td>
<td>Participants review performance of exercise sessions recorded in log book against planned goals, and consider modifying goals accordingly with physiotherapist in supervised exercise sessions.</td>
</tr>
<tr>
<td>Discrepancy between current behaviour and goal</td>
<td>1.6</td>
<td>Physiotherapist informs participant if there is a discrepancy between current behaviour and goal.</td>
</tr>
<tr>
<td>Feedback on behaviour</td>
<td>2.2</td>
<td>Feedback on performance of exercise programme delivered by physiotherapist during supervised exercise sessions (phase 1 and 2) and telephone calls (phase 3).</td>
</tr>
<tr>
<td>Self-monitoring of behaviour</td>
<td>2.3</td>
<td>Participants asked to record exercise carried out each week in log book. Heart rate monitoring used in supervised and independent exercise sessions to monitor behaviour being carried out at target intensity.</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>2.6</td>
<td>Heart rate monitoring of aerobic exercise effort.</td>
</tr>
<tr>
<td>Instruction on how to perform the behaviour</td>
<td>4.1</td>
<td>Supervised exercise sessions with physiotherapist who instructs/teaches participant how to perform behaviour.</td>
</tr>
<tr>
<td>Information about health consequences</td>
<td>5.1</td>
<td>Physiotherapist and log book provides information about effects of exercise for health in context of myeloma.</td>
</tr>
<tr>
<td>Monitoring of emotional consequences</td>
<td>5.4</td>
<td>Participants encouraged to complete weekly reflections in log book.</td>
</tr>
<tr>
<td>BCT Label</td>
<td>BCT No. (BCTT v1)</td>
<td>Component of Intervention</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Information about emotional consequences</td>
<td>5.6</td>
<td>Physiotherapist and log book provide information about effects of exercise on emotional wellbeing.</td>
</tr>
<tr>
<td>Demonstration of the behaviour</td>
<td>6.1</td>
<td>Physiotherapist demonstration and teaching of exercise programme in supervised sessions.</td>
</tr>
<tr>
<td>Behavioural practice/rehearsal</td>
<td>8.1</td>
<td>Exercises taught/demonstrated in supervised sessions are practiced within those sessions and independent sessions (phase 1 and 2).</td>
</tr>
<tr>
<td>Generalisation of target behaviour</td>
<td>8.6</td>
<td>Advice to perform exercise programme, learned in supervised session, in independent sessions, during hospital admission and post discharge.</td>
</tr>
<tr>
<td>Graded tasks</td>
<td>8.7</td>
<td>Progression of exercise sessions throughout exercise period.</td>
</tr>
<tr>
<td>Credible source</td>
<td>9.1</td>
<td>Education and prompting from a physiotherapist with expertise in myeloma/haematology and provided in log book.</td>
</tr>
<tr>
<td>Pros and cons</td>
<td>9.2</td>
<td>Prompts to consider advantages and disadvantages of exercising through discussion with physiotherapist and recording in log book.</td>
</tr>
<tr>
<td>Adding objects to the environment</td>
<td>12.5</td>
<td>Provision of heart rate monitors, resistance exercise bands and exercise programme sheets/log book for use in independent sessions.</td>
</tr>
<tr>
<td>Verbal persuasion about capability</td>
<td>15.1</td>
<td>Verbal support and supervision of physiotherapist to encourage exercise sessions before, during and after transplant treatment.</td>
</tr>
</tbody>
</table>
3.8.3 Adaptations to the intervention during Coronavirus COVID-19 outbreak 
(March 2020-July 2020)

Following restrictions introduced by Government and the NHS in March 2020, study intervention visits ceased for the period under restriction. Participants in phase 1 of the intervention (pre-ASCT) had their ASCT treatment delayed or postponed by their medical teams, most for at least three months in the first instance. A non-substantial amendment to ethical approval was gained to adapt the study in the early stages of the pandemic (Section 3.3).

To ensure the safety of research study participants, all those participants allocated to the intervention group and already undertaking exercise under guidance of the study physiotherapist in Phase 1 of the intervention, were asked if they wished to continue their participation in the study. All participants wished to continue in the study and continued undertaking the exercise programme at home. They had ongoing physiotherapist support via telephone. As the research physiotherapist and myself were redeployed, the intervention telephone support was continued by me. The frequency of the telephone support was reduced to fortnightly or monthly depending on participant preference and continued until they were admitted for their ASCT.

3.8.4 Amendments to the intervention following initial Coronavirus COVID-19 surge for remainder of study (July 2020 onwards)

Continued changes to the pre-COVID clinical pathway meant that further amendments to the trial were required in order to continue to deliver an intervention, whilst reducing unnecessary travel and use of hospital sites as per trust and clinical team policies. Those allocated to usual care continued in the study as per the original protocol. Participants allocated to the intervention arm continued to be supported to undertake an aerobic and resistance exercise programme as detailed previously, with the following procedural differences.

The programme was completely home-based in Phase 1: prior to transplantation. Participants were asked to partake in a once weekly group exercise session, supervised remotely by a physiotherapist, via an online video platform. They were also requested to complete two additional unsupervised exercise sessions each week.
Newly allocated intervention participants were posted resources, including the printed intervention booklet and variety of strengths of resistance bands, and had their first remotely supervised exercise session with the physiotherapist in a one-to-one remote video session. This allowed personalisation and in-depth introduction of the exercise programme. Subsequent remotely supervised sessions took place in a group setting, with a maximum of 6 participants per session. Phase 2 and 3 of the intervention, as described previously, continued as per original protocol. Participants in Phase 3 post-transplant continued to have regular input from the physiotherapist via telephone to continue to increase their physical activity post-transplant.

### 3.9 Statistical analysis

Baseline demographic and disease characteristics of both study groups are presented using descriptive statistics (mean ± deviation (SD), median and inter-quartile range (IQR) and range, or frequencies and proportions). Linear regression analysis was used for continuous variables and Chi squared test was used for categorical variables to examine differences between group characteristics. Primary outcomes of trial feasibility are reported as frequencies and proportions.

Adherence to the intervention in terms of physiotherapy sessions attended are reported as median with IQR. Number of weeks from randomisation to ASCT were calculated to assess number of weeks available for phase 1 of the intervention. For those participants who were withdrawn prior to ASCT admission, number of weeks available for intervention was calculated from date of randomisation to date recorded as withdrawn from the study. These values were rounded down to the nearest whole number to report actual available calendar weeks.

Changes to secondary outcomes over the trial timepoints was explored using linear mixed-effect models (LMEM) for repeated measures to assess within-group and between-group differences in outcomes over time. LMEM was chosen over repeated measures ANOVA as the models use unbiased estimation of missing data, considered missing at random, and result in more comprehensive analysis particularly in small samples (Detry & Ma, 2016). All models included allocation × timepoint as fixed effects and study participants as random effect. As age and gender were stratified for during
randomisation, as well as due to sample size limitations, they were not included within the model as covariates as initially planned in the study protocol. Due to variability in time between baseline (T0) and timepoint 1 (T1), as a result of ASCT delays due to the COVID pandemic, outcomes were examined using scatterplot to explore potential interaction between time between baseline and ASCT and difference in each outcome over this time. Most scatterplots showed differences between group trends indicating that time possibly had a greater effect on one group over the other for some outcomes, therefore time between baseline and ASCT was included in the model as a covariate. Allocation was coded using simple contrast (comparison of intervention with control) and timepoint using repeated contrast (comparing each timepoint to the subsequent timepoint). The LMEM model used maximum likelihood estimation to produce group means and within-group and between-group differences for each timepoint, with 95% confidence intervals (95% CI). Due to the feasibility study design and sample size constraints, significance (p-value) has not been reported for these post-hoc tests. Data was assessed for normal distribution using histograms and QQ plots and consideration of Shapiro-Wilk test for normality. All statistical analysis was conducted using the statistical software package Jamovi (The jamovi project, 2021).

Secondary outcomes of functional capacity were altered during the necessary amendments in response to the COVID-19 pandemic, with some measures discontinued (six minute walk test, hand grip strength testing, accelerometry) and others changed in terms of testing protocol (STS test). Unlike the secondary measures using PROMS/questionnaires which were continued consistently for the study follow-ups, the functional capacity measured altered significantly resulting in very small samples for each measure and smaller numbers of participants completing the same measures for baseline and all follow-ups. Therefore these functional capacity measures are presented descriptively.

The sit to stand testing protocol changed from a 30 second timed STS to a 1 minute STS. Comparison of both testing protocols carried out in patients with COPD reported good agreement between the protocols (r=0.68, p<.001; intraclass correlation coefficient (ICC)= 0.77, 95%CI 0.46-0.9, p<.001) (Morita et al., 2018). This comparison of protocols indicated that the 30 second and 1 minute STS test did not differ significantly in terms of speed of effort, although differences in change in oxygen saturation, heart rate and
fatigue score before and after the two protocols were evident, with the 1 minute STS eliciting greater physiological demand than the 30 second test, as would be expected by a longer test (Morita et al., 2018). Participants in this study undergoing the amended virtual protocol underwent a 1 minute STS testing protocol, with number of repetitions completed at both 30 seconds and 1 minute recorded. Correlation analysis was undertaken on subjects with both a 30 second and 1 minute measure and a prediction equation from the model was used to predict calculated 1 minute measures in other subjects who only underwent a 30 second STS (see Section 3.7.3.1). This extrapolated variable allowed increase sample size of at least one functional measure to analyse possible change over timepoints.

### 3.10 Summary

This chapter has outlined the study methods for the PERCEPT pilot RCT. The results of the trial are reported in Chapter 5, Chapter 6 and Chapter 7. As a wide range of outcomes were included in the study the results have been reported separately to focus presentation and discussion of findings. Chapter 5 will focus on the primary outcomes of feasibility and describe the characteristics of the study sample. Chapter 6 and Chapter 7 report the secondary outcomes assessed during the study, those related to functional capacity and PROMs, respectively.
4.1 Background

Randomised controlled trials (RCTs) are often considered a ‘gold standard’ experimental research design (Begg et al., 1996) and are commonly used to evaluate health care interventions, yet up to fifty percent do not successfully recruit their target sample size without extension of funding and or time (Houghton et al., 2020). Trials delayed by recruitment challenges do not only cost more, but also delay hypothesised benefits from reaching the target population and can lead to misrepresentation of findings (Houghton et al., 2020). As well as reduced target numbers of participants recruited, validity of studies can be compromised by bias introduced into RCTs through selection bias, underrepresentation of participants with particular characteristics, socio-economic background or those with particular interest in the intervention being trialled.

RCTs of behavioural interventions, such as exercise interventions are considered particularly challenging to recruit to with estimated uptake differing depending on recruitment strategies and research setting (Foster et al., 2011). Primary care based exercise trials have reported recruitment rates as low as 10-30% using postal invites (Kerry et al., 2018) with greater success evident in trials that recruit from the same setting as the intended intervention delivery (Foster et al., 2011). A meta-analysis of recruitment and retention of exercise RCTs in people with multimorbidity found the pooled recruitment rate of 21 RCTs to be 74% (95% CI 66%, 83%) (Harris et al., 2021). Specifically in cancer exercise research recruitment rates have been reported to be between 10-44% in solid tumour patient groups (Strandberg et al., 2022) with higher rates reported in those with advanced cancer diagnoses (mean 49%; range 15-74%) (Sheill et al., 2019). Another systematic review including 65 studies, most of which were conducted among women with breast cancer, reported median uptake of 63% [IQR 33-80%], with characteristics related to patients or the exercise programme on trial found to be influential on uptake (Maddocks et al., 2009). Recruitment rates of 50% have been reported in other exercise trials delivered during stem cell transplant (Wood et al., 2016). A previous myeloma survivorship exercise RCT at our centre, which used an
adapted Zelen design, had a uptake of 57% (Koutoukidis et al., 2020). However the single-arm pilot study preceding that RCT recruited 80% of approached patients (Groeneveldt et al., 2013). The lower uptake among participants randomised to the intervention arm of the RCT was explained by participants citing the extra time or travel commitment involved in taking part in the intervention but the reason for such a difference in uptake between the pilot and RCT is not clear. Variations in uptake across trials are possibly related to heterogeneity of study design, recruitment strategies and follow-up procedures but this variation presents uncertainty when planning future exercise oncology RCTs, even those with successful pilots.

Reporting guidelines for research studies, such as the Consolidated Standards of Reporting Trials (CONSORT) guidance (Schulz et al., 2010), advise provision of reasons for potential participants declining or being ineligible in information related to enrolment of a RCT. This information is to allow readers to make an assessment of the representativeness and external validity of study (Moher et al., 2012) as well as the acceptability of the intervention. However, reasons for declining to take part are often provided as brief descriptions without context and do not contribute to understanding peoples’ decision-making in relation to acceptability of the trial design or intervention on offer. Using pilot studies to estimate recruitment rate is important part of establishing feasibility for a larger trial but it is also vital for evaluation of any potential volunteer bias. Exercise trials among cancer patients have reported greater participation from people with higher income, higher educational attainment, those reporting greater levels of social support as well as those who are younger and experiencing lower levels of fatigue and distress than non-participants (Strandberg et al., 2022). Identifying why differences between participants and non-participants may occur is important for ensuring appropriate targeting of interventions and determining generalisability of their evaluations (Normansell et al., 2016).

This qualitative study embedded within the recruitment process of the PERCEPT pilot RCT was incorporated to contribute to understanding possible issues with recruiting to an exercise study of this kind, taking place during intensive treatment for myeloma and will inform the planning of future research should the pilot trial progress to a full trial, or if recruitment was deemed not feasible.
4.2 **Aim**

The aim of this study was to explore the experiences of myeloma patients referred to a specialist centre for consideration for autologous stem cell transplant (ASCT) who were approached to take part in the PERCEPT trial but declined. Engagement with and understanding of study information as well as reasons for declining to take part were explored. As the research study that participants had been initially approached for was an exercise study, their experiences of discussing physical activity with healthcare team since diagnosis was also investigated.

4.3 **Methods**

4.3.1 *Ethical approval*

Ethical approval for this study was obtained as part of the NHS Health Research Authority approval for the PERCEPT myeloma transplant prehab study from the London – Camden & Kings Cross Research Ethics Committee (REC reference 19/LO/0204). See letter confirming favourable opinion in Appendix C.

4.3.2 *Participants and Procedure*

Participants were exercise trial ‘decliners’, who were deemed eligible to take part and were sent a participant information sheet (PIS) about the trial but ultimately declined. After initial approach, time to consider and confirmation that they did not wish to take part in the trial, participants were asked if they would be willing to participate in a qualitative interview discussing their reasons for declining. In line with HRA ethical committee approval, these participants were asked to complete a consent form (see Appendix F) which had a specific check box for those who did not wish to take part in the trial but consented to a decliner interview. Initially participants were offered a choice between participating in a face-to-face interview during a routine visit to the myeloma clinic or by telephone at a time convenient to them. As the study progressed participants were only offered telephone interviews as access to private space within the clinic environment to conduct face-to-face interviews was limited. Interviews were conducted between June 2019 and January 2020. All interviews took place prior to declaration of the coronavirus pandemic. The interviews were audio recorded, fully
anonymised and transcribed verbatim by a professional transcription service. Participants were not offered any incentives for participation.

4.3.3 Interview schedule

The interviews were conducted using a semi-structured interview guide (see Appendix G) developed as part of the PERCEPT trial protocol. The interview guide was developed to explore the myeloma patients’ reasons for declining to take part in the exercise trial, to gather information on their understanding of research processes and their experience of being approached, receiving the trial PIS and insights on decision making for not taking part in research of this kind. The guide also included questions exploring any experience of receiving information about physical activity since diagnosis and their opinions on physical activity or exercise since being approached for the trial.

4.3.4 Analysis

Demographics of the participants were collected from medical notes. In order to provide context for understanding the geographical challenges explored in the study, distances between each participant’s home and the specialist cancer centre at UCLH were calculated by shortest estimated land route using an online mapping tool (https://www.freemaptools.com/distance-between-uk-postcodes.htm). Another online mapping tool (https://www.carcaptain.com/postcodes-within-the-m25-london/) was used to distinguish where participants’ home addresses were located in relation to the Greater London area capturing regional context.

4.3.4.1 Reflexive Thematic Analysis

Analysis of the dataset was undertaken using thematic analysis (TA). TA is distinguishable from other approaches in that it is not aligned to one particular theoretical framework or required methodological constraints such as those of grounded theory. It incorporates procedures and underlying research values that are fully qualitative (Braun & Clarke, 2021) and is considered a robust method for novice qualitative researchers but an approach that can potentially result in nuanced, interpretive and complex analysis (Braun et al., 2016). Although TA is considered theoretically flexible, this does not permit the exclusion of a theoretical basis for the
analysis undertaken. Any qualitative analysis requires consideration of theoretical choices and acknowledgment of assumptions determined by those choices within the analysis (Braun & Clarke, 2021). TA offers researchers, particularly those working across disciplines or within mixed-methods research, an analytic process through which patterns of meaning (“themes”) can be identified and interpreted across a dataset but it does not specify particular ontological or epistemological philosophical underpinnings (Braun & Clarke, 2021). Not to be considered atheoretical, instead TA (particularly “reflexive TA” as described by Braun and Clarke (Braun & Clarke, 2006; Braun & Clarke, 2013)) requires the researcher to take an active role in choosing how they ground their approach to engaging with and interpreting the data (Braun et al., 2016) and be explicit in describing their ontological or epistemological positioning through which their analysis is conducted (Braun & Clarke, 2013).

Analysis using reflexive TA is an iterative process involving six phases (1. Familiarising with the dataset; 2. Coding; 3. Generating initial ideas; 4. Developing and reviewing themes; 5. Refining, defining and naming themes; 6. Writing up). The analysis process requires moving through these method stages, not necessarily in a direct or linear way but through moving forwards and possibly back, through the stages to conceptualise the themes from the dataset. The interaction between the theoretical assumptions, professional or disciplinary knowledge and experiences, research skills and the data itself enables meaning to be drawn through the analysis. Themes are then described and interpreted in a number of different ways to draw meaning and importance from the data (Braun et al., 2016).

The interviews were listened through repeatedly for familiarisation with the content and to check the transcripts for accuracy. They were then analysed inductively through repeated reading and assignment of coding labels to the text. A second researcher (Dr Abigail Fisher; AF) double coded two (11%) of the transcripts. Double-coded transcripts were discussed for agreement of coding. Memos and notes were recorded throughout the coding phase which informed and confirmed ideas generated through engaging with the data. The initial codes were then grouped into sets related to broader content, mapped and linked before less analytically relevant codes were discarded. Repeated rounds of analysis were carried out iteratively revising and discarding codes and sets
until the themes and subthemes were developed and described. Data analysis was conducted using NVivo (version 12. QSR International Pty Ltd.).

4.3.4.2 Role of researcher

Central to the method of reflexive TA is the position of the researcher and the active choices they make while engaging with the data. “Reflexivity in a research context refers to the process of critically reflecting on the knowledge we produce, and our role in producing that knowledge” (Braun & Clarke, 2013). As the researcher is part of the social world in which they are investigating, then they must seek to understand how they influence and are influenced by it (Maxwell, 2018). The subjectivity of the researcher informs the whole qualitative research process from conceptualisation of the research questions and choice of data collection methods, through the analysis of the dataset and the interpretation of its findings (Braun & Clarke, 2021).

Although ‘subjectivity’ from positivist-empiricist viewpoint of research instils a notion of ‘bias’ and something that should avoided in research in the quest to remain ‘objective’, it is argued that this cannot be the case within qualitative research (Maxwell, 2018). It should be acknowledged that the perspective of the researcher, their professional and personal beliefs, research and clinical values should serve as contributory resources to the research and inevitably the influence of the researcher is just one of numerous influences on the research process and should be viewed positively within the qualitative paradigm (Braun & Clarke, 2013; Maxwell, 2018). However, this subjectivity of the researcher can have ramifications on the validity of research results if data collection and analysis are purely based on personal ambitions or commitments to ideas/theories without critical assessment of the influence of these upon their findings. This is where importance needs to be placed upon effective reflexivity and reflective analysis by the researcher throughout the research process, unearthing and understanding the influences of their beliefs, values and prior experiences and the interaction of these with those of the participants (Maxwell, 2018). Reflexivity requires continual critical assessment by the researcher on the knowledge they produce and their role in producing the knowledge, both functionally (reflecting on the research tools and process may influence the research) and personally (bringing themselves into the research, becoming a visible part of the process). The latter should involve
acknowledging who they are as a researcher and how that may shape the research (Braun & Clarke, 2013).

4.3.4.3 Position/lens – critical realism

Alongside reflexivity, qualitative data analysis also requires deliberate and considered choice of ontological and epistemological frameworks that will underpin the methods of data collection and the findings generated from that process. Ontological principles refer to the believes and understandings about the state of being and the relationships that exist between the world and our understanding of that world. Epistemological principles relate to theories of knowledge generation and what is considered valid or accepted knowledge and how it is produced (Braun & Clarke, 2013).

My ontological orientation is one of realism (belief that the study, the process of being approached to take part, given a PIS and followed up in clinic to consent, exist in a real world way, independently of any perceptions or constructions) with an epistemological orientation of constructivism (that peoples’ understanding of the study, the approach and their reasons for not taking part are shaped by their prior experiences and assumptions). Therefore the onto-epistemology of critical realism has been chosen as the underpinning framework for the qualitative work in the thesis. Broadly, critical realism is considered to encapsulate a variety of positions that bring together ontological realism with epistemological constructivism (Maxwell, 2018) with an assumption of an ultimate reality, that is understood and interpreted through personal, historical and social framing (Maxwell, 2018; Mukumbang, 2021). Therefore the meanings and beliefs held by participants are considered part of the reality that the research aims to understand although distinct from observational elements considered ‘real’ epistemologically (Maxwell, 2018).

Critical realism also places an importance upon context in the role of understanding causal interactions (Maxwell, 2018). Individuals are considered to possess generative powers, that when interacted with social structures can result in individual actions. These actions resulting from generative powers can be critically interpreted as mechanisms through which causality may be explained. However, there is an emphasis within the literature that these powers are reliant on context and it is the context that has the potential to change the actions and therefore any proposed mechanism
(Maxwell, 2018; Mukumbang, 2021). Qualitative analysis through a lens of critical realism focused on a particular context, such as the procedure for being approached to take part in the exercise trial, and the processes that participants go through in considering this approach was deemed a useful approach for gaining understanding of possible causal mechanisms that lead to participants decision making.

Critical realism underpinned an inductive and deductive approach to analysis with recognised assumptions that there is a real, objective existence and that observations of existence are considered to be shaped by multiple structures (personal, social, historical) as well as individual agency (thoughts, feeling, actions) acting upon it (Mukumbang, 2021).

4.4 Findings

Between June 2019 and January 2020 58 people were approached for the PERCEPT myeloma transplant exercise study. Of these, 29 consented to take part and 29 declined. All of those who declined were approached for the decliner interview study. Of these, 23/29 (79%) completed a consent form and provided an email address and telephone number to be contacted to arrange an interview. 3/29 (10%) participants could not be contacted to arrange an interview and 1 (4%) participant withdrew consent and declined an interview. 19/23 (83%) took part in interviews. Data collection was ceased at 19 interviews as no new views relevant to the main research questions were arising from interviews (Saunders et al., 2018). One interview was not recorded in error, therefore 18 were available for analysis. Interview time ranged from 14 to 37 minutes (mean 24 minutes). Sixteen interviews were conducted over telephone. Of the two interviews conducted face-to-face; one participant had their wife present and the other had their son present.

The sample of 18 participants interviewed ranged in age from 41 to 73 years (mean age 62 years [SD 8]) and 10 (56%) were male. Participants were median 7 months post-diagnosis (range 3-80 months). Participants lived on average 38 miles by shortest land transport route (SD 22, range 5-73 miles) from the central London cancer centre. The majority of participants (13/18, 72%) lived outside of the Greater London region.
Table 4.1 Interviewee Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pseudonym</th>
<th>Age at interview</th>
<th>Sex</th>
<th>Time since diagnosis (months)</th>
<th>Living within Greater London</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Ben</td>
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<td>Male</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Jim</td>
<td>69</td>
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<td>9</td>
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<td>3</td>
<td>Ian</td>
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<td>Pete</td>
<td>58</td>
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<td>7</td>
<td>Tim</td>
<td>55</td>
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<td>8</td>
<td>Dave</td>
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<td>Tom</td>
<td>64</td>
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</tr>
<tr>
<td>11</td>
<td>Sally</td>
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Analysis of the interview transcripts led to identification of four main themes with related subthemes from the coded dataset: 1. Travelling to the specialist centre is challenging, not just logistically; 2. Individualised approach valued but recall of research information variable; 3. Being less active has profound impact yet ameliorative support is lacking; 4. Common side-effects of treatment are expected and endured but personal impact underestimated and unaddressed.
Most common reason recorded for declining to take part in the PERCEPT study was because of travel. It was believed that further exploration of reasons for declining in these interviews would provide deeper clarity to what else may have influenced decisions to decline. Overwhelmingly travelling to the centre was shared by interviewees as a decisive factor in declining to take part in the main study with many highlighting the idea of having to attend the centre more frequently, the time commitment of these extra visits, as well as the journey required were prominent factors. It was difficult to tease out which of these were most problematic and the following subthemes were conceptualised to describe the challenges perceived by interviewees when considering the possible travel required to take part in the study.
4.4.1.1 Not wanting to travel to specialist centre more than necessary

Many expressed that they lived ‘far’ from the centre and described complex, multi-modal routes involving public and private transport and taking substantial amount of time, however many also acknowledged how location of the specialist centre near major rail links and availability of high speed train routes could make the journey quite convenient also. For most interviewees, travelling into the specialist centre was only experienced once prior to interview as they were only recently referred for ASCT. There was a sense from the data that many participants anticipated that the addition of ASCT related appointments, as well as coordinating continuing appointments at their local hospitals, would be too much.

“The thing is, it’s so consuming, coming up here and what you have to do and the travelling and the amount of appointments, plus we were fitting [local hospital] in with it as well, we had to go to [local hospital] as well for the two corresponding times. To be honest it was a nightmare, to try and arrange and get that in your head... But we’ve come here today and it wasn’t too bad. We’ve still got to come another four or five times or maybe more, but put that on top of the others as well, it’s a lot” Dave, 68

There was an acknowledgment by some that alignment of study visits with routine appointment visits was a welcome consideration but weekly travel was not feasible. Some suggested less frequent visits, such as monthly would be acceptable. Anticipation of frequent appointments at the specialist centre was also compounded by interviewees reporting the time commitment of travelling and attending appointments there. Alongside detailed descriptions of their journeys and the time taken, there was also a sense that waiting around for appointments as much as the appointments themselves took a significant amount of time. Most interviewees felt a visit to the specialist centre took the best part of the whole day and they seemed to believe that visits for the study gym attendance would result in a similar commitment which was central to decision not to take part.

From a design viewpoint the PERCEPT study was focussed in part on the idea of utilising the routine treatment-free period between induction chemotherapy and ASCT as potentially an ideal time to introduce an exercise intervention in preparation for the next phase of treatment. However, it was underappreciated that this treatment-free period would also be considered by participants as an opportunity to take time away
from recurrent hospital visits and therefore an intervention based at the specialist
centre may not be welcomed by people at this stage.

“We had just gone through six months of chemo, going into hospital
every week, once a week, I’ve now got an opportunity for a month off from
hospitals before the stem cell treatment starts again, and I need that time really
to live life a bit. So the thought of going into hospital once a week for the next
six to eight weeks is not really in line with what I want to do at the moment.”
Pete, 58

4.4.1.2 Journey is a physical challenge

Fatigue is the most common side-effect of treatment experienced by people with
myeloma and unsurprising fatigue was a key feature across the dataset. Underlying the
logistical reasons for not taking part in the study, there were explicit references by most
interviewees to how tiring travelling to the centre is as well as how physically demanding
some considered the journey. In similarities to how interviewees described the impact
of side-effects on ability to undertake daily activities (discussed later), some also
highlighted how aspects of travel were difficult or not possible due to physical concerns
related to impairments from diagnosis or side-effects of induction chemotherapy.

“I’m much more mobile now than what I was, but it’s still quite a physical
challenge for me to get around for any length of time – walking along long
connecting tube tunnels, for example, or dealing with loads of stairs and things
like that, I can do it but it’s very very tiring.”    Lara, 66

Some mentioned overt references to not being ‘fit’ enough to undertake aspects of the
journey by public transport or not wishing to travel unaccompanied for fear of being
pushed in moving crowds or worries about having to undertake prolonged standing on
trains.

“I think essentially if I was fit enough to travel backwards and forwards,
I think it would benefit me no doubt, but unfortunately, because I’m not in that
state at the moment, it’s not convenient for me.”    Andy, 73

“And rush hour and the rest of it, I think I’m going to be pushed about a
bit. I had my son with me so that was a shield, if you like, and he’s keeping an
eye on me, but if I’m coming up here on my own that would be an issue, certainly
on the train journeys and underground”    Ben, 72
There was a sense from many that being accompanied to travel for study visits would be a necessity, in a similar nature to how they considered it important to have their partner or family member with them for medical appointments. For some this was related to concern from their loved one regarding their safety in travelling alone, with one referring to a fear of collapsing on the train making their partner “dead against” his participation. For others there was a sense of low confidence around travelling to the specialist centre alone.

4.4.1.3 Anticipation of further side-effects influence preference to avoid travel

All the interviewees had been approached to take part in the PERCEPT study in the week leading up to their first appointment with the ASCT team and for many it was the first time they had been counselled on what the process would involve, including additional tests prior to the stem cell harvesting, admission for transplant and the possible side-effects to expect. There was a sense from the data that interviewees were not only cognisant of the side-effects of treatment that they had already experienced but now aware of further possible consequences of their future treatment. Weighing up the possibility of these additional or possibly amplified side-effects appeared to influence some people’s weariness of additional travel.

“There only thing that did put me off was that I didn’t know how I’d be on the treatment that I was going to receive, the stem cell treatment. That was the only thing that put me off, not knowing how it would be, because I’ve been briefed about all the things that could happen to me.” John, 69

There was an indication that some interviewees were anticipating side-effects to occur earlier in the process then to be expected, for example some referred to not knowing how they would feel after ASCT but were relating those uncertain feelings to their reluctance to travel in the period prior to transplantation.

4.4.2 Individualised approach valued but recall of research information variable

Participants described that the point in their treatment journey when they were approached (on referral for consideration for ASCT), that the additional information and building expectations related to the next phase of treatment made the additional task of considering taking part in a research study or exercise intervention too difficult to
fully consider. There was unanimous acceptance by interviewees to being approached about a study of this kind at this point in the pathway. So receiving additional engagement about the research study was not considered burdensome or unwelcome but it is possible that participation in the study did not receive the interviewees’ full consideration due to the amount of other information they report having to take on at this time.

Many expressed sentiments of gratitude for being considered to approach with some even sharing expressions of feeling wanted or sought out. This was coupled with a sense of regret by most of not being able to take part in the trial, both for loss of potential personal gain and in an altruistic sense of contributing to work that may help others with myeloma.

“I’m sorry that I couldn’t participate or didn’t want to participate in it because it sounded very interesting and anything that can help other people in a similar position I’m encouraged to do, but it was just logistics-wise it was not good for me.” Greg, 65

This combination of altruism and regret at not participating in the exercise study may in reality have been the influencing factors for most wanting to take part in this qualitative study, with the sentiment of ‘if it will help others’ a feature across the dataset.

4.4.2.1 Personalised discussion, not just a leaflet

There was a clear pattern of engagement described by interviewees that gave insights into how taking part in the PERCEPT study was considered. It was clear that being contacted individually by phone call prior to their ASCT clinic appointment and followed up in clinic a few days later rather than just receiving written information was appreciated by all those who were interviewed with many expressing gratitude for time taken to be sought out, spoken with and followed up in person in clinic.

“I think the personal approach... It's such a complicated thing, isn't it? I think it's hard to get things over just on paper... I was quite happy to listen to what you said, and I could ask questions, and you could explain in more detail. I think the personal approach is nice. It's a good way.” Ann, 69
“You took the time to come and see me. It could have just been a piece of paper, but you contacted me and you put a lot of effort in, and came to see me, and tried to explain it to me. And obviously that pleased me as well.”

Ian, 66

There was a general opinion by participants that they received all the information they required to make their decision from the discussion in the phone call, introducing the study. Many expressed the approach allowed them to come to their decision without feeling pressure. Overall, there was a sense that despite also receiving written information, after the phone call, most participants had made their decision not to take part based on the information received and the discussion that took part during the phone call to introduce the research study.

4.4.2.2 Participant information sheet less influential than verbal information when deciding to participate

There was much variation between interviewees regarding recall of the research study details and interaction with the PIS provided after initial approach by phone call. Nearly all reported they did not read the PIS fully or some did not read it at all. Interviewees expressed that the phone call had provided sufficient information for them to make their decision and that was why they did not read the PIS fully.

“I think a phone call was exactly the right approach. Because actually, although I didn’t continue to read on all the paperwork, and what have you, I didn’t feel I needed to in order to make my decision.”

Lara, 66

Others felt they were overwhelmed with information or lack of time to engage further with the written information.

“It has been quite overwhelming and all the things that I’m going to be going through. Do you know what I mean? My mind is boggling from that without reading something extra at this moment.”

Pam, 60

Many interviewees discussed their decision making in the context of assumed allocation to the exercise arm and therefore contemplating the commitment of the regular attendance was key to declining participation. Specific questioning and probing about specific details related to the study revealed mixed recall and inaccuracies about the nature of the research, particularly in relation to awareness of randomisation or
allocation to group. The inaccuracies of recall of study details as well as confirmation of many that they had not further engaged with the written information indicated that for many the early research information introduction via the phone call discussion principally informed their decision making and hindered further consideration of study information in the PIS.

4.4.3 Being less active has profound impact yet ameliorative support is lacking

The impact of initial diagnosis and/or subsequent induction chemotherapy treatment on levels of physical activity or function was highlighted by nearly all the interviewees, with fatigue, low energy or low stamina described as the main precipitating factor. Daily activities and ability to walk or run as a form of exercise were described by some interviewees as more challenging.

“I can walk for an hour, but nowhere near the distance or speed that I could do before. Gardening is much more difficult now than it was before. So my mobility is certainly affected by the myeloma.” Pete, 58

A number described experiencing the cycle of fatigue, resulting in less activity, leading to less capability carry out certain activities, although many did not recognise this debilitating cycle. There was a sense of fear in not knowing how fatigue might affect their ability to carry out an activity, especially outside of the home, so these activities were avoided.

“I do try and move about but if I move about for about five, ten minutes, I have to sit down. It’s like I can’t walk round to the shop all the way and then come back. I could go one way, but I couldn’t come back.” Sarah, 49

Interviewees reported changes to their ability to undertaking shopping, engage in the work that they were previously employed in, as well as changes to hobbies or sports. Most striking were references to resultant inability by some to engage in social or family activities.

“I don’t go out. I don’t walk as much. I don’t participate in going out with family and the like as much as I used to.” Greg, 65

One interviewee spoke of stopping routine running he had engaged in for a number of years, firstly due to uncertainty about whether he could run following diagnosis,
although he received no advice in relation to this, and subsequently due to worsening levels of fatigue.

“I was running six miles a week, every week, and I’ve been doing that for three years, so it’s come as a big hell of a shock. I can’t run anymore… I didn’t want to pack up, I loved it, definitely. Because I’d run with my daughter, so father and daughter, we loved it. It was really bonding and good.” Dave, 68

What was clear on questioning most participants about the changes to their levels of activity or reduced ability to function was that it clearly had an impact of their perceived QOL but nearly all had not brought up these changes with their health care team or received advice on how to manage the effects of treatment on daily life. Twelve of the eighteen participants interviewed could not recall receiving any advice regarding physical activity since diagnosis. Others mentioned being aware of references to keeping active in leaflets they were given at the beginning of treatment.

4.4.3.1 Encouragement to be physically active and specific advice would be welcomed

Given that the majority of interviewees could not recall ever discussing physical activity as part of their treatment, the qualitative interview was the first discussion on this topic for most. Universally across the dataset there was a sense of agreement that physical activity and exercise should be encouraged by the healthcare team. Many expressed a desire to receive encouragement and reassurance about continuing to be active.

“It was the first time I’ve actually heard anybody talking about supporting myeloma patients with exercise, and that was exactly what I had been looking for, to support my recovery, much earlier on”. Lara, 66

Some expressed a preference to receive specific instructions regarding how much activity to do or to receive a prescribed programme, and that having to report back to a professional might facilitate participation. For one interviewee welcoming physical activity advice, simply receiving information on the exercise research study prompted him to be active.

“More formalising the encouragement to do exercise, because it’s easy not to do exercise and just sit on a chair and fall asleep again as opposed to getting up and actually sort of doing something, which as I said, the paperwork did inspire me to do some.” Greg, 65
Most interviewees were generally supportive of the exercise research study as a good idea, despite not suiting them to take part. A number of them enquired during the interview about specific components of the planned exercise study and whether they were things that they could undertake independently. This demonstrated a desire among patients to seek further information regarding exercising at this point in their treatment journey.

4.4.3.2 Vague, over cautious or lack of response to requests for advice

Some interviewees shared experiences of seeking or receiving advice around physical activity or functional concerns. Two participants who had spinal disease related to their myeloma and had been required to wear a hard, spinal brace as part of their treatment shared similar experiences around lack of advice living in and out of their brace. Both recalled receiving basic information at the fitting of their brace but felt that the little follow-up advice or practical review from physiotherapy was not in keeping with what they expected to happen during this process.

“[It was] excellent in terms of getting the brace fitted and applied, but when I went to have the brace removed, it was literally a case of, ‘off you go,’ and there was no real physio given at that stage, so it must be [their] opinion that no physio is required... I felt personally that was perhaps lacking in the treatment, or perhaps it wasn't explained to me why no physio was required?”

Pete, 58

There was a sense from many that clearer responses to requests for information on physical activity would be welcomed, for some any response at all would have potentially helped them continue to keep active. A perception of being ‘left to it’ featured among the interviews with regards to physical consequences of treatment up to this point in their journey to ASCT.

“We did ask various questions about, ‘Was she familiar with a series of exercises I could do at home?’ and, basically, I haven’t had any response from that... I only just get asked basic questions about my wellbeing and the only thing was, ‘Are you getting out and about? Are you able to walk?’ and that was basically it, end of conversation regards that... it’s almost as if you’ve got the medical treatment and then you’re basically just left to your own devices to sort of like recover in your best way possible physically.”

Andy, 73
One example described by an interviewee, was their experience attending a generic pre-chemotherapy induction information session with their partner. It provided a stark insight into how delivery of advice from health professionals can have profound consequences on how someone may adapt their life to such advice. Over-cautious advice surrounding avoiding scenarios where the patient went out alone, instilled a fear in both them and their partner that resulted in restrictions of activity outside of the home, made worse by the fact their partner worked during the day.

“When I went first to my chemotherapy, they had a nurse give you an introduction or an induction course, and they said to me, well they said to all of us ‘Don’t go out exercising or walking unless you have someone with you.’ That goes in the back of your mind and you think I’d better not go out. You know. That’s quite a downer to be honest…”

“It’s just the fact that they said ‘Don’t go walking unless someone’s with you’ and you think hello, well you’d better not do anything then. That’s probably why I don’t go anywhere or do anything. Plus my partner was with me and she said to me ‘Don’t go out unless I’m with you’ so she goes to work all day and I’m at home. So I don’t go out, which is criminal really I suppose, isn’t it? I should go out.”

Interviewer: How does it make you feel then having that information given to you?

“Very cautious, I just feel cautious, maybe I shouldn’t go out, I’d better not go out, and if someone doesn’t find me, I fall over or something…”

John, 69

The general feeling from the data was that input for advice and tailored support in relation to physical activity was lacking, most did not recall any conversations about physical activity or physical recovery and there were explicit references to lack of access to physiotherapy. This lack of specialist or reliably informed advice may be resulting in missed opportunities to receive trustworthy, encouraging advice about being physically active that could counteract the potentially damaging vague or over-cautious advice some patients encounter as they navigate life during cancer treatment and beyond.
Exploring experiences of discussing exercise and physical activity during treatment led to interviewees highlighting the impact of treatment side-effects they had experienced and naturally resulted in discussion surrounding advice or support given for managing these consequences of treatment. As previously described, fatigue was the most commonly reported but weakness, breathlessness, poor appetite, gastrointestinal symptoms, ‘chemo brain’, as well as the role of steroid medication impacting upon sleep and weight were all mentioned.

4.4.4.1 Side-effects are considered inevitable but individual impacts are wide ranging

Interviewees shared a level of awareness of these symptoms as side-effects associated with myeloma and its treatment through the information received at the beginning of treatment, mostly in packs of written resources. There was no expression of surprise or unawareness that these side-effects would occur, but a level of inevitability did appear to result in lack of action in reporting these concerns, and particularly in discussing the impact on aspects of their everyday lives, with their medical teams. For some there was a sense of expecting more input from their health professionals but also an acknowledgement that they themselves did not initiate seeking additional input for side-effects and therefore it may be their own fault they did not have any.

“I think it’s probably in a sense my own fault, because if I had attended the classes and the clinics I might have found out a few of these things because other people are there. But I’m not one for pushing that forwards. [CNS] said ‘I’ll look after it’, didn’t she? Her words were, before I started the treatment, ‘Don’t worry, I’ll look after you’ and then I never saw her again for four months… She did reassure me and then you’re left on your own.”

“I’m not saying I’m strong-willed or minded but I can see someone with less than I’ve got who would really take it to heart and really worry about it, rather than try and sort it out yourself, or put up with it or make allowances for it or try and get through it how you would get through it, without any advice from her.”

Dave, 68

A number of participants stressed the concept of ‘getting through it’ and looking forward to completing their induction chemotherapy soon with a presumption that side-effects would subside, therefore did not see any point in raising concerns.
“They tick it off on a chart and that’s about it really. They don’t do anything. I can’t see what else there is to do. You’ve got to have the treatment, so it’s one of the side effects. Can’t really do anything about it I suppose... I’ve only got one cycle left anyway so it doesn’t matter.” Sally, 41

“As I say, the attitude is just, ‘Sadly that’s part of the effects of the treatment’.” Jane, 58

Although some interviewees shared their insights into the possibility that their upcoming ASCT may worsen or lead to new side-effects, many did not acknowledge that this next phase of treatment could possibly lead to or sustain consequences of treatment beyond the end of their induction chemotherapy.

4.4.4.2 ‘You’re getting away lightly’ (minimisation of side-effects/concerns)

Central to the discussions surrounding reporting of treatment side-effects was the notion that their experiences are normal or par for the course. Others reported they were made to feel that their experience may not be as bad as it could be or it could be worse, reinforcing the tendency to underreport.

“I suppose it’s the medication I have. It does make me very tired, which gets mentioned a lot when I go for the pre-chemo treatment, but again I’m always told that is normal, and that is part of it.” Jane, 58

Across the dataset there was sharing of incidences recalling when asked by their health care team about side-effects, interviewees projected a feeling that this was generally 'tick box' questioning with little potential to discuss the individual impact of side-effects on their life. There was also a perception that their concerns were minimised to not being as bad as others or as they could be. Some questioned that despite being told their negative consequences of treatment were not ‘too bad’ comparatively and understanding that their myeloma was improving, why they did not feel better or when would they feel better?

“They did say ‘Your side-effects etcetera, you’re doing well, you’re getting away with...’ And every time I have the testing, ‘Oh yes it’s good, it’s improving, it’s better.’ I say ‘Well why don’t I feel better?’ And they said ‘Well, it will come.’ Long time coming...” Dave, 68

There was an impression across the data that perhaps interviewees’ felt their concerns were not considered comprehensively enough up to this point in their treatment.
Although interviewees shared experiences of lack of enquiry or minimisation of their concerns by their medical team, it was also clear that interviewees did not initiate reporting of some of their concerns, particularly where symptoms impacted on daily activities, to their health care team.

4.5 Discussion

This qualitative interview study explored the experiences of people with myeloma, recently referred to a specialist tertiary cancer centre for consideration for ASCT, who had been approached for and declined to take part in the PERCEPT pilot RCT of an exercise intervention delivered pre- and post-ASCT. The research questions focussed on investigating reasons for declining the exercise RCT and experiences of discussing physical activity with their healthcare team and the themes that were shaped from the dataset sit under the following broad areas: engagement with and interpretation of information related to their disease, it's treatment and the research study; paucity of advice regarding physical activity despite an awareness of its benefit and desire to receive it; and deficiencies in communication related to side-effects and concerns.

As expected, distance and travel requirements to reach the tertiary centre was the overwhelming reason for declining to take part in the exercise RCT. Travel or distance is a common reason cited by many cancer exercise RCTs when reporting uptake to trials (Sheill et al., 2019) but there is little literature exploring in depth, the reasons people do not participate in studies of this type. This qualitative study discovered deeper understanding of this common reason for declining trials. Underlying the logistical challenges of travelling or distance were concerns related to fitness, mobility, levels of fatigue, confidence travelling alone as well as the existing time burden of attending specialist care at a tertiary cancer centre.

One qualitative study exploring reasons for declining a community-based walking programme in primary care asked those declining the trial to complete a non-participant questionnaire and conducted qualitative interviews in a purposeful sample of 30 decliners. Reasons for not enrolling in the RCT, were categorised into internal (medical problems, perception of being fit enough) and external (travel required, commitments) motives (Normansell et al., 2016). My interpretations of reasons for declining the
PERCEPT trial indicate that participants’ internal and external reasons were interconnected. Travel as an external factor was very much more problematic for many due to internal factors of perceived lack of fitness, mobility and symptom concerns. The interconnectedness of these issues is of importance as participants felt the exercise intervention would benefit them in terms of potentially improving their fitness. Most recognised that their fitness or functional capacity limited their ability to travel more regularly or utilise public transport instead of more costly hospital or private hire transport.

Other important experiences related to travel as a given reason for declining included the cumulative time burden of travel and time spent waiting in clinic. The design of the original face-to-face study assessments to coincide with clinic visits was therefore not as convenient as I initially believed and some participants were put off by the perception that attending the intervention would result in a ‘whole day’ time burden similar to that experienced with a clinic visit. These findings resonate with quantitative data reported in a systematic review of exercise studies in advanced cancer which found lack of time, multiple hospital commitments and transport issues to be the most commonly cited reasons for declining participation (Sheill et al., 2019). Mawson et al. (2021) conducted a single arm feasibility study of prehabilitation for myeloma patients awaiting ASCT and included qualitative interviews of study decliners. Although only briefly described alongside quantitative study results, their qualitative findings of six non-participants are very closely aligned with the reasons for declining reported in my study. They report that although distance to travel and the location of the exercise venue were the most common reasons given by non-participants, the impact of fatigue, reduced ability to engage in activities of daily living (ADLs) and management of clinical appointments were also highlighted as important reasons for declining (Mawson et al., 2021).

Preferences of myeloma patients related to exercise support stress a desire for individualised programmes delivered by professionals with knowledge of the disease (Craike et al., 2017; Land et al., 2022). Physiotherapists are seen by patients to be best placed to provide exercise support (Craike et al., 2017; Nicol et al., 2020) with supervised sessions motivating patients to adhere to exercise prescriptions and challenges maintaining similar levels of exercise in unsupervised sessions (Land et al., 2022). But preference for location of such exercise programmes is mixed. Some studies have found
equal preference for programmes based at specialist myeloma centres and for home-based programmes (Craike et al., 2017). More recent survey based research among Australian myeloma survivors found preferences for programmes that were flexible in terms of time and delivered close to home, with no clear preferences related to specific location in terms of clinical centres or within home (Nicol et al., 2020). Increased experience of remotely engaging in virtual health delivery through different forms of telehealth offers an opportunity to explore the effectiveness of remotely supervised, home-based exercise interventions (Bland et al., 2020). A virtual approach that incorporates the specialist knowledge and supervision by physiotherapists, delivered conveniently at home would eliminate the barrier to participation related to travel and may appeal to the preferences of exercise delivery.

In contrast to other literature that has found perceptions of already being active enough or not being interested in physical activity as significant reasons for declining recruitment to physical activity studies (Attwood et al., 2016), our interviewees shared an understanding of being physically active as important. Positive beliefs related to exercise and its role in managing symptoms and recovery from treatment amongst myeloma patients have previously been reported (Coon & Coleman, 2004; Craike et al., 2013b; Craike et al., 2017). Indeed, as described in detail in Chapter 1 more physically active myeloma patients have less comorbidity, improved tolerance of treatment and potentially better response to treatment (Moller et al., 2021). Interviewees were welcoming of physical activity advice but most reported not receiving any since diagnosis. This is in line with research exploring provision of physical activity advice among those with cancer (Barnes & Schoenborn, 2012; Fisher et al., 2015) and specifically myeloma (Walpole et al., 2018; Nicol et al., 2020). Although lack of discussion of physical activity advice was an unsurprising finding, the additional findings around underreporting or lack of communication of treatment side-effects and impacts on ADLs with their clinical teams was unexpected.

The concept of supportive care in cancer is considered corner stone to the management of the disease and is defined as ‘the prevention and management of the adverse effects of cancer and its treatment’ (Rittenberg et al., 2010). Good supportive care requires education of patients regarding consequences of their treatment, as well as routine screening for side-effects, to provide them with the opportunity to discuss their
experience across the continuum of cancer treatment and any effects on their QOL with their clinical team (Olver et al., 2020). Our interviewees were generally well informed regarding the consequences they expected from treatment in terms of side-effects but appeared to underestimate the effects on their day to day lives and ability to maintain ADLs, particularly social engagement. What was striking was the realisation that they had often not informed their clinical teams of the effect that treatments and living with myeloma was having on their ability to engage in usual activities. More often they shared a feeling of not being asked or that enquiry was tokenistic in nature therefore held assumptions that nothing could be done to mitigate. It is also important to highlight that interviewees were all ASCT eligible patients considered the ‘most fit’ of myeloma patients undergoing treatment and mostly only a few cycles into their induction chemotherapy but yet their physical activity and daily lives were already hugely impacted by treatment so far, and so concerns are likely to be much more evident in those having subsequent lines of treatment following relapse. It may be possible that their experience of routine screening of symptoms has been interpreted as ‘tick-box’ and perhaps less personalised than supportive care advocates for, so discussions regarding the effects on them as individuals have not taken place.

In contrast, interviewees were wholly accepting of the individualised approach taken to recruit for the exercise RCT. The appeal and resounding positive experiences related to receiving an individualised approach for the lifestyle related research trial was clear from most interviewees. The addition of the interview drew out concerns related to their treatment to date and how it related to inactivity and changes to everyday living. The approach by telephone followed by face-to-face encounter with researcher and written information resources provided in between, provided them with adequate information to make a personal decision to take part. Participants reported variable engagement with the written study information. Although written study information is required and known to benefit research participants by allowing time for reflection, trial information delivered verbally, in person by an approachable clinician or researcher with good communication skills is known to be preferred by those being approached for RCTs (Houghton et al., 2020).

Given the acceptability and positive experiences reported by interviewees of being sought out to receive a one to one interaction and follow-up discussion related to
research participation, could this model of approach be incorporated into clinical services to enhance individualised supportive care? Participants shared a recognised gap in provision of opportunity to comprehensively discuss their disease and ongoing treatment and expressed a desire to receive guidance and support for physical activity, which may extend to other lifestyle and self-management interventions. The definition of supportive care includes reference to enhancing rehabilitation and survivorship as integral to supportive care (Rittenberg et al., 2010), yet despite substantial evidence base for inclusion of a rehabilitative approach to address symptoms as part of clinical pathways, the provision of such is sparse and subject to much variability (Robb & Davis, 2015; Transforming Cancer Services Team (TCST), 2019). Approaching provision of physical activity/lifestyle advice or review of symptoms and concerns by using a process similar to research trial recruitment may be valuable to patients. But rehabilitation goes far beyond just delivery of exercise (Silver et al., 2015). Delivery of a model of supportive care that encompasses all its intended elements requires coordinated, multidisciplinary collaboration built around patients and accessible across the continuum of cancer treatment (Silver et al., 2015; Bayly & Lloyd-Williams, 2016; Snowden et al., 2017; Olver et al., 2020). Exploring with patients how well equipped they are to manage their recovery as well as provision of generic information regarding life after treatment could be delivered within patient education programmes (Walpole et al., 2018). However, offering individualised opportunities to discuss consequences of treatment specific to them and the impact on their lives, with relevant resources and time to consider and reflect before a follow-up discussion, may provide better conditions to deliver holistic, biopsychosocial approach to care and instigation of signposting for psychological support and early rehabilitation to minimise symptoms and decelerate or prevent impact on function.

4.5.1 Limitations

As discussed in section 4.3.4.2 like all qualitative research my role as the researcher will have influenced all elements of this study. My role as the chief investigator and sole recruiter for the pilot exercise RCT, for which these interviewees were approached for, may have led to mostly positive feedback regarding research approach. This known ‘ownership’ of the study as part of my PhD may have led interviewees to consider their responses differently than if approached for a generic study recruited to by a research
Involvement of a second researcher (AF) in the coding provided independent input and discussion related to theme development.

Like much exercise and lifestyle related research, the pilot RCT and subsequent qualitative decliner study may also have attracted participants already interested in being physically active or seeking support for physical activity. As well as being purposefully recruited from one centre, like all qualitative research this limits the transferability of these findings to other people with myeloma. However, it is positive to note that there was a good response from decliners to taking part in this interview study (83%) and that the findings of this study does align with other qualitative literature.

Finally, due to this study being conducted and completed prior to the COVID-19 pandemic, discussion about virtual delivery was not part of this interview but may have revealed useful insights into differences in engagement with research recruitment and communication of consequences of treatment that do not feature in this dataset.

### 4.5.2 Considerations for future research

This study has produced interesting and valuable insights that require consideration in the development of future research related to this thesis. Firstly, assumptions that aligning study visits and intervention delivery with hospital visits would be attractive but actually presents an additional burden on patient time and so is unattractive. This finding, as well as the overwhelming reason for not participating being due to travel and distance, confirms the need for remote intervention delivery despite regular travel to centre to for clinical visits and treatment. Some trials have used non-randomised designs allocating participants based on being within or outside of a geographical area to increase likelihood of participation (Christensen et al., 2019). Although a potentially useful strategy for increasing accrual whilst providing a non-exercise comparator group, this method may lead to socio-economic disparities between groups, particularly where geographical selection could lead to unequal proportions of urban versus rural dwellers.

It was also evident that those who make an early decision not to partake are likely only going to consider the information received in the phone call. This may be important for designing schedules and information shared during initial approach for studies going
forward, as it is likely that the PIS may only be read by those who are already agreeable to take part.
Chapter 5  PERCEPT trial results: Feasibility outcomes

5.1  Introduction

Chapter 3 described the protocol for the PERCEPT myeloma pilot trial of an exercise intervention delivered before, during and after autologous stem cell transplant (ASCT) among people with myeloma. Over the next three chapters the outcomes of the trial will be presented in relation to the primary feasibility outcomes (Chapter 5), secondary outcomes related to physical function and physical activity (Chapter 6), and secondary outcomes related to fatigue and quality of life (Chapter 7).

This chapter will outline the results of the feasibility outcomes and describe the study sample in terms of demographics, disease characteristics and transplant hospital admission details. Feasibility results in this chapter are presented for the study overall, but also according to the original protocol and the amended virtual protocol. The protocol changes, required in response to the novel coronavirus (COVID-19) pandemic, provided the opportunity to explore distinction between face-to-face and remote delivery of the study assessments and intervention. I hypothesised that barriers to participation (and therefore recruitment and uptake) could be different for each and therefore they are presented separately.

5.2  Recruitment rate and uptake

Recruitment to the original face-to-face protocol began in June 2019 and was planned to end December 2020. However, recruitment was paused in February 2020, initially due to gap in provision of a research physiotherapist to deliver the intervention, then subsequently as a result of the COVID-19 pandemic. Therefore, no participants were approached between March and August 2020. Following major amendment to the study design as previously described in Chapter 3, recruitment recommenced in August 2020 then ceased in early October 2020 with the emergence of another wave of COVID-19 causing further disruption to the myeloma ASCT clinical pathway.

5.2.1  Recruitment: overall

Figure 5.1 shows the flow of participants through the trial and outlines the numbers of participants approached when the original (face-to-face) versus amended (virtual)
exercise protocol was in place. 123 potential participants were identified and screened for eligibility over 11 months. Of these, 14 (11%) did not meet the inclusion criteria leaving 109 that were eligible to approach. Of these, 50 (46%) consented to take part and were randomised and 59 (54%) declined. Reasons for not being eligible or declining differed depending on the protocol and are discussed in subsequent sections. Reasons for declining were explored in more detail in the qualitative study reported in Chapter 4.

Allocation to trial arms was uneven due to the randomisation software being set to reach an overall target recruitment of 75 participants, and recruitment stopping at 50 for the reasons provided above. Therefore, slightly more participants were allocated to the control (n=27) than the intervention arm (n=23).

5.2.2 Recruitment: original face-to-face protocol

Recruitment to the original trial protocol took place over 9 months with 90 potential participants screened for eligibility. Of the 90 potential participants identified and screened 8 (9%) did not meet the inclusion criteria. Reasons for not being eligible were; clinical decision not to proceed with ASCT after initial clinic appointment (n=3; 37%), non-English language (n=2; 25%), patient decision not to proceed to ASCT (n=1; 13%), too close to ASCT admission (n=1; 13%) and unable to take part in an exercise programme due to restricted mobility (n=1; 13%). This left 82 that were eligible to approach. Of these, 36 (44%) consented and were randomised and 46 (56%) declined. The main reasons for declining were related to travel and/or distance (n=12; 26%), not being interested (n=10; 22%), too many hospital appointments (n=8; 17%). Six people (13%) did not respond to follow-up calls or email after being approached by phone or in clinic. Other less common but important reasons for declining included self-reported poor mobility (n=4; 9%), working commitments (n=2; 4%), caring responsibilities (n=2; 4%), fatigue (n=1; 2%) and planning a holiday pre ASCT (n=1; 2%).
Figure 5.1 Consolidated Standards of Reporting Trials (CONSORT) diagram detailing allocation specific to study protocol and flow through the study assessments

* One control participant returned a T3 assessment but had not returned a T2 assessment
# Two intervention participants returned T3 assessments but had not returned a T1 or T2, and a T2 assessment respectively
5.2.3 Recruitment: amended virtual protocol

Following substantial amendment and approval to recommence recruitment as a virtually delivered study, a further 33 potential participants were identified over 2 months. Of these 6 (18%) did not meet the eligibility criteria, leaving 27 potential participants to approach. Reasons for ineligibility were; less than four weeks to scheduled ASCT admission date (n=3; 50%), unable to access/use the internet (n=1; 17%), non-English language (n=1; 17%) and significant neurological deficits (n=1; 17%).

Of 27 eligible, 14 (52%) consented to take part and were randomised, and 13 (48%) declined. Reasons for declining were not responding to follow-up (n=5; 39%), not being interested in the study (n=4; 31%), working commitments (n=2; 15%) and having too much going on (n=2; 15%).

5.3 Demographics and disease characteristics

50 participants were enrolled and randomised. 62% (n=31) were male, with a mean age of 60.4 years (SD=9, range 37-72). Most participants were younger than 65 years (n=31, 62%). The majority were married (n=38, 76%), living with a spouse/partner only (n=21, 42%), retired (n=18, 36%) and self-identified as white ethnicity (n=37, 74%).

The intervention group were slightly younger on average (59.3 years versus 61.3 years) and had a greater proportion of participants under the age of sixty-five years (70% versus 56%). The control group had a greater proportion of male participants (67% versus 57%) and higher levels of education with more participants reporting graduate level qualifications (59% versus 26%). Other than level of education, no other demographic characteristics between groups were significantly different. Baseline demographics by group allocation are detailed in Table 5.1.

Most participants had immunoglobulin G (IgG) type myeloma (n=33, 66%) and were categorised as ‘fit’ (n=40, 80%) using the International Myeloma Working Group (IMWG) Frailty Assessment. Seventy-six percent (n=38) of participants had myeloma related bone disease, all of whom had axial bone disease and 24% (n=12) had both axial and peripheral bone disease. Eighteen participants (36%) had required immobilisation in a spinal brace prior to the study, 5 (10%) had previous surgery and 7 (14%) had previous
radiotherapy. Half of the sample self-reported ongoing disease related pain (n=25, 50%). The median time from diagnosis or most recent relapse to baseline assessment for the whole sample was 6.5 months (IQR 5,10; range 3-82). A small proportion of the participants (n=9, 18%) had undergone ASCT prior to enrolment and were experiencing their second transplant.

Disease characteristics for each group are detailed in Table 5.2. The groups were broadly similar in terms of disease type, bone disease, previous radiotherapy, surgery, ongoing symptoms of bone disease, history of previous ASCT and time from diagnosis to baseline. A greater proportion of the control group were categorised as ‘fit’ on the IMWG Frailty Assessment (81% versus 78%) and no control participants were categorised as ‘frail’, whereas the intervention group had two participants (9%) categorised as ‘frail’ at baseline. There was a higher proportion of participants in the intervention group that had required spinal bracing (39% versus 33%), radiotherapy (17% versus 11%) and/or surgery (13% versus 7%) as a component of disease management at some point prior to enrolment. No statistically significant differences in disease characteristics were found between the groups.
Table 5.1 Baseline demographics by group

<table>
<thead>
<tr>
<th></th>
<th>Control (n=27)</th>
<th>Intervention (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>61.3 ± 8.7</td>
<td>59.3 ± 9.4</td>
</tr>
<tr>
<td>range</td>
<td>40-72</td>
<td>37-72</td>
</tr>
<tr>
<td>&lt;65 n (%)</td>
<td>15 (56)</td>
<td>16 (70)</td>
</tr>
<tr>
<td>≥65 n (%)</td>
<td>12 (44)</td>
<td>7 (30)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (67)</td>
<td>13 (57)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (33)</td>
<td>10 (43)</td>
</tr>
<tr>
<td><strong>Weight (kg), mean ± SD</strong></td>
<td>78.6 ± 16</td>
<td>84.1 ± 14.9</td>
</tr>
<tr>
<td><strong>Body Mass Index (BMI) (kg/m²), mean ± SD</strong></td>
<td>26.9 ± 4.4</td>
<td>29.7 ± 4.5</td>
</tr>
<tr>
<td><strong>BMI status, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>10 (37)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Overweight</td>
<td>10 (37)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>Obesity</td>
<td>6 (22)</td>
<td>9 (39)</td>
</tr>
<tr>
<td><strong>Self-assigned Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>21 (78)</td>
<td>16 (70)</td>
</tr>
<tr>
<td>Black or Black British</td>
<td>6 (22)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Asian or Asian British</td>
<td>-</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>2 (9)</td>
</tr>
<tr>
<td><strong>Marital Status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married, civil partnership or cohabiting</td>
<td>21 (78)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>Single</td>
<td>2 (7)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Separated, divorced/civil partnership dissolved</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Widowed</td>
<td>3 (11)</td>
<td>-</td>
</tr>
<tr>
<td>Rather not say</td>
<td>-</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Social situation, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lives with spouse/partner only</td>
<td>13 (48)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Lives with immediate family (incl children)</td>
<td>7 (26)</td>
<td>13 (57)</td>
</tr>
<tr>
<td>Lives alone</td>
<td>7 (26)</td>
<td>2 (9)</td>
</tr>
<tr>
<td><strong>Education, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher (Level 6 degree education or greater)</td>
<td>16 (59)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Lower (Level 5 or less)</td>
<td>10 (37)</td>
<td>15 (65)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (4)</td>
<td>2 (9)</td>
</tr>
<tr>
<td><strong>Employment status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>10 (37)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>On temporary or sick leave</td>
<td>7 (26)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Working full time</td>
<td>5 (19)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Working part time</td>
<td>4 (15)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
Table 5.2 Myeloma disease characteristics by group

<table>
<thead>
<tr>
<th></th>
<th>Control (n=27)</th>
<th>Intervention (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>5 (19)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>IgG</td>
<td>18 (67)</td>
<td>15 (62)</td>
</tr>
<tr>
<td>Light Chain</td>
<td>8 (30)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Oligosecretory</td>
<td>-</td>
<td>2 (9)</td>
</tr>
<tr>
<td><strong>IMWG Frailty Assessment Score, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit</td>
<td>22 (81)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Intermediate Fit</td>
<td>5 (19)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Frail</td>
<td>-</td>
<td>2 (9)</td>
</tr>
<tr>
<td><strong>Time from diagnosis or relapse to baseline, months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (IQR)</td>
<td>6 (5,10)</td>
<td>7 (6,11)</td>
</tr>
<tr>
<td>range</td>
<td>3-12</td>
<td>4-82</td>
</tr>
<tr>
<td><strong>Previous ASCT, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (19)</td>
<td>4 (17)</td>
</tr>
<tr>
<td><strong>Bone Disease, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial disease</td>
<td>20 (74)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Axial and peripheral disease</td>
<td>15 (56)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>No bone disease</td>
<td>5 (19)</td>
<td>7 (30)</td>
</tr>
<tr>
<td><strong>Required spinal brace, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (33)</td>
<td>9 (39)</td>
</tr>
<tr>
<td><strong>Previous radiotherapy, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (11)</td>
<td>4 (17)</td>
</tr>
<tr>
<td><strong>Previous surgery for myeloma disease, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyphoplasty</td>
<td>-</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Vertebroplasty</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Ongoing symptoms of bone disease at baseline,n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease related pain</td>
<td>13 (48)</td>
<td>12 (52)</td>
</tr>
<tr>
<td>Restricted mobility</td>
<td>1 (4)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>None/asymptomatic</td>
<td>9 (3)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Non myeloma related pain</td>
<td>4 (15)</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

5.4 Transplant admission characteristics

Thirty-nine out of fifty participants (78%) recruited proceeded to undergo ASCT. Overall, median time from baseline assessment to ASCT day 0 was 83 days (IQR 56,224.5) with a large range of 14 and 436 days due to transplant admissions being delayed due to the COVID-19 pandemic. Most participants (n=36, 92%) commenced their transplant admission in ambulatory care with seven (18%) participants remaining in ambulatory care for their whole transplant admission. Mean (SD) length of stay (LOS) in ambulatory care...
care and overall total transplant admission LOS were 9.7 (3.8) days and 17 (2.8) days respectively.

Transplant admission characteristics for each group are presented in Table 5.3. The median time from baseline to ASCT was 8.5 days less in the intervention group compared to the control. Both groups had similar overall transplant admission and ambulatory care LOS. All intervention participants commenced their admission in ambulatory care and 25% of them (n=4) remained in ambulatory care for their whole ASCT admission, compared to 13% (n=3) of those in the control group. In the approximate three month period following ASCT, 26% (n=6) of the control group were readmitted to hospital compared to 19% (n=3) of the intervention group. No group differences in transplant admission were statistically significant.

Table 5.3 Transplant admission characteristics by group

<table>
<thead>
<tr>
<th></th>
<th>Control (n=23)</th>
<th>Intervention (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time baseline to ASCT D0, days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>128.4 ± 102.6</td>
<td>138.3 ± 117.2</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>83 (56.5,184.5)</td>
<td>74.5 (54.8,241.3)</td>
</tr>
<tr>
<td>range</td>
<td>21-436</td>
<td>14-385</td>
</tr>
<tr>
<td><strong>Transplant Admission Total LOS, days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>17 ± 2.4</td>
<td>17 ± 3.4</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>16 (16,18)</td>
<td>16 (15,17)</td>
</tr>
<tr>
<td>range</td>
<td>14-25</td>
<td>14-26</td>
</tr>
<tr>
<td>Died during admission (n)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Started admission in ambi-care, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (87)</td>
<td>16 (100)</td>
</tr>
<tr>
<td><strong>Remained in ambi-care for whole admission, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not admitted to ambi-care</td>
<td>3 (13)</td>
<td>4 (25)</td>
</tr>
<tr>
<td><strong>LOS ambi-care, days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>9.9 ± 3.8</td>
<td>9.5 ± 3.8</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>9 (8,10.3)</td>
<td>8 (7,11)</td>
</tr>
<tr>
<td>range</td>
<td>4-18</td>
<td>3-17</td>
</tr>
<tr>
<td>Not admitted to ambi-care (n)</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td><strong>Readmitted to hospital within 3/12 post ASCT, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died during admission</td>
<td>6 (26)</td>
<td>3 (19)</td>
</tr>
<tr>
<td><strong>AHP referral during admission, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>8 (34)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Number of contacts, median (range)</td>
<td>1 (0-8)</td>
<td>1.5 (0-4)</td>
</tr>
<tr>
<td>Number of contacts, mean ± SD</td>
<td>2.14 ± 2.8</td>
<td>1.83 ± 1.5</td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td>4 (17)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Dietetics</td>
<td>9 (39)</td>
<td>10 (63)</td>
</tr>
</tbody>
</table>
5.5 Attrition

5.5.1 Attrition: overall

The attrition rate for the trial was 34% with 33 out of 50 (66%) participants completing an assessment at the final timepoint. The main cause of attrition was participants being withdrawn from the study because they did not proceed to ASCT (n=10, 20%) due to relapsed/progressive disease or other clinical decision. Therefore, attrition mostly occurred before first follow-up assessment timepoint.

Attrition between T0 and T3 was 30% (n=8) and 39% (n=9) for the control and intervention arms respectively. Attrition due to participants being withdrawn for not proceeding to ASCT was 15% (n=4) in control arm and 26% (n=6) in the intervention arm. One participant in each arm died during the study. Both deaths followed a COVID-19 diagnosis and were unrelated to the study.

Despite the high proportion of participants withdrawn for not proceeding to ASCT, loss to follow-up for other reasons was low. Of those who proceeded to receive an ASCT and were contacted to complete the follow-up study assessments (n=39), 33 completed a final follow-up assessment with a completion rate of 85% (94% intervention arm; 78% control arm).

5.5.2 Attrition of participants recruited to original face-to-face protocol

Of those recruited to the original face-to-face protocol, the attrition rate was 31% with 25 of 36 (69%) of participants recruited prior to the pandemic completing a final study assessment. Attrition due to not proceeding to ASCT was 22% (n=8). Two participants (6%) were lost to follow-up and one (3%) died during ASCT admission. When examined by group, there were more participants withdrawn from the intervention group than from the control group (33% versus 14%), loss to follow-up was similar and proportion completing a final study assessment was 76% of control participants and 60% of intervention participants.
5.5.3 Attrition of participants recruited to amended virtual protocol

The attrition rate of participants recruited to the amended virtual study protocol was 43%, with 8 of 14 (57%) completing a final study assessment. Attrition due to not proceeding to ASCT was 14% (n=2), lower than the face-to-face recruits but loss to follow-up was greater (n=3; 21%). One participant (7%) died prior to ASCT admission. When examined by group, all those lost to follow-up belonged to the control group and the proportion completing a final study assessment differed by group (33% of control participants versus 75% of intervention).

5.6 Completion of study assessments

The number of face-to-face and virtual assessments carried out at each timepoint are shown in Figure 5.2.

From the participants who were assessed face-to-face at baseline using the original protocol (n=36) all completed hand grip strength testing and a six minute walk test (6MWT). One participant (3%) refused to complete a timed sit to stand (STS) test. All participants recruited using the virtual study protocol completed a timed STS test and 11 of 12 participants (92%) returned the questionnaires by post (two participants recruited using the virtual protocol were assessed in person during routine clinical visits).

All participants (n=24) who were assessed face-to-face at admission for ASCT (T1) completed hand grip strength testing but 1 (4%) refused to complete a 6MWT and timed STS test. Of the 15 T1 assessment questionnaire packs posted to participants 11 were returned (73%). Of those who did not return their postal questionnaires, 3 were in the control group and 1 in the intervention group.

On discharge from hospital (T2) twenty-two participants were offered a face-to-face assessment. One participant did not attend the face-to-face assessment and one participant was discharged prior to assessment so was posted questionnaires only. Of the 20 seen in person, one (5%) refused to complete hand grip strength testing, three (15%) refused to complete a 6MWT, two (10%) felt unable to complete a timed STS test and four (20%) refused. Of the sixteen T2 assessment packs sent for postal return, 9
were returned (56%). Of those who did not return their postal questionnaires 4 were in the control group and 3 were intervention.

Fourteen participants underwent face-to-face assessments for final follow-up (T3). Of those, one (7%) felt unable to complete hand grip strength testing and one (7%) refused, one (7%) felt unable to complete a 6MWT and two (14%) refused, one (7%) felt unable to complete timed STS test and one (7%) refused. Twenty-four T3 assessments were administered via postal return questionnaire, of which 19 (79%) were returned. Of those who did not return their postal questionnaires 4 were in the control group and 1 was intervention.

5.7 Adverse Events

There were two adverse events during the trial, one in each study arm. One participant in the control group was found to have a new spinal fracture at the site of a previously healed fracture. This was found on routine imaging done prior to ASCT admission. This adverse event was not related to taking part in the study. One participant in the intervention arm reported an episode of dizziness during a face-to-face supervised exercise session. This mild episode occurred after the participant had been aerobically exercising and resolved with two minutes of rest. This adverse event was thought to be related to the intervention.
Figure 5.2 Number of face-to-face assessments carried out, with number of objective tests not completed and number of virtual/postal assessments carried out, with number of questionnaire packs returned at each timepoint
5.8 Adherence and acceptability of the intervention

In this section adherence in terms of attendance of supervised physiotherapy sessions before, during and after ASCT, as well as the number of weeks available to receive the intervention in the pre-ASCT phase of the study (T0-T1) are described. Discussions during development of the original study protocol with myeloma ASCT clinicians raised uncertainty regarding the number of weeks available between referral for ASCT and admission for ASCT. In order to ascertain the window of opportunity in which to deliver a prehabilitation intervention an outcome of interest was determining the number of weeks typically available pre-ASCT in which to deliver an exercise programme. It was proposed that patients would have between 6-12 weeks between referral and ASCT based on clinician opinion.

Results related to adherence and acceptability and availability of weeks pre-ASCT for both the original protocol and amended virtual protocol participants have been hugely influenced by some experiencing delays to their ASCT because of the pandemic. Therefore, a sub-group analysis of participants who proceeded to ASCT prior to declaration of the COVID-19 pandemic (before March 2020) and progressed through the intervention as intended in the original protocol is also described (Section 5.8.1.1). This analysis was undertaken to provide some insight into feasibility and acceptability of intervention delivery as intended in the original study protocol published (McCourt et al., 2020) before the pandemic caused major disruption.

Participants were given a separate paper-based intervention booklet for each phase of the intervention and asked to return them, but adherence to this was poor. 26% (6/23) participants returned a prehabilitation pre-ASCT booklet. 25% (4/16) participants who were admitted for ASCT returned an ASCT admission booklet. 38% (6/16) participants returned a rehabilitation post-ASCT booklet. In total only three participants (19%) returned a booklet for all three phases.
5.8.1  **Adherence and acceptability: original face-to-face intervention**

15 participants were recruited and randomised to the intervention arm of the original protocol. Of these, 12 (80%) attended at least one supervised gym session with the physiotherapist in the pre-ASCT phase. The number of gym sessions attended by intervention participants ranged from 0 to 5 sessions. The median attendance was 1 session (IQR 1,3.5). The number of weeks between randomisation and admission for ASCT ranged between 2 weeks and 55 weeks. The median number of weeks available to receive the intervention was 13 (IQR 7.5,35.5). Five (33%) participants did not proceed to ASCT due to disease progression or other clinical reason not to proceed. When investigated separately, there was a small difference between median weeks available to receive the intervention between participants who proceeded to ASCT (median (IQR) 14 (7.25,35.8), range 5-55)) and those who were withdrawn (median (IQR) 9 (9,19), range 2-52)). The wide variance in range of weeks between randomisation and ASCT or withdrawal was due to a number of participants having their ASCT delayed due to the COVID-19 pandemic.

In phase two of the intervention during hospital admission for ASCT, 8 (80%) of the 10 face-to-face intervention participants who underwent ASCT received at least one telephone or face-to-face contact with the physiotherapist. The number of physiotherapist contacts during admission ranged between 0 to 3 with a median of 1.5 contacts (IQR 1,2).

In phase three of the intervention, following discharge from ASCT admission, 9/10 (90%) participants engaged in at least 4 telephone support sessions with the physiotherapist. During the approximate three month period between discharge and post-ASCT clinic attendance the number of contacts per participant ranged from 0 to 10 contacts. The median number of contacts with the physiotherapist was 8 (IQR 5,9.5).

5.8.1.1  **Sub-group of participants who proceeded to ASCT prior to COVID-19 pandemic**

In order to explore participant adherence and provision of intervention during the typical ASCT clinical pathway, an analysis of participants who completed the study prior to the COVID-19 pandemic was carried out. Six participants were randomised to the face-to-face intervention and underwent their ASCT prior to March 2020. Of these, 5
(83%) attended at least 1 gym session with the physiotherapist in the pre-ASCT phase with the number of gym sessions attended ranging from 0-5 sessions. The median attendance was 3.5 sessions (IQR 1.5,4.8). The median number of weeks available to receive the intervention in phase 1 for this subgroup was 7.5 (IQR 6.3,11.8) and ranged from 5 to 15 weeks.

In phase two of the intervention, during hospital admission for ASCT, 5 (83%) of the participants received at least two telephone or face-to-face contacts with the physiotherapist. The number of sessions during admission ranged between 0 and 3 with a median of 2 contacts (IQR 2,2).

In the post-ASCT discharge phase three of the intervention, 5 of 6 (83%) of the participants engaged in at least 5 telephone support sessions with the physiotherapist. During this approximate three-month period the number of contacts per participant ranged from 0-10 contacts with a median number of contacts of 9 (IQR 5.6,10).

5.8.2  Adherence and acceptability: amended virtual intervention

Following the amendment to virtual delivery, 8 participants were randomised to the intervention arm. Of these, 7 (78%) attended at least one virtual session with the physiotherapist in the pre-ASCT phase 1 of the intervention. The median attendance 3.5 sessions (IQR 1,10.8) and the number of virtual exercise sessions attended by participants ranged from 0 and 27 sessions. The number of weeks between randomisation and admission for ASCT ranged between 1 and 33 weeks for the virtual participants with a median of 8.5 (IRQ 6.5,21) weeks available to receive the intervention pre-ASCT. Two (25%) participants were withdrawn and did not proceed to ASCT. When explored separately, there were differences between the median number weeks available to receive the intervention between participants who proceeded to ASCT (median (IQR) 8.5 (6.5,21), range 1-33)) and those who were withdrawn (median (IQR) 15 (13.5,16.5), range 12-18)), with withdrawn participants having more opportunity to attend more virtual intervention sessions.

During admission for ASCT, in phase 2 of the intervention, 3 (50%) of the remaining 6 participants received at least one contact from the physiotherapist. The range of contacts was between 0 and 3 with a median of 0.5 contacts (IQR 0,1.8).
Following discharge from the ASCT admission, in phase three of the intervention, 4 (67%) of the remaining 6 participants engaged in at least 7 telephone contacts with the physiotherapist during their recovery. During this approximate three-month period the number of contacts per participant ranged between 0 and 11 contacts. The median number of contacts with the physiotherapist in this phase was 8 (IQR 1.8, 9.8).

Figure 5.3 provides a summary of adherence in terms of attendance of physiotherapy sessions at each phase of the study, and by study protocol recruited to.

![Figure 5.3 Summary of adherence to intervention at each phase of the study and by study protocol]

5.9 Discussion

This chapter summarised the results of primary outcomes related to feasibility of the pilot trial and described the characteristics of the study sample. Protocol adaptations in response to the pandemic posed challenges to interpretation of all of the trial outcomes. Although some analysis in terms of assessing feasibility was separated by enrolment to the face-to-face or virtual protocol, for the most part results were described collectively for the whole sample.

The overall recruitment rate was lower than the a priori target for feasibility of 50%, however there were marked differences in rates and reasons for declining depending on protocol. Face-to-face recruitment rate was 44% compared to 52% for the virtual approach. Travel or distance to the specialist centre was the main reason for declining
participation when approached for the face-to-face protocol, with many potential participants contemplating the weekly travel required if allocated to the intervention arm. Travel was eliminated for the virtual protocol and the reasons for declining the study were more related to not responding to study invite or not being interested. The recruitment rates are lower than those reported by other trials of exercise interventions during stem cell transplant (reporting uptake of 63-68%) (van Haren et al., 2018; Wood et al., 2020) and even lower than those from other myeloma samples who reported rates of uptake between 75-80% (Groeneveldt et al., 2013; Larsen et al., 2019). None of the forementioned studies were conducted in the UK and there may be different geographical factors at play when accessing specialist centres for trials. A single arm feasibility study of a prehabilitation intervention delivered prior to ASCT in myeloma conducted in the UK offers the closest comparable study. Mawson et al. (2021) reported a recruitment rate of 41%, with most eligible participants declining participation after being offered the intervention. Travel and distance to the study venue was cited as the foremost reason for declining and aligns with the results from this trial.

Differences in eligibility were evident with double the proportion of those screened for the virtual protocol being deemed ineligible compared to the original protocol. This difference was largely due to the virtually screened participants being too close to ASCT with imminent admission to hospital. Potential participants being identified from a waitlist following the first wave of the pandemic, rather than chronologically based on initial referral to the care pathway as intended in the original protocol, led to this discrepancy and may therefore be an unreliable estimate of ineligibility. However, virtually recruited studies have been found to recruit more geographically spread participants, at a faster rate to traditionally recruited studies (Moseson et al., 2020) and so given the uncertainty at the time due to the pandemic, future work should aim to better quantify recruitment and eligibility rates for a virtually delivered study enrolling at the beginning of the ASCT care pathway as was originally intended.

Attrition for the trial was acceptable with an attrition rate of 34% which is in line with other literature in the field. A review of nine pragmatic studies within exercise oncology reported attrition rates of between 22-56% (Czosnek et al., 2021). Exercise studies among myeloma patients range in attrition from 11-43% (Coleman et al., 2003; Coleman et al., 2008; Larsen et al., 2019; Koutoukidis et al., 2020; Mawson et al., 2021). Attrition
rates do seem to vary within the context of stem cell transplantation with some reporting rates as high as 70% (Santa Mina et al., 2020) and as low as 5% (Abo et al., 2021b) in allogeneic patients. The prominent reason for attrition was related to not proceeding to undergo ASCT and therefore most participants were lost prior to first follow-up assessment. Dropout for other reasons was low with a high study completion rate among those who actually underwent ASCT (85%). Whilst loss to follow-up and the proportion completing a final study assessment was similar between allocations in the face-to-face recruited participants, there was a notable difference in the virtual delivery. All those lost to follow-up in the virtual protocol were control participants and only a third of controls returned a final study assessment compared to 75% of intervention participants. This highlights a possible limitation in using postal return for study assessments, especially in studies with ‘inactive’ control conditions where participants may be disenchanted by allocation and lack motivation to continue contributing to the study. The strength of the original face-to-face assessments was their alignment with usual care appointments which resulted in better data completion, with only one out of ninety-eight assessments missed.

A positive outcome related to feasibility was the low occurrence of adverse events, with no serious adverse events occurring. The occurrence of a new spinal fracture in a member of the control group highlights the fragility of the study population and the continued need for close monitoring and individualised tailoring of exercise among people with myeloma. Over 75% of participants enrolled in this trial had myeloma related bone disease and over a third had previously required a spinal brace for spinal instability either due to presence of lesions or fracture or risk of potential fracture. Similar levels of bone disease have been reported in more recent myeloma exercise studies (Larsen et al., 2019; Larsen et al., 2020). Fractures in myeloma are common during the first three months of anti-myeloma treatment (Morgan et al., 2011). Management of spinal disease with either vertebral augmentation or spinal bracing, soon after diagnosis, is believed to improve QOL and patient reported outcomes in patients with spinal myeloma (Malhotra et al., 2016). However, presence of skeletal involvement has been associated with increased reporting of moderate or severe physical concerns in mainly ‘fit’, free-living myeloma survivors in remission of disease, including poorer QOL, greater pain and fatigue (Nielsen et al., 2021). Half of the study
sample reported disease related pain, although an objective measure of pain severity was not captured. The proportion of participants with bone disease and history of spinal bracing aligns with other studies and therefore indicates promise of representativeness of our sample at baseline assessment.

Analysis of data related to adherence and acceptability of the intervention was hampered by the effects of the COVID-19 pandemic. Participants recruited to the original face-to-face protocol just prior to the pandemic commenced the face-to-face intervention but when ASCT treatment was paused and restrictions placed upon research visits, they continued to receive contact from the physiotherapist but by telephone in the early part of the disruption. Analysis of attendance data for the supervised sessions in the prehabilitation phase of the intervention for these participants has resulted in variable length of time available to receive input and low median attendance, but this data is not a reliable measure of the intervention delivery as intended. The sub analysis of intervention participants who completed the prehabilitation phase prior to the COVID-19 pandemic gives a clearer indication of the feasibility related to attendance of a face-to-face protocol. This data, although only including a small number of participants, indicates that the time available to intervene with exercise prehabilitation in the original ASCT pathway is 7.5 weeks, although the timeframe ranged between 5 to 15 weeks among participants. Median attendance of supervised sessions was 3.5 face-to-face sessions, indicating that participants attended approximately half of the available weeks. Median weeks available and median attendance was similar for those recruited to the virtual protocol, who only received virtual prehabilitation delivery. However, again the effects of the second wave of the pandemic also influenced the variability in this data with both weeks available and number of weeks attended ranging widely as some participants had their ASCT postponed due to the second wave of the pandemic.

Attendance of supervised exercise sessions is only one measure used to describe adherence in exercise trials, and should be considered alongside measurement of completion rates based on exercise intensity and duration (Visek et al., 2011). Reporting of adherence to exercise is inconsistent among exercise literature with many continuing to focus on adherence as proportion of sessions attended (Hawley-Hague et al., 2016). To date, most studies of exercise among people living with and beyond cancer evaluated
adherence based on attendance of sessions with little reporting of whether participants completed the intervention as intended, which gives little interpretive information regarding intervention fidelity (Christensen et al., 2018). I had this in mind when the protocol for this trial was developed, designing an intervention booklet that not only facilitated intervention delivery, with incorporated behaviour change techniques, but also provided means of recording exercise behaviour. The intervention booklet (Appendix E) contained space for the physiotherapist or participant to report duration and intensity of the different types of exercise as well as reasons adaptation or inability to complete the prescribed programme. However, deeper investigation of adherence to the exercise programme as prescribed was not possible due to poor return of intervention booklets.

The study sample of 50 participants referred for consideration of ASCT was representative by age and sex compared to published real-world data from patients referred to our centre for ASCT during the study recruitment period (Camilleri et al., 2022). Both allocation groups were similar in demographic characteristics. The ethnicity of the sample was predominately of white background, with 26% of participants reporting being of Black, Asian or other ethnic background. Incidence of myeloma in the UK is approximately three times higher among those of Black ethnicity compared to those of White ethnicity (Shirley et al., 2013; Delon et al., 2022) and despite the disease disproportionately affecting those from racially minoritised populations, these groups are known to be underrepresented in myeloma clinical trials (Gormley et al., 2021; Habr & Corsaro, 2022). A pooled analysis of five UK clinical trials including 7,291 myeloma patients found only 5% were from Black, Asian or other ethnic background (Popat et al., 2021). The more diverse representation in this exercise trial is not fully understood but future exploration of participation in myeloma survivorship research should explore differences in acceptability and participation in different kinds of research.

The mean body mass index (BMI) for the study sample was within the overweight range and the majority of the sample (72%) were classified as overweight or obese. The increased incidence of myeloma with increasing age, coupled with obesity as a risk factor for the disease and its treatment requiring high-dose corticosteroid use, combine
to make myeloma patients particularly susceptible to ‘sarcopenic-obesity’. Prevalence of sarcopenia-obesity is high among intensively treated myeloma patients, and its presence is likely to affect clinical outcomes as well as having significant implications on health outcomes into survivorship (Greenfield et al., 2014). Importantly, both components of this phenotype are modifiable through aerobic and resistance exercise alongside nutritional intervention (Hsu et al., 2019; Koliaki et al., 2019) further warranting deeper exploration of lifestyle related research in myeloma (Shapiro et al., 2021). A limitation of this trial was lack of robust measurement of body composition, especially lean muscle mass, therefore assessment of sarcopenia and sarcopenic-obesity in this study sample was not possible.

5.10 Summary

In summary, this chapter described baseline characteristics of the study sample enrolled in the PERCEPT pilot trial, which despite being smaller than intended, appears to be generally representative of transplant eligible myeloma patients referred for ASCT. The inclusion of patients with significant bone disease, including those who required spinal bracing and high prevalence of pain reported by the sample demonstrates the complex nature of this cancer in the context of exercise delivery. Overall, results indicate feasibility of the pilot trial in relation to recruitment rate, attrition, and acceptability of the intervention. However, a number of process-related deficits became evident that undermined thorough evaluation of the intervention, most notably a reliance on paper-based intervention resources, therefore inability to fully investigate adherence to the exercise intervention and postal return of assessments when the study protocol was adapted in response to COVID-19. Despite the disruption of the pandemic, rapid adaptation of the trial allowed continuation of recruitment and opportunity to investigate feasibility of both face-to-face and virtually delivered research.

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4 Sarcopenic obesity is a phenotype defined as the concurrent presence of sarcopenia, a progressive reduction in skeletal muscle mass and function, in the presence of high fat mass or BMI (Koliaki et al. 2019).
Chapter 6  PERCEPT trial results: The effects of the exercise intervention on functional capacity and physical activity

6.1  Introduction

This chapter will summarise the secondary outcomes from the trial that relate to functional capacity and physical activity behaviour. Objective measures of functional capacity included timed sit to stand (STS) test, six-minute walk test (6MWT) and hand grip strength testing. Outcomes related to physical activity include a self-report questionnaire-based measure of physical activity recalling the week prior to assessment at each timepoint and an objective measure of physical activity and sedentary behaviour using accelerometry. Self-efficacy for exercise is also presented.

Due to adaptation of the study protocol in response to the COVID-19 pandemic (described in Chapter 3) the numbers of objective measures completed at all timepoints varied and are small at follow-up timepoints therefore analysis of most outcomes is solely descriptive and no distinction has been made between face-to-face and virtual intervention recipients. For a number of objective measures a sub analysis of participants who provided data at all timepoints is also described.

6.2  Functional capacity

6.2.1  Timed sit to stand test

Two different STS test protocols were used and have been described in the Chapter 3 Section 3.7.3.1. As previously explained a correlation analysis indicated good agreement and provided an equation to extrapolate an “calculated 1 minute STS score” for all participants who had undergone the 30 second STS test under the original protocol. These calculated scores were combined with the scores of those who underwent the longer protocol to provide increased sample size for analysis. A calculated 1 minute STS score was extrapolated for 35 participants at T0, 21 at T1, 13 at T2 and 12 at T3. The raw scores for both the 30 second, 1 minute test protocols and the combined calculated 1 minute scores at all timepoints are presented in Appendix H Table 1.

The calculated 1 minute STS variable was analysed using a linear mixed effect model (LMEM) for repeated measures adjusted for time from T0 to ASCT, as described in the
Chapter 3 Section 3.9. Time T0 to ASCT was not significant within the model (F(1)=0.01, p=.936) but timepoint (F(3)=10.5, p<.001) and the interaction between allocation × timepoint was significant (F(3)=5.0, p=.003). The difference in change between groups from T0 and T1 was 5.7 (95% CI 1.5, 10, SE 2.2, p=0.01) in favour of the intervention group and was significant. The fixed effect parameters estimates from the adjusted model are presented in Table 6.1.

Table 6.1 Fixed effect parameter estimates with 95% confidence intervals (CI) and p-values for calculated 1 minute sit to stand scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation (Intervention – Control)</td>
<td>0.71</td>
<td>-4.4, 5.8</td>
<td>0.79</td>
</tr>
<tr>
<td>Timepoint (T0 – T1)</td>
<td>-3.02</td>
<td>-5.2, -0.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Timepoint (T1 - T2)</td>
<td>4.48</td>
<td>1.9, 7.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Timepoint (T2 - T3)</td>
<td>-6.58</td>
<td>-9.3, -3.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time between T0 to ASCT</td>
<td>-0.0</td>
<td>-0.03, 0.02</td>
<td>0.94</td>
</tr>
<tr>
<td>Allocation × T1</td>
<td>-5.73</td>
<td>-10, -1.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Allocation × T2</td>
<td>1.4</td>
<td>-3.8, 6.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Allocation × T3</td>
<td>-4.39</td>
<td>-9.8, 1.1</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Figure 6.1 Mean calculated 1 minute sit to stand repetitions (95% confidence intervals) between timepoints for both groups (adjusted model)
Mean estimates and between group differences at each timepoint from the adjusted model are presented in Table 6.2 and plotted in Figure 6.1. Group mean values at T0 were lower in the intervention group compared to the control, with a between group difference that is in line with a MID (Control: 26.3 ± SE 1.8; Intervention: 22.3 ± SE 2.1). At all follow-up timepoints the intervention group had greater mean values, most notably at T3 with a between group difference beyond a MID of 3-4 (mean difference +4.7 ± SE 3.2).

Table 6.2 Mean estimates ± standard error (SE) and between group contrasts for calculated 1 minute sit to stand scores (model included time from T0 to ASCT as a covariate)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Between group difference ± SE (Intervention-Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean estimate ± SE</td>
<td>Mean estimate ± SE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Calculated 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>minute sit to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stand (repetitions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>26.3 ± 1.8</td>
<td>22.3 ± 2.1</td>
<td>-4 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>22.7, 29.9</td>
<td>18.1, 26.6</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>26.5 ± 1.9</td>
<td>28.2 ± 2.2</td>
<td>1.7 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>22.6, 30.3</td>
<td>23.8, 32.7</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>22.7 ± 2.1</td>
<td>23 ± 2.5</td>
<td>0.4 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>18.5, 26.9</td>
<td>18.1, 27.9</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>27.1 ± 2.1</td>
<td>31.8 ± 2.2</td>
<td>4.7 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>22.9, 31.3</td>
<td>27.4, 36.3</td>
<td></td>
</tr>
</tbody>
</table>

Within-group differences are presented in Table 6.3. As seen in Figure 6.1, the greatest within-group changes were evident in the intervention group, following a pattern of improvement in the pre-ASCT phase, with deterioration between admission and discharge from ASCT hospital stay and followed by improvement again in the post-ASCT phase. The intervention group changes at all timepoints were greater than the reported MID for the 1 minute STS test. Between T0 and T1 in the prehab phase there was a difference in the intervention group (+5.9, 95% CI 2.5, 9.3) but not the control group (+0.2, 95% CI -3.1, 2.8). Both groups deteriorated during admission for ASCT (T1-T2) and improved again between T2 and T3. Improvement between following discharge from hospital (T2 and T3) within the intervention group was twice that of the control group (Control: +4.4, 95% CI 0.4 to 8.3; Intervention: +8.8, 95% CI 4.7 to 12.9). Overall change in calculated 1 minute STS values across the length of the study (T0 to T3) for the intervention group (+9.5, 95% CI 6.1 to 12.9) was more than three times the MID than
that of the control group (+0.8, 95% CI -2.7 to 4.2). The unadjusted model estimates are presented in Appendix H Table 2.

### Table 6.3 Within-group differences across timepoints for calculated 1 minute sit to stand scores

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Control Estimate</th>
<th>95% CI</th>
<th>Intervention Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated 1 minute sit to stand (repetitions)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0 to T1</td>
<td>0.2</td>
<td>-3.1, 2.8</td>
<td>5.9</td>
<td>2.5, 9.3</td>
</tr>
<tr>
<td>T1 to T2</td>
<td>-3.8</td>
<td>-7.3, -0.3</td>
<td>-5.2</td>
<td>-9.2, -1.4</td>
</tr>
<tr>
<td>T2 to T3</td>
<td>4.4</td>
<td>0.4, 8.3</td>
<td>8.8</td>
<td>4.7, 12.9</td>
</tr>
<tr>
<td>T0 to T3</td>
<td>0.8</td>
<td>-2.7, 4.2</td>
<td>9.5</td>
<td>6.1, 12.9</td>
</tr>
</tbody>
</table>

### 6.2.2 Six minute walk test (6MWT)

The 6MWT was assessed at baseline in n=36 participants prior to the study being amended to virtual recruitment. Of these thirty-six, n=25 completed the study and 11/25 (44%) underwent a 6MWT at all timepoints. Given the small samples per group at each timepoint, particularly reduced in the intervention arm and the non-normality of the data only descriptive analysis of data was carried out.

### Table 6.4 Raw scores for six minute walk test per group at each timepoint

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>N</th>
<th>Control Mean ±SD</th>
<th>95% CI Range</th>
<th>Intervention Mean ±SD</th>
<th>95% CI Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six minute walk test distance (metres)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>21</td>
<td>487.8 ± 141.1</td>
<td>427.4, 548.1</td>
<td>470.4 ± 123.4</td>
<td>408, 532.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>540 (391.5, 590.8)</td>
<td>252.1-690</td>
<td>487.7 (404,561.4)</td>
<td>180-673.9</td>
</tr>
<tr>
<td>T1</td>
<td>15</td>
<td>516.5 ± 113.9</td>
<td>458.9, 574.1</td>
<td>541.6 ± 120.6</td>
<td>458.1, 625.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>530.4 (433.9, 607.5)</td>
<td>261.3-666.5</td>
<td>561.5 (467.6,644.8)</td>
<td>341.7-662.8</td>
</tr>
<tr>
<td>T2</td>
<td>12</td>
<td>404.1 ± 122.8</td>
<td>334.6, 473.6</td>
<td>521.0 ± 75.9</td>
<td>454.5, 587.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>408.5 (343.4, 492.4)</td>
<td>172-579</td>
<td>549.1 (523.1,569.1)</td>
<td>390-573.9</td>
</tr>
<tr>
<td>T3</td>
<td>7</td>
<td>506.4 ± 71.5</td>
<td>453.5, 559.4</td>
<td>625.0 ± 63</td>
<td>563.3,686.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>506.9 (457.6,558.9)</td>
<td>402.1-603.1</td>
<td>638.5 (597.7,665.8)</td>
<td>540-683.2</td>
</tr>
</tbody>
</table>

Raw scores for 6MWT are presented in Table 6.4. The median percentage of predicted 6MWT value for the whole sample at T0 was 79% (IQR 60.1,84.9) and 19/36 (53%) had
a baseline 6MWT score lower than 80% of their predicted value. The control group had a better 6MWT group median score at T0 (Control: 540m (IQR 391.5,590.8); Intervention: 487.7m (IQR 404,561.4)) but the intervention group had better median scores at all follow-up timepoints. Figure 6.2 shows the median scores (IQR) plotted for each timepoint. Changes are seen in both groups with improvement in intervention group score between T0 and T1 (Median change Control: -9.6m vs Intervention: +73.8m), greater deterioration in the control group between T1 and T2 (Median change Control: -121.9m vs Intervention: -12.4m), and improvement in both groups between T2 and T3 (Median change Control: +98.4m vs Intervention: +89.4m). The intervention group showed improvements greater than the MCID between T0 and T1, whereas the control group deteriorated. The control group score also decreased more than three times the MCID between T1 and T2, with both groups improving approximately three times the MCID between T2 and T3. Overall, across the length of the study (T0-T3) the intervention group 6MWT median score increased by over five times the MCID, whereas the control group median score suffered a deterioration in the range of the MCID (Median change Control: -33.1m vs Intervention: +150.8m). Figure 6.2 also shows that all group median scores were below predicted scores calculated for the whole sample at baseline with the intervention group median at T3 being the closest to expected scores.
Due to the small numbers of participants who completed follow-up 6MWTs possibly conflating these provisional results, a further descriptive analysis of a subgroup of participants who completed a 6MWT at all timepoints was conducted. Of the eleven participants, seven were randomised to the control group and four to the intervention. Figure 6.3 shows the median scores (IQR) for these participants by group at each timepoint. Both groups show a similar pattern of change between timepoints. Both groups improved beyond the MCID between T0 and T1, with greater improvement in the intervention participants (Median change Control: +33.3 vs Intervention: +54.6m). Both group median scores decreased during ASCT admission (T1-T2) with the intervention group showing less deterioration (median change Control: -148.7m vs Intervention: -76.8m). Both groups improved again between T2 and T3. Over the length of the study period (T0-T3) the intervention group 6MWT median score increased beyond that considered MCID, albeit much more modest than the full sample analysis, but the control group median score suffered a deterioration in the range of the MCID and equal to that of the full sample (Median change Control: -33.1 vs Intervention: +57.1). This analysis of completers, although it only included a very small number of participants, may indicate a more accurate indication of changes in 6MWT between groups over time.

**Figure 6.3 Median (interquartile range) six minute walk test distances per group across timepoints for n=11 participants who completed a 6MWT at all timepoints. The red line indicates the median predicted distance expected for this sample**
6.2.3 Hand grip strength

Hand grip strength was assessed at baseline in n=37 participants prior to amendment to the virtual protocol. Of these n=26 completed the study and n=12/26 (50%) had hand grip strength assessed at all timepoints. Raw scores for hand grip strength in the dominant hand are presented in Table 6.5. The median percentage of predicted hand grip strength value (dominant hand) for the whole sample at T0 was 85.2% (IQR 72.1,102.6) and 11/36 (31%) had a baseline hand grip strength value lower than 80% of their predicted value. Figure 6.4 shows the median scores (IQR) plotted for each timepoint. The error bars representing IQR indicate large variation in values in both groups with overlap at all timepoints indicating little difference. There was little change in hand grip strength across the study timepoints. The only differences that were within the range considered MCID was the increase in median for the intervention group between T1 and T2 (Median change Intervention: +6.5kg) and over the study period (T0-T3) for the control group (Median change Control: -5.2kg vs Intervention: -2.5kg). But MCID for hand grip strength are based on limited literature and should be used cautiously (Bohannon, 2019a) so this value at the lower end of that considered MCID may not be important. A sub analysis of participants who completed hand grip strength testing at all timepoints (Control n=8, Intervention n=4) indicated no meaningful change within or between groups at any timepoint (Appendix H Table 3).

Table 6.5 Hand grip strength (dominant hand)

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean ±SD Median (IQR)</td>
</tr>
<tr>
<td>T0</td>
<td>21</td>
<td>30.6 ± 8.7 33.7 (24.3,37.3)</td>
</tr>
<tr>
<td>T1</td>
<td>16</td>
<td>31 ± 8.7 31.2 (25.8,37.8)</td>
</tr>
<tr>
<td>T2</td>
<td>13</td>
<td>29.1 ± 9.5 28 (23.7,37.3)</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>28.5 ± 7.3 28.5 (26.2,34)</td>
</tr>
</tbody>
</table>
Figure 6.4 Median (interquartile range) hand grip strength values for dominant hand per group across timepoints. The red line indicates the median predicted value expected for the sample.

6.3 Physical activity and exercise behaviour

6.3.1 Self-reported physical activity: International physical activity questionnaire – short form (IPAQ-SF)

Administration of the IPAQ-SF questionnaire of self-reported physical activity was possible for both the original and virtual study protocols therefore data available at each timepoint was more complete than other outcomes described in this chapter. At baseline (T0) n=49 participants provided a score, n=35 at T1, n=30 at T2 and n=32 at T3.

The IPAQ-SF is presented using median and interquartile range as advised in scoring guidance due to the non-normal distribution of energy expenditure which is typical in most populations (IPAQ, 2005). Indeed, data collected in this study was shown to also be highly skewed and non-normally distributed at all timepoints for both groups. A LMEM was run but the model did not meet the assumptions required with highly significant Shapiro-Wilk test (0.9, p<.001) and a residual-predicted scatterplot that indicated clustering and therefore data has been presented descriptively. Due to the recall nature of self-reported physical activity questionnaires, scores at each timepoint refer to physical activity in the week prior to assessment, most notably T1 refers to
physical activity in the week prior to admission to hospital for ASCT and T2 refers to physical activity in the week prior to discharge from hospital.

Both groups had similar levels of total self-reported physical activity in metabolic equivalent task (MET) minutes per week at T0 with changes observed between groups over subsequent timepoints. Figure 6.5 shows changes in median total self-reported physical activity per week for each group at each timepoint. The amount of total physical activity reported by the intervention group improved in the prehabilitation phase between T0 and T1 greater than the control group (Control: median 1512 MET.mins/week, IQR 639, 2094.8; Intervention: 2910 MET.mins/week, IQR 1138.5, 4172), with both groups dropping their physical activity levels to zero prior to leaving hospital (T2) and improving again between T2 and T3 with greater improvement in the intervention group (Control: 924 MET.mins/week, IQR 678, 2430; Intervention: 2259 MET.mins/week, IQR 887.3, 3877.5). Overall, across the length of the study period the control group levels of self-reported physical activity were lower at T3 compared to T0, whereas the intervention group reported higher levels of physical activity than at baseline. At T1 after the prehabilitation phase and at T3 three months post-ASCT the intervention group reported levels of self-reported physical activity approximately twice
IPAQ-SF responses were used to ascertain proportion of participants meeting physical activity guidelines at each timepoint (Figure 6.6). At T0, overall 22% of participants were reporting activity levels that met recommendations for aerobic physical activity. At T3, three months post-ASCT thirty-two percent of the sample were sufficiently active. There was a small difference between groups in the number meeting guidelines at baseline with the intervention group more active than the control (Intervention: 26%; Control: 19%). There was no change in the proportion of control participants meeting guidelines in the week prior to ASCT admission (T1) whereas there was a small increase in the intervention arm (Intervention: +7%; Control: +1%). One participant in the intervention group provided scores at T2 in line with meeting physical activity guidelines. At T3, three months following ASCT there were more participants in the intervention group reporting physical activity in line with recommended levels (Intervention: 40%; Control: 25%). Across the length of the study (T0-T3) the proportion of those meeting physical activity guidelines rose by 14% in the intervention group compared to 6% in the control group.

Figure 6.6 Proportion of participants meeting aerobic physical activity guidelines per group at each timepoint as reported using the IPAQ-SF (Meeting guidelines was defined as reporting ≥150 minutes of moderate or vigorous activity per week or ≥30 minutes on at least 5 days per week)
The IPAQ-SF questionnaire item related to time spent in sitting showed similar changes between timepoints for both groups with decreases in sitting time at T1 and increased time spent sitting reported at T2. The intervention group showed a greater reduction in sitting time between T0 and T1 and had lower levels of sitting time at T2 and T3 compared to the control group. Self-reported physical activity and sitting time from the IPAQ-SF are presented in Table 6.6.

### Table 6.6 Self-reported physical activity and sitting time measured by the IPAQ-SF per group per timepoint

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>Physical Activity (MET minutes per week)</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>26</td>
<td>1180 (519.8, 2655)</td>
</tr>
<tr>
<td>T1</td>
<td>20</td>
<td>1512 (639, 2094.8)</td>
</tr>
<tr>
<td>T2</td>
<td>18</td>
<td>0 (0, 24.8)</td>
</tr>
<tr>
<td>T3</td>
<td>17</td>
<td>924 (678, 2430)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sitting time (Minutes per week)</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>25</td>
<td>300 (240, 480)</td>
</tr>
<tr>
<td>T1</td>
<td>17</td>
<td>330 (240, 480)</td>
</tr>
<tr>
<td>T2</td>
<td>16</td>
<td>930 (345, 1380)</td>
</tr>
<tr>
<td>T3</td>
<td>13</td>
<td>480 (240, 600)</td>
</tr>
</tbody>
</table>

#### 6.3.2 Objectively measured physical activity and sedentary behaviour – accelerometry

Adaptation of study assessment protocols due to the COVID-19 pandemic resulted in objective physical activity data from smaller than planned numbers per group, particularly in follow-up timepoints when accelerometers where not provided post study amendment. ActivPAL accelerometers were provided to n=48 participants at baseline, from which data was obtained from n=44 (92%). Two (4%) participants did not return their accelerometer, 1 (2%) returned their accelerometer with no valid wear time recorded and 1 (2%) participant’s accelerometer was lost during postage. For follow-up timepoints, in total 52 accelerometers were provided, of these n=3 (6%) were returned unworn, n=2 (4%) participants declined to wear it and n=1 (2%) accelerometer could not be downloaded. In total during the study 90 accelerometers were returned and
downloaded, from these the average number of valid days of wear was 6.7 days and average non-wear time was 2.3 minutes (range 0-37.5 minutes). Only one download was removed from the analysis for not including sufficient valid days of wear (>3 days including 1 weekend day). Eight participants provided accelerometer data at all timepoints. Given the small samples per group at each follow-up timepoint, particularly reduced in the intervention arm and the non-normal distribution of the accelerometer data only descriptive analysis of raw data was carried out. Contrary to self-reported physical activity, accelerometer data was recorded for the week following each timepoint, therefore T1 data refers to physical activity and sedentary behaviour during first week of hospital admission for ASCT and T2 data refers to the week following hospital discharge.

On assessment at baseline (T0) the sample median step count was 6297 (IQR 3876.5, 8928) and time spent stepping was 83.2 minutes per day (IQR 59.1, 109.8). The control group had greater average daily step count and stepping time than the intervention group. During the first week of admission for ASCT (T1) and during the week following discharge from hospital (T2) the intervention participants undertook more steps and spent more time stepping than the control group. Overall change between T0 and T3 shows a reduction in steps and stepping time for the control group but an increase for the intervention group. Median and range of values are presented in Table 6.7.

Additional data for average number of sit to stands and overall activPAL activity score are presented in Appendix H Table 4. A subgroup analysis of participants who provided accelerometer data for T0 and T3 (Control: n=8, Intervention: n=4) demonstrated a similar pattern of change across timepoints, although the intervention group had a greater stepping time at T0 than then control group (see Appendix H Table 5).
Table 6.7 Average daily accelerometer scores from activPAL

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Control</th>
<th></th>
<th>Intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (IQR)</td>
<td>Range</td>
<td>N</td>
</tr>
<tr>
<td><strong>Step count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>23</td>
<td>7415 (5267, 9281.5)</td>
<td>3406-14228</td>
<td>20</td>
</tr>
<tr>
<td>T1</td>
<td>11</td>
<td>3379 (2005, 4237.5)</td>
<td>912-4798</td>
<td>8</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
<td>2965 (2117.3, 3578.8)</td>
<td>1050-4682</td>
<td>5</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>6200.5 (5151.8, 8150.5)</td>
<td>3575-10807</td>
<td>4</td>
</tr>
<tr>
<td><strong>Stepping time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>23</td>
<td>95.7 (69.9, 111.4)</td>
<td>49.8-155.5</td>
<td>20</td>
</tr>
<tr>
<td>T1</td>
<td>11</td>
<td>40.5 (26.1, 50.1)</td>
<td>17.1-58.2</td>
<td>8</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
<td>41.1 (32.3, 48)</td>
<td>16.2-66.6</td>
<td>5</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>77.5 (71, 88.9)</td>
<td>44.9-119</td>
<td>4</td>
</tr>
<tr>
<td><strong>Sitting time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>23</td>
<td>477.2 (420.5, 635.5)</td>
<td>307.1-776.4</td>
<td>20</td>
</tr>
<tr>
<td>T1</td>
<td>11</td>
<td>493 (448.9, 584)</td>
<td>392.7-639.7</td>
<td>8</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
<td>544.4 (486.1, 681.9)</td>
<td>361.9-756.5</td>
<td>5</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>560.1 (497.3, 587.6)</td>
<td>459.5-695.6</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total sedentary time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>23</td>
<td>614.7 (484.9, 695.9)</td>
<td>398.5-904.8</td>
<td>20</td>
</tr>
<tr>
<td>T1</td>
<td>11</td>
<td>735.9 (663.4, 824)</td>
<td>597.4-974.4</td>
<td>8</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
<td>784.8 (661.8, 829.4)</td>
<td>548.5-909</td>
<td>5</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>596.9 (555.1, 639.8)</td>
<td>498.1-825.6</td>
<td>4</td>
</tr>
</tbody>
</table>
Figure 6.7 shows changes in time spent stepping at each timepoint. The intervention group maintained higher levels of time in stepping at all timepoints, with increased stepping time during admission (T1) and immediately post discharge (T2) from hospital and a similar rate of increase to the control group in the months following ASCT.

6.3.3 Self-efficacy for physical activity – Self-efficacy for Exercise scale (SEE)

An exploration of change in self-efficacy for exercise scale scores between T0 and T1 with time in days between T0 and ASCT using scatterplot indicated an inverse difference between groups and that time possibly had a positive effect on the intervention group scores but a negative effect on control group scores (see Appendix H Figure 1). Therefore, time from T0 to ASCT was included in the LMEM as a covariate but was not found to be significant ($F(1)=0.8, p=0.7$). Timepoint was significant ($F(3)=4.7, p=.004$) but there was no effect of group allocation by timepoint ($allocation \times time, F(3)=2.3, p=0.09$).
Mean estimates and between group differences at each timepoint from the adjusted model are presented in Table 6.8. A difference in pattern of change in SEE score across timepoints between groups can be seen in Figure 6.8.

![Figure 6.8 Mean self-efficacy for exercise score (95% confidence intervals) between timepoints for both groups (adjusted model)](image)

Figure 6.8 Mean self-efficacy for exercise score (95% confidence intervals) between timepoints for both groups (adjusted model)

Intervention group score increased between T0 and T1, significantly decreasing at T2 before increasing significantly again between T2 and T3, whereas the control group scores appear to show gradual worsening between T0 and T2 with slight increase between T2 and T3. Within-group difference are presented in Table 6.9. Across the length of the study the intervention group scores at T3 were greater than T0 baseline scores indicating potential improvement of self-efficacy, whereas control group scores were worse at T3 compared to T0, indicating possible reduction in self-efficacy after ASCT, however these changes were not statistically significant. Raw scores for SEE between groups at each timepoint and the unadjusted model estimates are presented in Appendix H Table 6 and Appendix H Table 7.
Table 6.8 Mean estimates ± standard error (SE) and between group contrasts for SEE outcome measure of self-efficacy for exercise (model included time from T0 to ASCT as a covariate)

<table>
<thead>
<tr>
<th></th>
<th>Control Mean estimate ± SE</th>
<th>95% CI</th>
<th>Intervention Mean estimate ± SE</th>
<th>95% CI</th>
<th>Between group difference ± SE (Intervention-Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-efficacy exercise score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>6.8 ± 0.6</td>
<td>5.6, 7.9</td>
<td>5.9 ± 0.7</td>
<td>4.6, 7.2</td>
<td>-0.9 ± 0.9</td>
</tr>
<tr>
<td>T1</td>
<td>6.1 ± 0.6</td>
<td>4.9, 7.3</td>
<td>6.7 ± 0.7</td>
<td>5.4, 8.1</td>
<td>+0.7 ± 0.9</td>
</tr>
<tr>
<td>T2</td>
<td>5.4 ± 0.6</td>
<td>4.2, 6.6</td>
<td>4.2 ± 0.7</td>
<td>2.8, 5.7</td>
<td>-1.2 ± 1.0</td>
</tr>
<tr>
<td>T3</td>
<td>5.8 ± 0.6</td>
<td>4.6, 7.0</td>
<td>6.5 ± 0.7</td>
<td>5.1, 7.8</td>
<td>+0.6 ± 0.9</td>
</tr>
</tbody>
</table>

Table 6.9 Within group differences across timepoints for SEE score

<table>
<thead>
<tr>
<th></th>
<th>Control Estimate</th>
<th>95% CI</th>
<th>Intervention Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-efficacy exercise score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0 to T1</td>
<td>-0.7</td>
<td>-1.8, 0.5</td>
<td>+0.9</td>
<td>-0.4, 2.2</td>
</tr>
<tr>
<td>T1 to T2</td>
<td>-0.7</td>
<td>-1.5, 0.5</td>
<td>-2.5</td>
<td>-4.0, -1.0</td>
</tr>
<tr>
<td>T2 to T3</td>
<td>+0.4</td>
<td>-0.8, 1.7</td>
<td>+2.2</td>
<td>0.7, 3.7</td>
</tr>
<tr>
<td>T0 to T3</td>
<td>-0.9</td>
<td>-2.1, 0.3</td>
<td>+0.6</td>
<td>-0.7, 1.9</td>
</tr>
</tbody>
</table>

6.4 Discussion

This chapter outlined the results from analysis of secondary trial outcomes related to functional capacity and physical activity behaviour of the pilot trial sample. At the outset of the trial design, measures related to functional capacity and physical activity were important to the overall assessment of the intervention despite the unpowered nature of this pilot trial. Consistent collection of these secondary outcomes was hampered by the disruption caused by the COVID-19 pandemic and the subsequent requirement to amend the study protocol. Outcomes particularly affected were the 6MWT and hand grip strength testing which were not possible to conduct virtually and therefore discontinued for new participants and those in follow-up following the amendment. Objective assessment of physical activity using accelerometry was continued in the virtual protocol for baseline (T0) assessment only as measurement at follow-up timepoints was not possible due to the resources required to continue sending and receiving the devices by post. Adaptation of study assessment protocols due to the
pandemic resulted in smaller than planned sample sizes per group, particularly in follow-up timepoints, and limited the analysis of most outcomes to descriptive statistics. The continued administration of a self-reported measure of physical activity, the IPAQ-SF questionnaire, and a measure of self-efficacy for exercise did allow for more complete data regarding physical activity behaviour.

There were differences in baseline scores between groups for the functional capacity outcomes, with the intervention group recording lower mean and median scores than the control group for timed STS, 6MWT and hand grip strength. Despite the unavoidable lack of data for some outcomes at follow-up assessments, the larger baseline samples are of an adequate size to provide useful insights into the functional capacity of patients with myeloma at referral for ASCT following initial induction chemotherapy. Due to baseline group differences and small numbers of follow-up data, discussion related to functional capacity outcomes will focus on within-group differences. Where differences are seen in longitudinal data, particularly those considered meaningful or important, these may indicate signals of possible intervention effects that should be examined in future research.

The data for the timed STS test provided the most complete measure of functional capacity for the sample. Change of test protocol from 30 seconds to 1 minute was instigated during amendment to a virtual study design because the 1 minute STS test has been shown to elicit similar physical responses in terms of lower limb fatigability and heart rate to the 6WMT (Gephine et al., 2020), which was to be discontinued. Baseline mean estimates for both groups were lower than average compared to those expected of healthy subjects (Strassmann et al., 2013). People between the age of 60-70 are expected to be able to perform 35 repetitions in 1 minute STS with performance of less than 28 and 31 repetitions considered below average for healthy women and men aged 60-64 years respectively (Strassmann et al., 2013). Only the intervention group achieved mean scores greater than this below average cut off for health subjects at T1 and T3. The low scores demonstrated at baseline for both groups indicate possible severe impairment of lower limb endurance and strength on referral for ASCT. Loss of lower limb muscular strength and endurance is seen with increasing age but can be exacerbated by chronic conditions including cancer and pulmonary disease. However, reduced muscular strength and endurance is amenable with exercise. Meta-analyses...
have shown significant positive effects of exercise interventions on lower limb muscle strength for haematological patients who have undergone transplant (Liang et al., 2018; Abo et al., 2021a) with one indicating that significant effects were seen when exercise was initiated pre-transplant but not if exercise started post-transplant (Liang et al., 2018). Despite the underpowered nature of this pilot trial, there were important signals of improvement in lower limb strength and endurance with the intervention group. The intervention group demonstrated improvements of 27% in the pre-ASCT and 38% post-ASCT phases of the study compared to 1% and 19% in the control group. These differences were also greater than the MID of 3-4 repetitions described in similar populations (Segura-Orti & Martinez-Olmos, 2011; Vaidya et al., 2016; Crook et al., 2017). Between baseline to 3 months post-ASCT the intervention mean increased three times the MID and 40% from baseline (compared to 3% in control group), indicating potentially meaningful changes. Calculated 1 minute timed STS was the only measure in the whole that showed significant change between groups, with a significant difference in favour of the intervention in the pre-ASCT prehabilitation phase of the study. These results indicate further investigation of the intervention is warranted.

Baseline median scores for 6MWT in this pilot trial were higher than those reported in another single arm feasibility study of a pre-ASCT exercise intervention for myeloma patients (Mawson et al., 2021). However, baseline values were still lower than expected compared to reference values for predicted 6MWT values based on age and sex (Gibbons et al., 2001). Over half the sample at baseline had scores less than 80% of predicted, indicative of abnormal functional capacity (White et al., 2005). Impairments in functional capacity have been seen in people with haematological cancer as early as diagnosis. A cross-sectional study comparing newly diagnosed patients prior to any chemotherapy with healthy controls, found significant reduction in functional capacity as measured by 6MWT (Celik et al., 2022a) with similar proportion of subjects producing a walking distance less than 80% predicted as seen in the PERCEPT trial. This study excluded subjects older than 65 years but provides interesting insights into the effects on physical functioning of diagnosis even among younger patients with haematological cancer, which are likely to be further compounded by systemic anti-cancer treatment and increasing age if not mediated with rehabilitative interventions.
6MWT data from the PERCEPT pilot trial indicates positive trends for potentially influencing functional capacity in the pre- and post-ASCT phases of treatment. These results are interpreted with caution due to small sample sizes at follow-up but show signals worth discussion. The descriptive analysis of all the 6MWT data and the subgroup analysis of the eleven complete data sets indicate similar patterns of change. Both groups showed improvement in their walking distance in the pre-ASCT phase, followed by deterioration during between admission and discharge from transplant admission and improvement again in the post-ASCT period. In both analyses the intervention group showed improvement in scores greater than MCID of 30.5m (Bohannon & Crouch, 2017) in the pre- and post-ASCT phases and less than half the deterioration of that seen in the control group during admission. The improvement in the pre-ASCT phase was more modest than that of Mawson et al. (2021) who reported a mean change of 104.9m (SD 71.4) in their pre-post assessment of myeloma patients who underwent a six week exercise prehabilitation intervention prior to ASCT.

The 6MWT is the most commonly used measure of functional capacity in exercise intervention trials of haematological cancer patients undergoing transplantation with moderate quality evidence of significant improvement in exercisers (Abo et al., 2021a). The improvement in functional capacity prior to transplant and its maintenance during admission may be an important factor not only in optimising function and its role in QOL but also in facilitating timely discharge from hospital and early initiation of restorative rehabilitation following treatment (Santa Mina et al., 2020). Over the course of this study the intervention group improved beyond MCID, to result in better functional capacity at three months following ASCT, whereas the control group had worsened median score. The deterioration in control group was equivalent to a 0.09 metres per second (m/s) reduction pre- to post-ASCT. A 1-m/s reduction in walking speed is associated with a 20% increase in mortality (HR 1.20; 95% CI 1.12, 1.29; p<.0001) and a 33% increase in unplanned hospital admissions (OR 1.33; 95% CI 1.16, 1.51) in older people with haematological cancer (Liu et al., 2019). Median 6MWT distance of the control group at T3, 3 months post-ASCT, is in line with mean 6MWD of 500m reported in a cross-sectional study of myeloma patients in remission post-ASCT (Tuchman et al., 2015). Participants in the Tuchman et al (2015) cohort were on average 17 months post-ASCT, indicating that reduction in functional capacity may be sustained following
treatment (Tuchman et al., 2015). These patterns and similarities with other studies, albeit to be interpreted with caution due to limitations related to the analysis, go towards refuting the concept that people with myeloma naturally return to baseline or expected functional abilities with time following ASCT and the consequences could be particularly impactful for patients who are older. Further investigation is required to reliably demonstrate these possible positive findings.

The patterns of change for both groups were similar for both the timed STS and 6MWT, with improvements pre- and post-ASCT and over the course of the study for the intervention group but little or no change in the control group. Despite limitations on drawing any conclusions from these outcomes due to the small, unpowered sample size and loss of follow-up data because of protocol changes, the similarity between these measures of functional exercise capacity may indicate promise for this type of intervention. Surprisingly, the results related to hand grip strength did not follow a similar pattern. There was large variation in hand grip strength values for both groups at all timepoints in the pilot trial. Contrary to all other outcomes in the trial, median hand grip strength appeared to increase between the T1 and T2 timepoints in the intervention group and is likely to be a random result. Although no meaningful differences were seen longitudinally overall, or in sub analysis of participants who provided hand grip strength data at all timepoints, a third of participants had measurements indicative of impaired hand grip strength at baseline. The control group median hand grip strength reduced by 5kg over the course of the study. A 5kg reduction in hand grip strength has been associated with a 24% increase in mortality (HR 1.24; 95% CI 1.02, 1.51) among older haematological cancer patients with good performance status (ECOG 0-1) (Liu et al., 2019). Given that hand grip strength is considered a valuable screening tool for frailty and impaired strength (Bohannon, 2019b), there may still be value in using hand grip strength pre-ASCT to identify recipients most in need of exercise training to optimise function and future long-term outcomes, especially in patients with myeloma who will inevitably require further anti-myeloma treatment in the years proceeding ASCT. Despite showing no indication of promising changes in this study, hand grip strength remains an important measure of functional capacity and should continue to be assessed in any future powered trial in conjunction with objective
measures of lower limb strength and/or walking speed to provide comprehensive evaluation of overall muscular function.

Higher levels of physical activity are associated with better QOL (Jones et al., 2004b; Vermaete et al., 2013; Smith et al., 2015) and reduced fatigue (Knips et al., 2019) among people with haematological cancer. Investigation of possible intervention effects on physical activity and sedentary behaviour were important secondary outcomes and may provide insight into the role of behaviour change techniques incorporated into the exercise programme delivery. Myeloma patients are known to have reduced levels of physical activity both during and after treatment (Jones et al., 2004b; Nicol et al., 2020). This study included both self-report and objective physical activity measurement however as a result of the COVID-19 and necessary protocol adaptions complete data for objective physical activity is lacking.

Continued distribution of questionnaire measures throughout the study allowed for more complete data on self-reported physical activity at all study timepoints. Baseline total physical activity (MET minutes/week) calculated from the IPAQ-SF were similar for both groups and in line with those reported among myeloma patients recruited to a prehabilitation study in the UK (Mawson et al., 2021). The proportion of participants active to levels in line with physical activity guidelines for aerobic physical activity (22%) calculated from the IPAQ is higher than previously reported levels among myeloma patients during treatment. Lower percentages of myeloma patients meeting physical activity guidelines have been reported, most used other measures of self-reported physical activity such as the GODIN lifestyle questionnaire. One of the first studies to report physical activity levels in myeloma, based on survey responses from 156 participants, found only 7% of participants were active to recommended levels during treatment, with an increase to 20% in those off treatment (Jones et al., 2004b). Another survey based study of 226 participants with myeloma also used the GODIN and found 20% of participants to be sufficiently active post-diagnosis in accordance with guidelines (Craike et al., 2013a). More recently published survey research (n=126) found 13% of myeloma patients undergoing active treatment were meeting guidelines and off treatment 17% were (Nicol et al., 2020). Comparably, the proportions meeting guidelines at baseline in this trial indicate that the sample may have been more active than pre-ASCT myeloma patients described previously.
At baseline, although more participants in the intervention arm met physical activity guidelines compared to the control arm (22% versus 19%), the median amount of physical activity in terms of MET minutes per week was the same for both arms. The sample baseline physical activity in MET minutes per week was in line with that reported in another UK based myeloma prehab study using the same self-report instrument (Mawson et al., 2021). Over the course of the study deviations in group scores for self-reported physical activity in favour of the intervention were seen. At T1, on admission for ASCT after the prehabilitation phase of the study, there was an increase in the number of intervention participants meeting physical activity guidelines and greater levels of overall levels of weekly physical activity. Over the course of the study (T0-T3) median weekly physical activity doubled in the intervention group and numbers meeting physical activity guidelines increased by 14% but overall levels of physical activity deteriorated in the control group. There are several limitations with self-report physical activity instruments. Firstly, research participants are known to overestimate levels of physical activity in self-report questionnaires (Adams et al., 2005) and variation in group scores is typical in most populations (IPAQ, 2005). Because of these limitations measurement of objective physical activity data was included in trial outcomes.

Objective measurement of physical activity, using activPAL accelerometers, was highly acceptable to participants with high proportions of devices returned with valid data. The impact of the COVID-19 pandemic resulted in incomplete follow-up data for the sample however baseline objective physical activity was collected for over 90% of participants, providing useful observational insight into physical activity of myeloma patients on referral for ASCT. Reporting of objective physical activity data varies greatly within the literature. Different devices, metrics and cut points are used, making comparison between studies challenging (Purswani et al., 2018; Kos et al., 2021). This trial reports data as analysed using activPAL software. The sample average step count and time spent stepping is in line with other published data within oncology populations. Daily step count and time spent stepping have found to be positively associated with performance status in cancer patients (Kos et al., 2021). Average daily steps counts between 4600 and 8100 have been reported in patients with good performance status (ECOG-PS 0) across multiple solid tumour groups, even among those with advanced disease receiving palliative treatment. However, most studies also report wide variation within groups
(Ferriolli et al., 2012; Maddocks & Wilcock, 2012; Gresham et al., 2018). Similarities between the baseline data in our sample, who as ASCT eligible myeloma patients would be ECOG-PS 0, and that of other studies indicate that baseline physical activity was within an expected range for cancer patients.

Analysis of objective physical activity data across timepoints was limited by low follow-up sample size, however patterns of promise were seen in within-group changes in the overall sample and sub-group sample of participants who provided data at both baseline and final follow-up. Despite an indication that the control group had greater median step count and time spent stepping at baseline, the intervention group appeared to maintain higher levels of physical activity at all follow-up timepoints. Over the course of the study the intervention group had greater levels of objective physical activity at T3 compared to baseline, whereas the control group became less active.

6.4.1 Limitations

The original protocol included a number of reliable and valid measures that could be pragmatically adopted into the clinical environment. Firstly, this allowed seamless delivery of the research within an existing clinical pathway, without the requirement for additional clinic space or clinic visits by participants. Secondly, this approach could be used to facilitate translation into usual clinical practice if the trial showed promise. However, the adaptation necessary because of the pandemic introduced many limitations to analysis and interpretation of physical and functional outcomes.

Additional efforts to maximise available data for assessment of functional capacity were made by combining results of two timed STS protocols. Correlation analysis using data from participants who were timed over both 30 seconds and 1 minutes indicated good agreement and allowed for extrapolation of an calculated score which increased sample numbers for analysis, however this approach is not without drawback.

A number of limitations related to physical activity measurement within the trial exist. Firstly, although the inclusion of both self-report and objective physical activity instruments is a strength, the timing of both measures differed therefore restricting direct comparison. An oversight in protocol design resulted in self-report measures being collected on the day that activPAL accelerometers were fitted, meaning self-
report data represents perceived physical activity in the week prior to prospective collection of objective physical activity by accelerometer. Although this may not affect T0 and T3 timepoint comparisons greatly, it does limit comparison of data at T1, where self-reported physical activity was the week prior to hospital admission whereas objective physical activity was measured for the first week of admission, and at T2, where self-reported data relates to final week prior to hospital discharge but objective data represents the first week at home following discharge. Despite these limitations, results provide insight into levels of physical activity across the continuum of ASCT, including during active hospital treatment and patterns of change, albeit in small numbers, do indicate possible effects and potential promise of the intervention on physical activity behaviour during ASCT.

6.5 Summary

Despite the limitations resulting from adaptation of the trial in response to the pandemic and the discontinuation of some objective measures of functional capacity and physical activity, there is indication of promise in the available data, although caution is warranted when interpreting these results. It is particularly promising to see clinically important differences in favour of the intervention in exercise performance and lower limb strength and indications of increased physical activity engagement. The potential benefits on functional capacity and physical activity behaviour before, during and after ASCT warrant further investigation in future studies with adequate sample size.
Chapter 7  PERCEPT trial results: The effects of the exercise intervention on fatigue and quality of life

7.1 Introduction

This chapter will summarise the secondary outcomes from the trial that relate to fatigue and quality of life (QOL) examined using a range of patient reported outcome measures (PROMs). It was not known at the outset of the trial design which PROMs instruments would be best for a future powered trial, therefore a range of PROMs were used in the pilot study. Each PROM incorporates a number of common and distinct domains related to QOL. As a number of different PROMs were used, analysis and interpretation was focussed on reporting total or summary scores for each measure rather than individual domains. Each measure and their minimally important difference (MID) have been described in detail in Chapter 3 Section 3.7.4.

The impact of the study protocol amendments required due to the pandemic did not impact upon continued collection of these secondary outcomes as they were all questionnaire-based. The questionnaire-based outcomes were sent to participants in follow-up during the initial wave of the pandemic and then routinely sent to all those recruited via the virtual protocol for postal return using provided freepost envelopes. Therefore, sample numbers for analysis were better than those of the objective secondary outcomes.

7.2 Fatigue

7.2.1 Functional Assessment of Cancer Therapy - Fatigue (FACT-F) questionnaire

An exploration of change in FACT-F scores between T0 and T1 with time in days between T0 and ASCT using scatterplot indicated possible difference between groups and that time possibly had a greater effect on the intervention group scores (see Appendix I Figure 1). Therefore, time from T0 to ASCT was included in the linear mixed effect model (LME) as a covariate and was significant (F(1)=5.12, p=0.03), as was timepoint (F(3)=50.26, p=<.001) but there was no effect of group allocation by timepoint (allocation × time, F(3)=0.17, p=0.92).
Mean estimates and between-group differences at each timepoint from the adjusted model are presented in Table 7.1. Both the intervention and control group had similar mean fatigue scores at T0. The intervention group had better mean scores at each follow-up timepoint, most notably at T1 and T3, although these differences were not statistically significant.

Table 7.1 Mean estimates ± standard error (SE) and between-group contrasts for FACT-F fatigue score (model included time from T0 to ASCT as a covariate)

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Control Mean estimate ± SE 95% CI</th>
<th>Intervention Mean estimate ± SE 95% CI</th>
<th>Between group difference ± SE (Intervention-Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatigue FACT-F (0-52)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>35.3 ± 2.2 30.9, 39.6</td>
<td>36.4 ± 2.5 31.3, 41.4</td>
<td>+1.1 ± 3.5</td>
</tr>
<tr>
<td>T1</td>
<td>38.5 ± 2.3 33.0, 43.1</td>
<td>42.0 ± 2.7 36.7, 47.3</td>
<td>+3.5 ± 3.7</td>
</tr>
<tr>
<td>T2</td>
<td>18.7 ± 2.4 14.0, 23.5</td>
<td>21.0 ± 2.8 15.4, 26.6</td>
<td>+2.3 ± 3.8</td>
</tr>
<tr>
<td>T3</td>
<td>39.2 ± 2.3 34.5, 43.8</td>
<td>42.2 ± 2.6 37.0, 47.4</td>
<td>+3.0 ± 3.7</td>
</tr>
</tbody>
</table>

Figure 7.1 Mean Fatigue scores (95% confidence intervals) measured by FACT-F between timepoints for both groups (adjusted model)
Figure 7.1 shows changes in fatigue scores between timepoints by group. In both groups, changes were observed, with improvement between T0 and T1, significant decrease between T1 and T2, followed by a significant improvement between T2 and T3. Although these differences were similar for both groups, there was a steeper upward slope of the intervention group between T0 and T1.

Within-group differences are presented in Table 7.2. All group differences were within range of the reported MID of 3-4 for the FACT-F (Cella et al., 2002b; Nordin et al., 2016) with the intervention group improvement in fatigue score being beyond MID for prehabilitation phase (T0 to T1) and for the study overall (T0 to T3). Raw scores for FACT-F between groups at each timepoint and the unadjusted model estimates are presented in Appendix I Table 1 and Appendix I Table 2.

### Table 7.2 Within group differences (95% confidence intervals) across timepoints for fatigue measured by FACT-F (adjusted model)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>Intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>Estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>T0 to T1</td>
<td>+3.3</td>
<td>-1.5, 8.1</td>
<td>+5.7</td>
<td>0.1, 11.2</td>
</tr>
<tr>
<td>T1 to T2</td>
<td>-19.8</td>
<td>-24.8, -14.7</td>
<td>-21</td>
<td>-26.9, -15.1</td>
</tr>
<tr>
<td>T2 to T3</td>
<td>+20.4</td>
<td>15.3, 25.5</td>
<td>+21.2</td>
<td>15.3, 27</td>
</tr>
<tr>
<td>T0 to T3</td>
<td>+3.9</td>
<td>-1, 8.8</td>
<td>+5.8</td>
<td>0.4, 11.2</td>
</tr>
</tbody>
</table>

### 7.3 Quality of life

#### 7.3.1 EuroQol EQ-5D-5L Questionnaire

Descriptive data detailing the number and proportion of participants’ reported levels of health status for each dimension across timepoints from the EQ-5D-5L measure are shown in Table 7.3. There were differences to note within a number of dimensions between groups and across the study timepoints. At baseline the intervention group had a higher proportion of participants reporting some level of mobility problem (61%) compared to the control group (42%). The proportion of those reporting mobility problems reduced in both groups on admission for ASCT (Intervention: 26%; Control: 35%) which may be due to those with mobility problems being withdrawn between T0 and T1. On discharge from hospital there was a similar proportion of participants
reporting moderate or worse problems in both groups. At T3 more intervention participants reported no problems with mobility than control participants (Intervention 67%; Control: 50%).

More participants in the intervention group reported problems with self-care at baseline compared to the control groups (Intervention: 30%; Control: 12%), levels of those reporting problems were similar at T1 follow-up. At T2 follow-up, on discharge from hospital, more intervention participants reported problems with self-care than in control group (Intervention: 25%; Control: 11%) and those reporting problems related to self-care at T3 were again similar between groups.

Both groups had similar percentage of participants reporting no problems related to pain/discomfort at T0 and T1 assessment, however of those reporting some level of pain/discomfort the control group had higher proportions reporting severe or extreme pain at T1. On discharge from hospital, there was a notable difference in the proportion of participants without pain/discomfort between groups on discharge from ASCT (Intervention: 58%; Control: 22%). At T3, approximately three months following ASCT, both groups had similar proportions of participants reporting no pain/discomfort or slight pain/discomfort but the control group had a larger percentage of participants reporting moderate or worse pain/discomfort (Intervention: 29%; Control: 13%).

Levels of anxiety/depression were similar between groups across timepoints. At baseline the intervention group had a small proportion of participants (9%) reporting to feel severely anxious/depressed. Despite the intervention group having a smaller proportion of participants reporting any level of anxiety/depression at final follow-up (T3) (Intervention: 40%; Control: 50%), most control participants reporting problems were slightly anxious/depressed (44%), whereas the intervention had a greater proportion of moderately anxious/depressed participants (Intervention: 20%; Control: 6%).
Table 7.3 Number and proportions of responses for each EQ-5D-5L dimension by group at all timepoints (N(%))

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Control</th>
<th></th>
<th></th>
<th></th>
<th>Intervention</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>T0 N=26</td>
<td>T1 N=20</td>
<td>T2 N=18</td>
<td>T3 N=18</td>
<td>T0 N=23</td>
<td>T1 N=15</td>
<td>T2 N=12</td>
<td>T3 N=15</td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No problems</td>
<td>15 (58)</td>
<td>13 (65)</td>
<td>11 (61)</td>
<td>9 (50)</td>
<td>9 (39)</td>
<td>11 (73)</td>
<td>7 (58)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Slight problems</td>
<td>6 (23)</td>
<td>5 (25)</td>
<td>1 (6)</td>
<td>7 (39)</td>
<td>6 (26)</td>
<td>2 (13)</td>
<td>2 (17)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Moderate problems</td>
<td>5 (19)</td>
<td>2 (10)</td>
<td>4 (22)</td>
<td>1 (6)</td>
<td>6 (26)</td>
<td>2 (13)</td>
<td>1 (8)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Severe problems</td>
<td>-</td>
<td>-</td>
<td>2 (11)</td>
<td>1 (6)</td>
<td>2 (9)</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Unable to walk</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Self-care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No problems</td>
<td>23 (88)</td>
<td>19 (95)</td>
<td>16 (89)</td>
<td>18(100)</td>
<td>16 (70)</td>
<td>15(100)</td>
<td>9 (75)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Slight problems</td>
<td>3 (12)</td>
<td>1 (5)</td>
<td>2 (11)</td>
<td>-</td>
<td>3 (13)</td>
<td>-</td>
<td>2 (17)</td>
<td>-</td>
</tr>
<tr>
<td>Moderate problems</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 (17)</td>
<td>-</td>
<td>-</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Severe problems</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Unable to wash or dress</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Usual activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No problems</td>
<td>11 (42)</td>
<td>10 (50)</td>
<td>2 (11)</td>
<td>7 (39)</td>
<td>7 (30)</td>
<td>8 (53)</td>
<td>4 (33)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Slight problems</td>
<td>10 (38)</td>
<td>6 (30)</td>
<td>6 (33)</td>
<td>6 (33)</td>
<td>6 (26)</td>
<td>3 (20)</td>
<td>3 (25)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Moderate problems</td>
<td>3 (12)</td>
<td>3 (15)</td>
<td>3 (17)</td>
<td>4 (22)</td>
<td>8 (35)</td>
<td>3 (20)</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Severe problems</td>
<td>1 (4)</td>
<td>-</td>
<td>5 (28)</td>
<td>1 (6)</td>
<td>1 (4)</td>
<td>-</td>
<td>3 (25)</td>
<td>-</td>
</tr>
<tr>
<td>Unable to do usual activities</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>2 (11)</td>
<td>-</td>
<td>1 (4)</td>
<td>1 (7)</td>
<td>1 (8)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No pain/discomfort</td>
<td>6 (23)</td>
<td>8 (40)</td>
<td>4 (22)</td>
<td>5 (28)</td>
<td>4 (17)</td>
<td>6 (40)</td>
<td>7 (58)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Slight pain/discomfort</td>
<td>14 (54)</td>
<td>7 (35)</td>
<td>10 (56)</td>
<td>8 (44)</td>
<td>12 (52)</td>
<td>6 (40)</td>
<td>4 (33)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Moderate pain/discomfort</td>
<td>5 (19)</td>
<td>3 (15)</td>
<td>3 (17)</td>
<td>3 (17)</td>
<td>5 (22)</td>
<td>3 (20)</td>
<td>-</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Severe pain/discomfort</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>2 (9)</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Extreme pain/discomfort</td>
<td>-</td>
<td>1 (5)</td>
<td>-</td>
<td>1 (6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Not anxious/depressed</td>
<td>13 (50)</td>
<td>9 (45)</td>
<td>10 (56)</td>
<td>9 (50)</td>
<td>11 (48)</td>
<td>8 (53)</td>
<td>8 (67)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Slightly anxious/depressed</td>
<td>10 (38)</td>
<td>7 (35)</td>
<td>5 (28)</td>
<td>8 (44)</td>
<td>6 (26)</td>
<td>6 (40)</td>
<td>3 (25)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Moderately anxious/depressed</td>
<td>3 (12)</td>
<td>3 (15)</td>
<td>3 (17)</td>
<td>1 (6)</td>
<td>4 (17)</td>
<td>1 (7)</td>
<td>1 (8)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Severely anxious/depressed</td>
<td>-</td>
<td>1 (5)</td>
<td>-</td>
<td>-</td>
<td>2 (9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Extremely anxious/depressed</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>
Exploration of the relationship between change in EQ-5D-5L visual analogue scale (VAS) scores between T0 and T1 and time between T0 and ASCT through scatterplot indicated a positive relationship between QOL and time that was seen in the intervention group but not in the control group (see Appendix I Figure 2). The repeat measures LMEM adjusted for time between T0 and ASCT showed timepoint to have a significant effect on VAS score (F(3)= 15.8, p=<.001) but allocation, time for T0 to ASCT and allocation × timepoint did not.

The EQ-5D-5L VAS score demonstrated inverse changes between groups in the prehabilitation phase (T0 to T1). Figure 7.2 shows a deterioration in group mean of the control group with improvement seen in the intervention. However, between-group differences (Table 7.4) and within-group changes (Table 7.5) between these timepoints were not significant and did not reach threshold for the suggested MID for EQ5D VAS for cancer patients, which is from 8-12 (Pickard et al., 2007). As seen in the other QOL measures both groups experienced significant and MID deterioration in QOL between T1 and T2, which improved again significantly beyond MID between T2 and T3. The overall change in EQ-5D-5L VAS score between T0 and T3 was greater for the intervention group and beyond the range considered MID (Intervention: +12.1, 95% CI 2.2,22; Control: +5.3, 95% CI -3.6,14.3).

Figure 7.2 Mean EQ-5D-5L VAS score (95% confidence intervals) between timepoints for both groups (adjusted model)
7.3.2 Functional assessment of cancer therapy – general (FACT-G) questionnaire

An exploration of change in FACT-G score between T0 and T1 with time in days between T0 and ASCT using scatterplot indicated that group scores over time were similar. The repeated measures LMEM showed timepoint was significant ($F(3)=22.37, p<.001$) but group allocation ($F(1)=0.13, p=0.7$), time between T0 and ASCT ($F(1)=3.09, p=0.09$) and allocation × timepoint ($F(3)=0.9, p=0.5$) were not.

Mean estimates and between-group differences from the adjusted model are presented in Table 7.4. Both groups had similar scores at T0, T2 and T3. The intervention group had a greater mean score at T1 compared to the control however this difference was not significant. Figure 7.3 shows a similar pattern as fatigue with changes observed for both groups, improving between T0 and T1, deteriorating between T1 and T2 and improving beyond T0 at T3. Within-group differences are presented in Table 7.5. Although both groups followed a similar pattern in terms of change between timepoints, the intervention group difference in the prehabilitation phase (T0 to T1) was twice that of the control group (Control: +4, 95% CI 1.5 to 9.5; Intervention: +8.4, 95% CI 1.9 to 14.8), indicated by the steeper upward slope in Figure 7.3, and is greater than the MID of 5-7 reported for the FACT-G (Cella et al., 2002a).

Figure 7.3 Mean FACT-G quality of life scores (95% confidence intervals) between timepoints for both groups (adjusted model)
Table 7.4 Mean estimates ± standard error (SE) and between-group contrasts for quality of life outcome measures (model included time from T0 to ASCT as a covariate)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Control</th>
<th>Intervention</th>
<th>Between group difference ± SE (Intervention-Control)</th>
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<tr>
<td><strong>EQ-5D-5L</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Visual Analogue Scale (VAS) (0-100)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>69.5 ± 3.7, 62.3, 76.8</td>
<td>66 ± 4.2, 57.6, 74.3</td>
<td>-3.6 ± 5.8</td>
</tr>
<tr>
<td>T1</td>
<td>67.6 ± 3.7, 60.2, 75</td>
<td>70.6 ± 4.5, 61.8, 79.5</td>
<td>+3.0 ± 6.1</td>
</tr>
<tr>
<td>T2</td>
<td>53.5 ± 3.9, 45.7, 61.2</td>
<td>52.3 ± 4.7, 42.9, 61.7</td>
<td>-1.2 ± 6.4</td>
</tr>
<tr>
<td>T3</td>
<td>74.9 ± 3.9, 67.1, 82.6</td>
<td>78.1 ± 4.3, 69.5, 86.7</td>
<td>+3.3 ± 6.1</td>
</tr>
<tr>
<td><strong>FACT-G Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0-108)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>74.9 ± 2.7, 69.4, 80.3</td>
<td>75.6 ± 3.2, 69.3, 81.9</td>
<td>+0.8 ± 4.4</td>
</tr>
<tr>
<td>T1</td>
<td>78.8 ± 2.8, 73.3, 84.4</td>
<td>84.0 ± 3.3, 77.4, 90.6</td>
<td>+5.2 ± 4.5</td>
</tr>
<tr>
<td>T2</td>
<td>66.7 ± 2.9, 60.9, 72.6</td>
<td>64.9 ± 3.5, 58.0, 71.8</td>
<td>-1.9 ± 4.7</td>
</tr>
<tr>
<td>T3</td>
<td>81.5 ± 2.9, 75.8, 87.2</td>
<td>82.4 ± 3.2, 75.9, 88.9</td>
<td>+0.9 ± 4.5</td>
</tr>
<tr>
<td><strong>FACT-BMT Total</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(0-148)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T0</td>
<td>102 ± 3.5, 95.0, 109.1</td>
<td>103.2 ± 4.1, 95.0, 111.3</td>
<td>+1.1 ± 5.6</td>
</tr>
<tr>
<td>T1</td>
<td>106.1 ± 3.6, 98.9, 113.3</td>
<td>113.5 ± 4.3, 105.0, 122.0</td>
<td>+7.4 ± 5.8</td>
</tr>
<tr>
<td>T2</td>
<td>88.8 ± 3.8, 81.3, 96.3</td>
<td>86.7 ± 4.5, 77.8, 95.5</td>
<td>-2.2 ± 6.1</td>
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<tr>
<td>T3</td>
<td>109.7 ± 3.7, 102.3, 117.1</td>
<td>112.1 ± 4.2, 103.8, 120.5</td>
<td>+2.5 ± 5.8</td>
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<tr>
<td><strong>FACT-BMT Trial Outcome Index score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0-96)</td>
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<tr>
<td>T0</td>
<td>63.6 ± 2.8, 58.0, 69.2</td>
<td>63.7 ± 3.3, 57.2, 70.1</td>
<td>-0.09 ± 4.5</td>
</tr>
<tr>
<td>T1</td>
<td>65.2 ± 2.9, 59.4, 70.9</td>
<td>71.3 ± 3.4, 64.5, 78.1</td>
<td>+6.1 ± 4.7</td>
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<tr>
<td>T2</td>
<td>47.3 ± 3.1, 41.2, 53.3</td>
<td>45.0 ± 3.6, 37.8, 52.2</td>
<td>-2.3 ± 4.9</td>
</tr>
<tr>
<td>T3</td>
<td>68.0 ± 3.0, 62.0, 73.9</td>
<td>71.4 ± 3.3, 64.6, 78.0</td>
<td>+3.4 ± 4.9</td>
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<tr>
<td><strong>EORTC QLQ-C30 Global QOL</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(0-100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>62.9 ± 3.8, 55.3, 70.5</td>
<td>62.7 ± 4.4, 54.0, 71.5</td>
<td>-0.2 ± 6.1</td>
</tr>
<tr>
<td>T1</td>
<td>68.3 ± 3.9, 60.5, 76.1</td>
<td>73.4 ± 4.7, 64.1, 82.7</td>
<td>+5.0 ± 6.4</td>
</tr>
<tr>
<td>T2</td>
<td>33.3 ± 4.1, 25.2, 41.5</td>
<td>26.7 ± 5.0, 16.8, 36.6</td>
<td>-6.6 ± 6.7</td>
</tr>
<tr>
<td>T3</td>
<td>68.8 ± 4.1, 60.7, 76.1</td>
<td>70.1 ± 4.6, 61.0, 79.1</td>
<td>+1.2 ± 6.4</td>
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<tr>
<td><strong>EORTC QLQ-C30 Summary score</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(0-100)</td>
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<tr>
<td>T0</td>
<td>76.0 ± 3.0, 70.0, 82.1</td>
<td>77.6 ± 3.5, 70.7, 84.6</td>
<td>+1.6 ± 4.8</td>
</tr>
<tr>
<td>T1</td>
<td>78.3 ± 3.1, 72.1, 84.4</td>
<td>85.1 ± 3.7, 77.8, 92.4</td>
<td>+6.8 ± 5.0</td>
</tr>
<tr>
<td>T2</td>
<td>49.6 ± 3.2, 43.2, 56.0</td>
<td>52.4 ± 3.9, 44.7, 60.1</td>
<td>+2.8 ± 5.3</td>
</tr>
<tr>
<td>T3</td>
<td>81.9 ± 3.2, 75.5, 88.3</td>
<td>84.0 ± 3.6, 76.9, 91.1</td>
<td>+2.1 ± 5.0</td>
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Table 7.5 Within group differences between timepoints for quality of life outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
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<th>Intervention</th>
<th></th>
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<tr>
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<td>Contrast</td>
<td>Estimate</td>
<td>95% CI</td>
<td>Estimate</td>
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<td>EQ-SD-5L</td>
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<td>-10.6, 6.7</td>
<td>+4.6</td>
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<td>VAS</td>
<td>T1 to T2</td>
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<td>-23.1, -5.1</td>
<td>-18.3</td>
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<td>T2 to T3</td>
<td>+21.4</td>
<td>12.2, 30.6</td>
<td>+25.81</td>
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<td>T0 to T3</td>
<td>+5.3</td>
<td>-3.6, 14.3</td>
<td>+12.1</td>
</tr>
<tr>
<td>FACT-G Total</td>
<td>T0 to T1</td>
<td>+4</td>
<td>-1.5, 9.5</td>
<td>+8.4</td>
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<tr>
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<td>T1 to T2</td>
<td>-12.1</td>
<td>-17.9, -6.3</td>
<td>-19.1</td>
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<tr>
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<td>T2 to T3</td>
<td>+14.8</td>
<td>8.8, 20.7</td>
<td>+17.5</td>
</tr>
<tr>
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<td>T0 to T3</td>
<td>+6.7</td>
<td>1, 12.3</td>
<td>+6.8</td>
</tr>
<tr>
<td>FACT-BMT Total</td>
<td>T0 to T1</td>
<td>+4.1</td>
<td>-2.9, 11.1</td>
<td>+10.3</td>
</tr>
<tr>
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<td>T1 to T2</td>
<td>-17.3</td>
<td>-24.7, -9.9</td>
<td>-26.8</td>
</tr>
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<td></td>
<td>T2 to T3</td>
<td>+20.9</td>
<td>13.3, 28.4</td>
<td>+25.5</td>
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<td>T0 to T3</td>
<td>+7.66</td>
<td>0.4, 14.9</td>
<td>+9</td>
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<td>FACT-BMT Trial</td>
<td>T0 to T1</td>
<td>+1.6</td>
<td>-1.5, 4.7</td>
<td>+7.6</td>
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<td>Outcome Index</td>
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<td>-24.4, -11.4</td>
<td>-26.3</td>
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<td>Score</td>
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<td>14, 27.4</td>
<td>+26.4</td>
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<td>T0 to T3</td>
<td>+4.42</td>
<td>-2, 10.8</td>
<td>+7.7</td>
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<td>EORTC</td>
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<td>-4, 14.8</td>
<td>+10.7</td>
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<td>QLQ-C30</td>
<td>T1 to T2</td>
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<td>-44.7, -25.3</td>
<td>-46.7</td>
</tr>
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<td>Global QOL</td>
<td>T2 to T3</td>
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<td>25.5, 45.4</td>
<td>+43.3</td>
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<td></td>
<td>T0 to T3</td>
<td>+5.9</td>
<td>-3.7, 15.6</td>
<td>+7.3</td>
</tr>
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<td>-4.6, 9.1</td>
<td>+7.5</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td>T1 to T2</td>
<td>-28.6</td>
<td>-35.7, -21.5</td>
<td>-32.7</td>
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<td>Summary</td>
<td>T2 to T3</td>
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<td>25, 39.5</td>
<td>+31.6</td>
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<tr>
<td>Score</td>
<td>T0 to T3</td>
<td>+5.8</td>
<td>-1.2, 12.9</td>
<td>+6.4</td>
</tr>
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</table>

Raw descriptive data for all quality of life outcome measures for both groups at each timepoint and the unadjusted model estimates are presented in Appendix I Table 4 and Appendix I Table 3.
7.3.3 Functional assessment of cancer therapy – bone marrow transplant (FACT-BMT) questionnaire

The repeated measures analysis again showed timepoint (F(3)=27.7, p=<.001) and time from T0 to ASCT (F(1)=4.05, p=0.05) to have a significant effect on FACT-BMT total score but allocation (F(1)=0.24, p=0.63) and the interaction of allocation × timepoint (F(3)=1.0, p=0.34) did not. The estimated means and between-group differences for each timepoint for the FACT-BMT total score from the LMEM are reported in Table 7.4 and plotted in Figure 7.4. The trajectory for both study groups across timepoints follows a similar pattern to the FACT-G and FACT-F scores with the between-group difference between T0 and T1 being within the range for a MID despite not being significant. Within-group differences, presented in Table 7.5, show greater changes in the intervention at between all timepoints, with a greater than MID difference in the prehabilitation phase (+10.3, 95% CI 2.1 to 18.5). As has been seen in the other QOL measures both groups deteriorated significantly during the transplant admission phase (T1-T2) and this deterioration was greater in the intervention group (-26.8, 95% CI -35.6 to -18) than the control group (-17.3, 95% CI -24.7 to -9.9), but then improved again in both groups between T2 and T3.

Figure 7.4 Mean FACT-BMT total scores (95% confidence intervals) between timepoints for both groups (adjusted model)
The repeated measure LMEM showed no relationship between FACT-BMT trial outcomes index (TOI) score and the interaction between allocation × timepoint (£F(3)=1.1, p=0.35) but timepoint did have a significant effect within the model (£F(3)=36, p=<.001)). The estimated means for each timepoint, presented in Table 7.4, indicate a similar trend in mean differences seen in the previously discussed PROM scores with the largest difference between groups seen at T1 (mean difference 6.1, SE=4.7). Figure 7.5 shows changes in FACT-BMT TOI scores at each timepoint by group. There were differences between groups observed in the prehabilitation phase with an upward slope evident in the intervention but not the control group. The within-group differences (Table 7.5) indicate that the intervention group had greater increase in QOL than the control group in both the prehabilitation phase (T0-T1) (Intervention: +7.6, 95% CI 0.4 to 14.9; Control +1.6, 95% CI -1.5 to 4.7) and the overall study period (T0-T3) (Intervention: +7.7, 95% CI 0.7 to 14.8; Control: +4.42, 95% CI -2 to 10.8). Although these differences were not statistically significant, the intervention group changes at these timepoints were in line with the defined MID.

Figure 7.5 Mean FACT-BMT trial outcomes index (TOI) score (95% confidence intervals) between timepoints for both groups (adjusted model)
7.3.4 European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) Core 30 (EORTC QLQ-C30)

Scatterplots representing change between T0 and T1 for EORTC global QOL score plotted against time between T0 and ASCT indicated that both groups followed a similar positive linear trend for change in global QOL over time. The scatterplot for the EORTC summary score against time between T0 and ASCT indicated no effect on the control group and a positive effect of time on QOL in the intervention group (see Appendix I Figure 3).

In the repeated measures LMEM examining effects on EORTC global QOL score, timepoint had a significant effect within the model (F(3)=49.8, p=<.001) but allocation (F(1)=0.0, p=1), time between T0 and ASCT (F(1)=1, p=0.33) and the interaction of allocation × timepoint (F(3)=0.8, p=0.49) did not. Mean estimates by group and between-group differences at each timepoint are presented in Table 7.4 and plotted in Figure 7.6. QOL changes between timepoints were similar for both groups. There were small increases in group means from T0 to T1, a large deterioration between T1 and T2, and a large improvement beyond baseline scores for both groups at the final timepoint. None of the group differences were MID.

Figure 7.6 Mean EORTC-QLQ-C30 Global QOL domain score (95% confidence intervals) between timepoints for both groups (adjusted model)
The within-group changes in EORTC global QOL score are presented in Table 7.5. As has been seen in the other QOL measures both groups had large and significant deterioration in QOL between admission for ASCT (T1) and discharge from hospital (T2) followed by large and significant improvement at three months following ASCT (T3). Although not significant, it is noted that the small improvement in global QOL score in the prehabilitation phase of the study (T0 to T1) for the intervention group (+10.7, 95%CI -0.3 to 21.6) was double that of the control group (+5.4, 95%CI -4 to 14.8) and within the range considered MID for patients with myeloma (Kvam et al., 2010; Kvam et al., 2011).

Repeated measures analysis showed timepoint (F(3)=57.3, p=<.001) had a significant effect on EORTC-QLQ-C30 summary score, but allocation (F(1)=0.9, p=0.36), time between T0 (F(1)=0.6, p=0.44) and ASCT and the interaction of allocation × timepoint (F(3)=0.4, p=0.75) did not. Within-group changes between timepoints are reported in Table 7.5. The intervention group demonstrated an improvement that was more than three times that of the control group between T0 and T1 (Intervention: +7.5, 95% CI -0.5 to 15.5; Control: +2.2, 95% CI -4.6 to 9.1) but were not significantly different from each other, and both groups deteriorated and improved significantly in a similar way between subsequent timepoints, as seen in other QOL measures. Group estimates and between-group differences by timepoint are presented in and plotted in Figure 7.7.

![Figure 7.7 Mean EORTC-QLQ-C30 summary score (95% confidence intervals) between timepoints for both groups (adjusted model)](image-url)
7.4 Discussion

This chapter has outlined results from the PERCEPT pilot trial related to PROMs of fatigue and QOL. There is considerable evidence demonstrating an association between physical activity and better outcomes in QOL (Jones et al., 2004b) and cancer-related fatigue. Two Cochrane reviews have evaluated the role of exercise interventions on multiple domains of QOL among people with cancer; one among those who were undergoing active cancer treatment (Mishra et al., 2012b) and a second among those who had completed treatment (Mishra et al., 2012a). A meta-analyses in the first review suggested that, from twelve studies with a control comparator, exercise interventions during active cancer treatment improved overall QOL (n=806; SMD=0.47, 95% CI: 0.16, 0.79) and decreased fatigue (n=971; SMD=-0.73, 95% CI: -1.14, -0.31) at 12 week follow-up (Mishra et al., 2012b). The second review and meta-analyses, among cancer survivors following treatment, also found significant improvement in overall QOL (n=826; SMD=0.48, 95% CI: 0.16, 0.81) from eleven studies and decreased fatigue (n=745; SMD=-0.82, 95% CI: -1.5, -0.14) from ten studies compared to control condition at 12 week follow-up (Mishra et al., 2012a). A meta-analyses of exercise trials among haematological cancer patients also demonstrated moderate-quality evidence that exercise can improve cancer-related fatigue from eight studies (n=523; MD=2.52, 95% CI: 0.42, 4.63) and overall QOL from eleven studies (n=624; MD=3.38, 95% CI: 0.37, 6.39) measured using the EORTC-QLQ-C30 (Abo et al., 2021a). Given that improved QOL and fatigue are evident among more active cancer survivors, measures of fatigue and QOL were considered important secondary outcomes to include in this pilot randomised trial.

One measure of cancer-related fatigue (FACT-F) and two different QOL instruments with additional related item subsets (EORTC QLQ-C30 and FACT-BMT) were used. Many PROM measures of QOL include multiple domains that are common and unique to each other. The EORTC QLQ-C30 includes domains that concentrate of physical and functioning dimensions of QOL whereas FACT-BMT contains domains that focus on impact of treatment and side-effects on QOL. Comparison analysis has indicated that both instruments complement each other and could be used together rather than in place of each other when assessing QOL in patients undergoing SCT (Kopp et al., 2000; Grulke et al., 2012). As both instruments are commonly used in different myeloma and exercise oncology trials, and there are evident domain differences between them, both
were included in the pilot study, with an objective to identify which instruments may be most suitable for a subsequent trial.

There was a consistent pattern of change across all of the PROMs measures in the pilot trial, particularly the distinctive deterioration of outcomes between T1 and T2 followed by recovery at T3, demonstrating the powerful effect of undergoing ASCT on cancer-related fatigue and QOL among people with myeloma. Prospective investigation of changes in physical and psychological domains of QOL have shown that myeloma patients experience significant deficits during the period between induction chemotherapy and post-transplant (Sherman et al., 2009). Deficits in QOL were evident at stem-cell harvest prior to ASCT. Differences compared to scores from age- and sex-adjusted norms and a reference group of transplant recipients from mixed haematological malignancies, indicate more pronounced symptom burden among myeloma patients prior to undergoing ASCT. Sherman et al. (2009) reported baseline scores for the FACT-G (mean 74 [SD=14.8]) and FACT-BMT subscale (25.2 [SD=6]) from 94 participants that are comparable to baseline scores in this study. However, only marginal decline in FACT-G (<3 point change) was reported in the immediate post-ASCT period (mean 9.4 [SD-5.1] days post-ASCT) (Sherman et al., 2009), whereas the group means in the PERCEPT trial deteriorated between 8 and 11 points between T0 and T2, baseline to hospital discharge. However, the interval in this trial is longer as recruitment occurred prior to harvest and discharge following ASCT was between 14-25 days post-ASCT, when deterioration in QOL is likely to increase in the immediate post-ASCT period prior to hospital discharge. Indeed inconsistency in outcomes and assessment timepoints used in the limited number of longitudinal studies of QOL during ASCT in myeloma makes estimation of typical course of symptom prevalence challenging. However, it has been established that people with myeloma experience high symptom burden and resultant deficits in QOL from early diagnosis and may worsening for up to 2-3 months post-ASCT (Ramsenthaler et al., 2016).

While there were no significant between-group differences for some measures in the pilot trial, there were promising improvements in favour of the intervention group, particularly in the prehabilitation phase (T0 to T1). Within-group improvements that reached the threshold considered a MID were evident at T1 for the FACT-G, FACT-BMT total scores, FACT-BMT TOI and EORTC global score of the intervention group that were
not achieved by the control group. The between-group differences at T1 for FACT-G and FACT-BMT total scores were also considered MID indicating potentially important differences between groups despite lack of statistical significance. Greater pre-ASCT symptom burden predicts greater treatment toxicity in the early post-ASCT phase (Campagnaro et al., 2008). Indications that the exercise prehabilitation intervention may reduce symptom burden and improve global QOL scores in the immediate pre-ASCT period warrant further investigation, including exploration of stratification of participants based on identified poorer baseline scores, as they may benefit most from personalised prehabilitation input. The EQ-5D-5L VAS score was the only QOL score to indicate inverse changes between groups in the prehabilitation phase of the study with deterioration of QOL evident among the control group but improvement in the intervention, however these changes were not clinically meaningful.

Over the length of the study, between baseline and final follow-up three months post-ASCT, both groups’ mean scores had improved indicating lower levels of fatigue and greater QOL. This would be expected given that baseline assessments took place during induction chemotherapy, on average 6.5 months following diagnosis or relapse and final follow-up was three months following last treatment for most. Fatigue, weakness, activity and enjoyment for life are individual symptom domains shown to worsen among myeloma patients between pre-ASCT (day -36 to -3) and day 0 (day of ASCT) and worsen again until blood counts reach lowest levels (nadir) post-ASCT. Although these domains have been shown to improve during recovery from ASCT, they may not improve to baseline scores by day 30 post-ASCT (Campagnaro et al., 2008). In the PERCEPT trial both groups had improved scores compared to baseline scores for all measures which may indicate better than expected recovery from ASCT. And although between T0 and T3 changes in scores were beyond MID for FACT-G total and FACT-BMT total for both groups, the intervention group gains in QOL were greater than MID for EQ-5D-5L VAS and FACT-BMT TOI but were not seen in the control group.

Previously published studies of exercise interventions in myeloma have also used PROMs measures. A single-arm pilot study of exercise in myeloma survivors recorded mean change in FACT-G total score of +4.1 (<0.001; n=37) following three months of exercise. Participants were median eleven months from completion of treatment and 93% had undergone ASCT (Groeneveldt et al., 2013). Between-group differences in
FACT-G between T0 and T1 prehabilitation phase of the PERCEPT trial were similar to this study (mean estimate: +5.2 ± 4.5) and within-group gains were similar to those seen within the control but increases in FACT-G scores doubled in the exercise arm (mean estimate: +8.4, 95% CI: 1.9, 14.8). Other results are mixed regarding the effect of exercise on QOL in myeloma patients. A comparable study investigating feasibility of exercise prior to ASCT at UK centre reported a decrease in FACT-G score (mean change: -2.8, 95% CI: -15.7, 10) in pre-post measures following a six week exercise programme in the same phase of treatment, however these scores were only assessed in six participants (Mawson et al., 2021). A larger powered RCT conducted in myeloma survivors reported no effect on physical or emotional function domains of the FACT-G after three months of partly supervised exercise, however the full FACT-G instrument was not used in this trial so interpretation of effects on QOL are limited (Koutoukidis et al., 2020).

Beyond MID gains in favour of the intervention group were also seen for levels of fatigue following the prehabilitation phase and over the length of the study. Although the control group mean scores also improved within the range of MID between these timepoints, the differences in between-group scores in favour of the intervention group were also within range of the MID, indicating promise for the intervention on fatigue. Previous reporting of changes in fatigue following exercise programmes in myeloma have indicated mixed results. Initial studies indicated no effect on fatigue with unsupervised exercise interventions carried out during treatment (Coleman et al., 2003; Coleman et al., 2012). Improvements in FACT-F fatigue scores were reported in a pilot study of myeloma survivors undertaking partly-supervised exercise following completion of active treatment reported similar mean change over three months (mean change: +3.1, p<.01; n=37) to those observed in the control group in both the prehabilitation phase and length of study overall (Groeneveldt et al., 2013). However, the subsequent RCT, powered to detect clinically significant changes in FACT-F, did not find any improvement in fatigue with three months of exercise in an intention to treat analysis (MD= 1.6, 95% CI: -1.1, 4.3; n=95) (Koutoukidis et al., 2020). Exploratory analysis of participants with clinically significant levels of fatigue at baseline, who attended more than 50% of prescribed exercise sessions, did however indicate benefit of the intervention when compared to clinically fatigued control participants (MD: Exercise...
10.7 vs 3.1 Control; n=15). As baseline levels of fatigue for this trial population were closer to the threshold considered as clinically significant (FACT-F score ≤ 34), as would be expected during active cancer treatment, this may have resulted in positive effects of the exercise intervention. The greater change than that seen in other studies, and beyond that considered MID, observed in the intervention group indicates further exploration of the effect of prehabilitation and rehabilitation during ASCT of fatigue is justified.

Although one hypothesis related to prehabilitation is that it may not only improve health or functional outcomes prior to a significant stressful health event (e.g. cancer surgery or stem cell transplantation) but it could also minimise any loss or deterioration in health status from such an event (Santa Mina et al., 2021). This was something that I considered in designing this trial, a hypothesis that if the intervention group were to improve in health or functional outcome, that this improvement may also mitigate or lessen any subsequent worsening of that outcome. What can be seen in all of the QOL measures in this trial is that the deterioration seen between T1 and T2, while an anticipated response to undergoing ASCT, was greater in the intervention group than in the control group despite the intervention group demonstrating greater than double the improvement of the control group in all these measures between T0 and T1. It may be possible that participants within the exercise group underwent ‘response shift’. Response shift is “a change in the meaning of one’s self-evaluation of a target construct as a result of: (a) a change in the respondent’s internal standards of measurement (scale recalibration, in psychometric terms); (b) a change in the respondent’s values (i.e. the importance of component domains constituting the target construct); or (c) a redefinition of the target construct (i.e. reconceptualization)” (Sprangers & Schwartz, 1999). It is thought to occur in any field in which a person is asked to self-report or evaluate one’s own self and is known to exist in assessment of health-related QOL. It could be proposed that improving participants’ perception of their QOL and reframing their expectations through the mechanism of tailored exercise support and realisation of benefit in the short period pre-ASCT, may have led to worse than expected deterioration in these outcomes during the acute phase post-ASCT when treatment toxicity and inability to engage in physical activity are most pronounced. Findings from the qualitative exploration of the experiences of trial completers (Chapter 8) demonstrated marked differences in
experience of recovery between control and intervention participants. Future research should focus on mixed-methodology, and perhaps the incorporation of earlier qualitative exploration, during admission for ASCT, could assist investigation into the experiences of exercisers and why their PROMs assessments may deteriorate following evidenced improvement, particularly when deterioration is worse than expected compared to control counterparts.

7.4.1 Limitations

As reported in the previous chapters, the amendments to the study required because of the COVID-19 pandemic had significant consequences on the delivery and completeness of the trial secondary outcome measures. The use of a range of paper-based PROMs allowed for consistent collection of these secondary outcomes throughout the study, including continuation of follow-up data collection during the initial stages of the pandemic before the need for full amendment of the trial was realised. All of these measures have been validated as self-complete measures and are routinely captured using postal data collection.

One limitation of the presentation of these measures is the use of summary or total scores rather than detailed reporting of the domains measured within each instrument. As fatigue and QOL were not the only secondary outcomes assessed, and more than one measure of QOL was measured, it was felt that reporting of summary scores was sufficient for describing the possible effects of participation within the trial on these measures. Although indications of promise were evident from analysis of summary scores, it was felt that detailed reporting of specific domains of QOL may be excessive among a wide range of measures already reported. However, it is important to note that although these measures of QOL and fatigue are commonly used in clinical trials and summarised using their total scores, many were originally designed to draw attention to different domains of QOL and aid identification of specific needs of cancer patients and their ability to evaluate the magnitude of intervention effects has been questioned (Kotronoulas et al., 2014).
7.5 Summary

Patterns of change measured with PROMs demonstrated similar trajectories for both trial groups. This study captured the notable deterioration in QOL and levels of fatigue associated with undergoing ASCT. There were promising indications of intervention effects on QOL and fatigue outcomes, particularly in the prehabilitation phase, with a number of outcomes indicating a group difference in scores beyond MID in favour of the intervention group.
Chapter 8   The experiences of people with myeloma who participated in the PERCEPT trial

8.1  Background

The perception of randomised controlled trials (RCTs) as the definitive research design for testing of health care interventions is not without challenge. The background to Chapter 4 outlines some challenges in conducting RCTs with respect to recruitment and generalisability. The findings described in Chapter 4 provide insight into the considerations made by people with myeloma when approached to take part in the PERCEPT trial of an exercise intervention at the beginning of the autologous stem cell transplantation (ASCT) treatment pathway and their experiences related to being physically active and seeking support to be active since diagnosis. To complement the quantitative data generated from the pilot RCT and additional qualitative findings from Chapter 4, which focussed on the research processes experienced by potential participants at the outset of the trial (e.g. approach, engagement with study information resources, decisions related to recruitment), the current chapter details a second qualitative study conducted among trial participants after their involvement, exploring their experiences as trial participants engaging in the research processes.

Rehabilitation interventions and interventions that aim to change health behaviours, such as engagement in an exercise programme, are considered complex interventions because of a multitude of factors in their delivery and receipt. Factors of importance go far beyond the target behaviour and include contextual factors such as the mechanisms through which the intervention is delivered, to whom, in what settings, the skills and expertise of the deliverer, as well as considerations related to quantification of exposure to the intervention in terms of dose or number of sessions (Skivington et al., 2021). Complexity arises when considering how to evaluate the effects of complex interventions. Generally considered the most rigorous approach to measuring effectiveness or efficacy of health care interventions, through minimising bias and fostering validity, RCTs traditionally focus on outcome effects. Use of the RCT design in evaluation of complex interventions requires adaptation in order to assess not just the outcome of such interventions but the process through which their implementation may cause an effect and further inform interpretation of results (Oakley et al., 2006). An
entirely quantitative approach to evaluation is no longer considered sufficient for assessing the effects of a complex intervention. The addition of qualitative investigation, as an element of process evaluation, is deemed necessary to better understand contextualised factors and their potential influence on the delivery and outcome related to an intervention (Skivington et al., 2021).

In addition to informing better understanding of the intervention and the context in which it acts, qualitative exploration of trial participants may uncover unintended consequences not considered during research development related to their exposure to research procedures. ‘Research participation effect’ is a construct proposed to inform better understanding of participant related biases that may be at play in behavioural intervention research and that might not be prevented through the process of randomisation (McCambridge et al., 2014b). The concept of research participation effects has evolved from the established notion of understanding that research participants may be influenced by being studied, whether intentionally or subconsciously, historically referred to as the Hawthorne effect (McCambridge et al., 2014b).

Research participation effects can manifest as early as during approach for consideration of research participation. It has been proposed that in considering the information related to the intervention provided in participant information sheets or exposure to the baseline research assessment may evoke emotions, cognitions and even change in the target behaviour. Indeed, nearly all RCTs will involve assessment of outcomes closely related to or indicative of the intervention behaviour. For some research participants engaging with these pre-randomisation elements of the trial may be enough to elicit change in the target behaviour that may not be discounted through randomisation (McCambridge et al., 2014a). Therefore, exploring participant interactions with pre-randomisation research activities, as well as assessment activities that may relate to the intervention behaviour (e.g. wearing an activity tracer or completing a log sheet), is necessary as they may have potential to induce unintended behaviour change in both allocation groups.

The process of randomisation for allocation in trials assumes that participants, as well as researchers, accept the process from a position of equipoise, however participant
preference for allocation, particularly in unblinded trials, is common and can affect continued participation and have implications for research validity (King et al., 2005). Acceptance of equipoise between allocation conditions requires a belief by participants that there is genuine uncertainty regarding the benefits of the intervention being investigated and that allocation to control may be as beneficial (Norris et al., 2019). An assumed belief that the intervention would be beneficial as opposed to an acceptance of genuine uncertainty of benefit questions the integrity of equipoise which not only requires ethical consideration but also consideration for the quality of design in RCTs (Toye et al., 2016).

Participant motivations for enrolling in a trial often come with a preference for the intervention as assumed to be superior to the control condition. Response to allocation in unblinded trials can induce post-randomisation research participation effects or biases, most notably within control participants who may be dissatisfied with allocation (McCambridge et al., 2014a). Expectations of research participants can even limit the validity of double-blinded placebo controlled RCTs and assessment of participant beliefs related to allocation and their potential to impact trial outcomes should be ascertained (Colagiuri, 2010). Dissatisfaction with allocation is thought to induce responses that may have deleterious effects on the control condition. Responses may manifest as attempts by control participants to access a form of the intervention condition outside of the trial, may induce contamination bias and minimise the observed effects of the trial intervention (Robinson et al., 2020).

Research participation effects may become evident through qualitative exploration of participation and therefore further justify the importance of qualitative studies embedded within trials or mixed methods research of behavioural interventions (Lewin et al., 2009; Skivington et al., 2021). Qualitative investigation as part of pilot RCTs is important yet underutilised (Baldeh et al., 2020). This qualitative study embedded within the concluding phase of the pilot RCT was added to the research design to understand considerations of participants who took part in the pilot study. Although a formal process evaluation was not conducted as part of the pilot trial, the addition of qualitative data generation was intended to complement quantitative feasibility data in informing the future direction of this research by exploring contextual factors and the
experiences of people with myeloma participating in exercise related research during ASCT.

8.2 Aim

The aim of this study was to explore the experiences of participants of the PERCEPT myeloma study who consented to the trial, were randomised and underwent ASCT. Factors related to research procedures (e.g. randomisation and research assessments) as well as experience of the intervention by those who were allocated to it were explored. As the trial was unblinded and participants were aware the intervention was an exercise intervention, their experiences of physical activity engagement and advice before, during and after ASCT were also examined.

8.3 Methods

8.3.1 Ethical approval

Ethical approval for this study was obtained as part of the NHS Health Research Authority approval for the PERCEPT myeloma transplant prehab study from the London – Camden & Kings Cross Research Ethics Committee (REC reference 19/LO/0204). See letter confirming favourable opinion (see Appendix C).

8.3.2 Participants and Procedure

Interviewees were participants who took part in the exercise trial. Purposeful sampling was used to select both intervention and control participants enrolled to the trial to gather insights related to fidelity and processes related to the trial, as well as their experiences. Participants were asked to take part in an interview at or around the time of their final follow-up study assessment and were asked to confirm their consent verbally prior to audio recording. Interviews were conducted either face-to-face or by telephone. The interviews were audio recorded, fully anonymised and transcribed verbatim by a professional transcription service with a UCL data sharing agreement.

8.3.3 Interview schedule

The interviews were conducted using a semi-structured interview guide developed as part of the trial protocol. The interview schedule was designed to capture content
related to experiences of ASCT, of being enrolled within a longitudinal study as part of
the ASCT pathway, feelings and experiences of being randomised and perspectives on
the study intervention and assessment processes (see Appendix J).

8.3.4 Analysis

Demographics of the participants were collected from trial assessment forms completed
at enrolment and are presented using descriptive statistics. Interview transcripts were
analysed iteratively using the six phase process of reflexive thematic analysis (TA) as
described in Section 4.3.4.1. A similar approach to that undertaken for the decliners
qualitative study using reflexive TA, as described in Chapter 4 was used for this study.
Reflexive TA for this study was also underpinned by the onto-epistemology of critical
realism using an approach that was both deductive and inductive (see Section 4.3.4.3).

The interviews were listened through for familiarisation with the content and to check
the transcripts for accuracy. Deductive coding was used to highlight explicit content that
was perceived as likely to arise related to trial procedures and assessments and content
of the exercise programme. Deductive codes were also preconceived prior to analysis to
identify more implicit content shared by intervention participants related to
components of the intervention including behaviour change techniques (BCTs) as
declared by the BCT Taxonomy v1 (Michie et al., 2013). Inductive codes were generated
through repeated reading and assignment of coding labels to the text. Two additional
researchers (AF and Joanne Land (JL)) reviewed three transcripts each, one transcript in
common and two others each. Therefore in total, five (31%) of the transcripts were
reviewed by at least two researchers. These transcripts were discussed among the three
researchers to confirm coding reliability. Throughout the coding phase memos and
notes were recorded and shared which informed and confirmed ideas generated from
the data. The initial group of codes was then grouped into sets related those related to
participation in the trial regardless of allocation (e.g. study procedures, experience of
ASCT etc.), those specific to group allocation as well as those unrelated to study
participation. The sets of codes were mapped and linked before less analytically relevant
codes were disregarded. Repeated rounds of analysis were carried out iteratively
revising and discarding codes and sets until the themes and subthemes were developed
and described. Qualitative data analysis was conducted using NVivo 12 (version 12. QSR International Pty Ltd.) and descriptive statistics were analysed using Microsoft Excel.

8.4 Findings

Between November 2019 and June 2021, 33 participants completed the pilot trial. From these, 16 participants (8 from each trial arm) were asked to participate in a qualitative interview and all approached participants (100%) agreed to be interviewed. Data collection ceased at 16 interviews as no new content relevant to the research questions were arising from interviews (Saunders et al., 2018).

Interviews were conducted by four researchers. I interviewed six participants (38%), three from each study allocation group, all of whom I recruited and assessed at each timepoint in the trial. JL, the physiotherapist who delivered the trial intervention, interviewed four (25%) participants from the control group only. The remaining interviews were conducted by health psychology researchers (AR, GB) who were not involved in recruitment or delivery of the trial. Interview length ranged from 23 minutes to 1 hour 14 minutes (mean duration 46 minutes). Mean interview duration was similar for intervention and control participants (Intervention: 47 minutes; Control: 46 minutes).

The mean age of the study sample was 61 years (SD 11, range 37-72 years) and 9 (56%) were male. Interviewee characteristics are detailed in Table 8.1
Three main themes were identified from the analysis of coded transcripts: 1. “It’s not just beneficial for me, it’s for people after me as well”; 2. Disparities in experience of recovery – expectations, feeling prepared and support; 3. “What I wanted to do was build myself back up and prepare”. An additional theme generated from deductive coding of the dataset describes components of the intervention that were highlighted by intervention participants during interview: Active ingredients – participants’ experience of the intervention.

### 8.4.1 “It’s not just beneficial for me, it’s for people after me as well”

Participants from both groups shared similar reasons for taking part in the trial, principally that there was a perceived opportunity for personal gain in terms of physiotherapist input and support to exercise, as well as a perceived contribution to improving future supportive care for people living with myeloma. However there were nuanced differences in outlook that were dependant on allocation (elaborated in Section 8.4.1.2). Experiences and reactions of some participants also indicated possible risk of contamination bias for the trial.
**Figure 8.1 Main themes and related subthemes**

8.4.1.1 *Perception of participation as advantageous personally and altruistically*

Generally, participants recalled a desire to take part in the trial from initial approach with few sharing any hesitation to enrol. Some mentioned consideration of the travel that would be required if allocated to the intervention group, but decided this was not a barrier. For many the trial was attractive due to physical or functional concerns related to their myeloma and a perceived lack of adequate advice or input.

“I was hoping to be part of the group that actually got the extra exercise because I had such severe back issues with the myeloma. That was the first reason I wanted to do it but then beyond that, I just recognised that any additional physio, we could get to get ourselves back to as much as a normal state as possible, could be beneficial”

*Rose, 51, Control*
Others described interest in participating as a way of ‘giving back’ for previous treatment and a feeling of taking part as being worthwhile and potentially having an influence on future care for people with myeloma undergoing ASCT.

“I just wanted to be involved with a research project. It’s like wanting to give something back really because of what happened before and I had a really long remission and I’m just interested in any sort of medical research but particularly to do with my condition, if you like, and also, before, I can remember all the details and how I weak I was for quite a long time afterwards and I thought well maybe there’s ways of looking into this and yes, making things easier for people to come through without losing health condition so much, if you like, and I said it’s worthwhile looking into.” Beth, 71, Control

8.4.1.2 Fortunate or disappointed – response to allocation

Most interviewees expressed clear desire for allocation to the intervention group at the outset of enrolment. Nearly all control participants used the word ‘disappointed’ to describe the feeling they experienced when notified of their allocation. Some described a sense of loss of personal benefit from participation as a control but also acknowledged that they committed to the study and therefore wanted to continue to contribute.

“I felt like I wasn’t going to get as much out of it in the short term... I agreed to do it, so I said okay, take it seriously and do whatever was needed for the study, even though I wasn’t going to get as much out of it as I had hoped in the short term.” Rose, 51, Control

In contrast, most intervention participants expressed strong feelings of elation and relief at their allocation and the prospect of receiving the exercise intervention. In contrast to the controls some reflected that their continued participation in the study may not have occurred had they been allocated to the control group.

“I can remember perfectly; it was relief. It was relief, I so wanted to be in the exercise, I so wanted to be in the exercise group and until I was told I was in the exercise group, it was like wishing for a lottery ticket [laughter]. So when I was told I was in the exercise group, I’d won the lottery.” Steve, 64, Intervention

“I was ecstatic, because I was told there were two parts of the study, and I was randomly chosen. And I did say to myself, if I’m not selected to be in the exercise, I don’t actually know if I’m going to do it.” Kate, 37, Intervention
A small number of participants expressed impartial views on their allocation and therefore were ambiguous about how they felt about it. One intervention participant reflected on how she enrolled hopeful of allocation to the control, with altruism as her motivation for participation and expressed initial disappointment at allocation to the exercise group, but later balanced this with gratitude given the benefits she experienced from engaging with the intervention.

8.4.1.3 Responses to allocation may indicate risk of contamination

A number of interviewees shared narratives that may indicate possible risks of contamination of the control group. Participants were not blinded to their allocation, and although all were asked not to disclose their allocation to me, as initially I was blinded as the study assessor, they had not been asked to avoid discussion about their participation in the trial with anyone else. Some intervention participants who found they were benefiting from the exercise intervention and regular support from the physiotherapist, reported sharing their positive experiences with other myeloma patients within the service and encouraging them to seek out support too.

“And then I’d mentioned I speak to my physiotherapist. And he said, “Well, how did you get one of those?” And I told him what I was doing, that I was part of the study, and I asked him, ‘Was it offered to you?’.”

Kate, 37, Intervention

Although it is not clear if this did in fact impact upon the trial, these discussions could potentially have encouraged or promoted patients seeking out physiotherapy or exercise support over and above usual care.

“I’ve already recommended it. There’s a chap, we were having chemo together. He walked with two sticks but didn’t look like he was using them so I got friendly with him and told him afterwards, and a friend of mine from childhood, she has myeloma, she had it a year before me... she fell over and was taken on a trial at [study hospital] and when she fell over I said ‘Do ask them to give you physio because it will help you no end’ and it has.”

Julie, 68, Intervention

Indeed, despite encouragement to continue their usual exercise behaviour during the trial period five control participants did report accessing additional physiotherapy support. These, and others, also described changes to their physical activity behaviour
after enrolling in the study, despite being requested to continue their usual patterns of behaviour during the trial.

“[Generic cancer physiotherapy service] were kind enough to see me and gave me an exercise handout and showed me a few of the myeloma exercises that I could do, and that was basically the replacement of not being able to be part of the exercise group... So once I had that information and all the exercises that I could do in the morning and the evening, I did start to do those exercises, which were of great help.”  

Fran, 60, Control

As well as indications of intentional access to physiotherapy support or exercise resources, some control participants received input from physiotherapists during their ASCT admission if they spent time on the inpatient hospital ward. Although this was expected as a possible confounder at the outset of the study, participants seeking out services in the pre- and post-ASCT phases of the study was not and may indicate possible contamination of the control or usual care comparison.

8.4.2 Disparities in experience of recovery – expectations, feeling prepared and support

Clear divergence in interviewees’ perspectives dependant on their trial allocation began to emerge when recounting their experiences of recovery following ASCT. Although their recollections were varied and strikingly individual, there were evident commonalities shared amongst group members that distinguished their experience by their trial allocation. These disparities in recovery were notable in terms of their expectation of the treatment journey, an implicit sense of control, or lack of control, they perceived to have in determining their progress post-ASCT. Interviewees highlighted exercise as having a role in making them feel physically prepared and reflected on the other support they felt they required and received.

8.4.2.1 Discord in perceived ability or rate of return to ‘normal’ self

There was universal acknowledgment by most intervention participants that their recovery was directly impacted by taking part in the trial intervention with many indicating their recovery was quicker or less daunting than expected. Most intervention participants shared reflections on feeling a shift in their focus from a negative one related to undergoing intensive treatment with an assumed slow trajectory of recovery
to a positive one that their recovery was better than they expected and recalled less negative features of their recovery.

“I think my recovery was probably better than I thought it would be because when you read about it you think it could be months recovery and it didn’t seem that bad after all.”

Carl, 72, Intervention

“You know what, to be honest, I think it was quicker than I thought. It was after first two weeks, maybe up to four weeks, that was the toughest. And later on you feel like it’s getting better and better, yes.”

Paula, 47, Intervention

Although there was common recall amongst all participants of the immediate consequences of ASCT treatment during admission (experiencing debilitating fatigue, gastrointestinal symptoms, nausea and reduced appetite) most intervention participants reported a trajectory of recovery that was at first slow but then ramped up quickly as they were able to build up their exercise through engagement with the physiotherapist. Most intervention participants reported feeling as physically recovered as they could possibly be and anticipated return to usual activities quicker than expected.

“I could start to see a way back to work, so for me it was like yes, it doesn’t matter how long it takes, it was the first time that I could really be positive about life after transplant. Life in remission meant I could be more myself, I suppose.

I’m so sure that there are going to be many more people like me that get this myeloma and have careers and things that they love to do that entail being physical. And if that’s who you are, then just knowing that it is possible to return to some level to that, it’s good for the soul. And if it’s good for the soul, it’s going to be good for your recovery.”

Steve, 64, Intervention

In contrast, control participants mostly recalled a consistently slow trajectory of recovery and at interview many reported not being anywhere near their pre-diagnosis function or abilities. Importantly, some control participants were explicit in their view that their expectations of returning to ‘normality’ were low or much further in the future. The concept of having control in one’s preparation for and recovery from ASCT was evident from how interviewees discussed their experiences of the process. Intervention interviewees were more optimistic and indicated active participation in
determining their ongoing recovery, whereas controls were more passive in their discussions indicating a notion of waiting for things improve.

“I think I’ve still got a long way to go because they say it’s going to take up to two years to get it back to really what I was... I know I’ve got a long way to go, still a long way to go, but I’m getting there, slowly but surely.”

Audrey, 69, Control

“Now I can only do, at the moment, a quarter of the things that I would be able to do pre-cancer. So I think it’s just frustration. But I’m hoping that, I’m going on to seven months after my transplant, that maybe towards the end of the year gradually things will get a bit better as well.”

Fran, 60, Control

This acceptance to living with the ongoing consequences of their treatment were only evident among control participants. There was a sense that they were counselled to expect a recovery that would be challenging and slow and having started their ASCT treatment with lower physical capacity and ongoing symptom burden from induction treatment, they did not see themselves returning to their pre-diagnosis physical self any time soon. On the other hand, the intervention participants indicated their trajectory of recovery was nearly complete and related this to engaging in exercise before ASCT and being supported to recoup the benefits of their pre-ASCT activity through ongoing rehabilitative support following ASCT.

“Well, it’s difficult to say has it affected my recovery because obviously I didn’t know how long it was to recover without exercise, but from my personal sort of fitness level and things like that, it’s certainly improved that. So that has obviously got to be a plus point, because I could imagine, because it’s individual perceptions, having exercises and encouragement shows that you can still do it, whereas if you think you’ve got some horrible illness and you can’t do a thing, as my first impressions were, at the very beginning when I got the diagnosis and started on chemo. Like I say, it took a little bit at the beginning, it took a few weeks in fact, because slowly I realised that I could do things more or less fairly normally”

David, 72, Intervention

8.4.2.2 Contrast between experiencing ongoing support and self-initiated support

Generally the interviewees reported positive experiences regarding support in the post-ASCT period. When this support was explored in depth, there was a notable contrast in access to and availability of specific support regarding their recovery. Control participants recalled receiving information about how to access urgent support via
telephone should they require it and reported a sense of reassurance that contact with their clinical team was only a call away. Those who reported accessing that resource were pleased that they received timely response to their concerns. Many control participants reflected on possibly requiring more general support related to their physical recovery, and that although they could have called for advice or input, they often did not initiate a request for support because it was not urgent or an emergency. Some felt that they may have benefited from someone checking in on them more regularly throughout their early recovery as opposed to needing to initiate input.

“It was a good thing because if I hadn’t have had that, I think I would have been just left and only phoned by the hospital when they wanted a blood test or something like that. It just encouraged me to do stuff, get me onto my two feet as it were.”    Josh, 60, Intervention

The intervention participants were collective in the value they placed upon the regular individual contact they received from the study physiotherapist. They expressed that it was not purely the exercise programme but also the personalised approach to discussing what they were going through at each stage of treatment that was an instrumental part of their experience in trial. Some highlighted how discussing the challenges they were experiencing as well as monitoring and reporting their progress with the physiotherapist helped them to normalise their experiences and feel more optimistic about their recovery, focussing on problem solving, pacing their activities and progressing their tailored weekly exercise goals.

“Apart from [study physiotherapist] making sure I was trying to do as much on the exercise front as possible, she also gave me tremendous back up because I went into complete decline.

[Study physiotherapist] took me in hand and told me what she expected and what I had to do and it was just what I needed at that time. In fact, her phone calls regarding physiotherapy on the trial became a much more extended support to me.”    Julie, 68, Intervention

One control participant summarised his thoughts on access of support and reflected that it may seem like there is little specific support but that confidence in asking for or seeking support was required.
“When you are going through a treatment, as soon as you are told that you are going to have treatment, you are checked, from never being checked before, to being checked every day, then every week, every month, and then transplant, it’s every day. I think most people you speak to will probably say, ‘And then it just drops off, and I didn’t get any help.’ But there is help there if you ask for it. There is help there if you look for it. It’s just that you have gone from everyday treatment and care to then going home, and then sitting on your own and going, ‘What the hell? What do I do now?’ So, I think it is really easy for people to say that there is no help, when actually, there is if you look for it, or ask for it.”

Mike, 41, Control

There was a sense from interviews that whilst most controls felt they would have benefited from more support in the post-ASCT period, most could not be specific about what this would have involved. The intervention participants shared consistent reports of regular input from the physiotherapist to discuss what they were going through, whether specific to physical function and exercise or more related to emotional or practical recovery, was important in facilitating active participation in their own recovery as opposed to waiting for recovery to occur.

8.4.3 “What I wanted to do was build myself back up and prepare”

In response to numerous areas of questioning participants referred to the role of exercise or being active as important for their preparation for ASCT, as well as their future recovery. There was commonality regarding the impact of diagnosis and early treatment on participation in physical activity, recollections of seeking specific advice in the context of having myeloma, and shared understanding that exercising or getting fitter in preparation for ASCT would be beneficial. However, information seeking was often met with conflicting or deficient advice, highlighting missed opportunities to influence patient initiated desire to self-manage in their treatment journey.

8.4.3.1 Early treatment substantially reduces physical activity

Nearly all of the interviewees underwent ASCT as first line treatment and had been diagnosed with myeloma in the region of six months prior to being approached for the trial. Although two interviewees reflected on being able to maintain their usual exercise routines on chemotherapy, most described how side-effects experienced during early treatment had a detrimental effect on their physical activity levels.
“Once I was diagnosed with myeloma, then I started taking chemotherapy, I had a lot of fatigue and that really hindered my physical activity levels.”

Fran, 60, Control

“I had four cycles, so it was four months and then the neuropathy hit me because the symptoms had been hidden by the steroids I was taking and then when I stopped the steroids the peripheral neuropathy really hit me badly, I was in quite a bad way. I was on crutches for a while because I couldn’t walk properly. It affected me quite a lot.”

Jack, 70, Control

Approximately half of the interviewed participants had had significant spinal bone disease at diagnosis that required time immobilised with a spinal brace. The sudden loss of ability to move and be active had a significant impact on these participants’ ability to participate in their daily activities and self-care, which had a profound impact on their outlook for the future.

“I think the whole thing about it for me – I mean, it’s probably true for most people – the diagnosis was a terrible shock and the initial few months were really horrible and traumatic, and particularly being put in a back brace and a neck brace and being really constrained in how you move your body and what you can do, and you feel like you’ve really lost everything.

It’s very difficult to have a perspective that’s long-term because you don’t know really over what period you’re going to be alive and whether the constraints on your body in the first few months, whether they’re going to carry on or at what point you’re going to be free of it. Though people tell you that you will be out of the brace and all the rest of it, in the moment it’s very hard to look ahead; well, it was for me.”

Chris, 56, Control

Overwhelmingly, interviewees recalled the impact of fatigue on reducing their activity engagement and it was also clear that most had noticed the impact that reduced activity had on their physical and mental health, as well as social engagement. Most interviewees reported realising that engaging in exercise was required to counteract the resulting impact of their post-diagnosis inactivity. However, this was coupled with a profound sense of not knowing what exercise they could engage in and how to do so without advisory or practical support.

8.4.3.2 Insufficient or restrictive advice regarding exercising with myeloma

Participants expressed a desire for advice and practical support specifically with regards to exercise. Most were seeking more than general advice to keep active, desiring more
individualised advice, personalised to how they could exercise during treatment. Most reported receiving little or no advice on physical activity. Alarmingly, some interviewees recalled being told by health professionals to avoid exercise all together. Those who reported seeking out additional information or accessing non-specialist physiotherapy input found that they encountered inconsistent advice or that it was in discord with previous guidance from their myeloma team or that was in conflict with what they believed about the importance of being active.

“I did get referred to physio... she just kind of said ‘when you go in for your stem cell transplant, book something two months after your transplant and come back’, because they kind of were like ‘you’re not going to be able to do anything during your recovery from that.’ So it was a bit black and white, instead of ‘maybe you could do a little bit’... But should I have pushed myself a little bit more during the transplant or recovery? I’m not sure”

Rose, 51, Control

When interviewees indicated that they engaged in exercise independently they commonly shared this concern around not knowing how much or how hard they could exercise and that again, they perceived that there was no one to turn to when dissatisfied with responses from their health care team.

There was greater dissatisfaction amongst the sample of interviewees who had had spinal disease and required a spinal brace. In contrast with the other interviewees, who had become inactive over the course of early treatment but were not specifically restricted in their function, interviewees who had experienced a period of bracing shared experiences of rapid loss of strength, function and confidence due to immobilisation. They shared overt frustration at the ambiguity regarding how to be safely active, albeit with limitations, and demonstrated a greater appreciated need to become fitter because of how physically depleted they felt on removal of their brace and the prospect of their upcoming ASCT.

“I understood it because they were worried about my skeleton. So I understood why the advice was, but the way I was feeling and I suppose because of my [profession] I’ve been taught to know and understand my body and what it feels like, and I suppose for me the restrictions were – I don’t know – it was too strong.”

Steve, 64, Intervention
The desire for some to exercise was strong enough to result in them taking part in exercise despite advised not to, as they felt an all or nothing approach was too restrictive.

“Even though I’d had the cautionary advice from the hospital, I thought ‘Well, I can see that they’re saying these things because they don’t know and they have to say it because they don’t want to risk somebody like me ending up with a broken back and then suing them, or giving the wrong advice.’ But I did feel that it was overly cautious, so I did do things that I felt that my body could withstand without being stupid about it.

I think my general sense of all the exercise advice I’ve received is that nobody really knows, and I’m as good as anybody else in making that assessment for myself.”    Chris, 56, Control

8.4.3.3 Exercise is preparation

Most interviewees expressed a perception that they had wanted to physically prepare for their ASCT, for some it was the main motivation behind enrolling in the trial. Having recalled the negative effects of diagnosis and early treatment on their fitness and strength nearly all reflected on the period around consideration for ASCT as key time for contemplating engaging in exercise.

“But by the time I was recruited and I was looking forward to the stem cell transplant, I’d been through six months of initial therapy… I was looking forward to the stem cell transplant but very anxious and worried about the impact that would have, so I was thinking I need to get my body to be in as good shape as possible to be as strong as possible to withstand the onslaught of what was to come.”    Chris, 56, Control

Interviewees did reveal a concern that the loss of strength and fitness following diagnosis may have lowered their capacity to take on further intensive treatment and therefore getting fitter prior to ASCT was crucial to put them in a position where they could tolerate any further consequences of treatment.

“They told me that the transplant would take a lot out of me, and in my mind there wasn’t much left to take out of me so I felt like I needed to do things to build up so that I had something to lose in the transplant stage.”    Steve, 64, Intervention
Nearly all expressed feelings that getting fitter through exercise would have or did better equip them to manage their ASCT in the immediate acute phase and into recovery from treatment.

“Oh being very weak, very weak and poorly. Yes, after the transplant for a while. I’m better now, but it’s taken a while to recover and I’m sure I would have recovered quicker had I been in better condition when it started.”
Jack, 70, Control

For those who did receive the input from the physiotherapist and intervention exercise programme as part of the PERCEPT myeloma trial there was explicit appreciation for its positive influence on their ability to tolerate and recover from their ASCT.

“I thought I’d go in, have it and bounce back. So it took me longer, but if I hadn’t got [study physiotherapist]’s support and the exercises, it would have taken twice as long. I don’t think I would have been fit enough to have the stem cell treatment.”
Julie, 68, Intervention

“I think the actual trial and everything else is an excellent programme. Without it, I would have struggled a lot more... I think it can only be a good thing. There’s not any negative about it. It brought me back... If I hadn’t have had that, I think I would have struggled a lot more without it.”
Josh, 60, Intervention

Experiences shared by participants in the control group highlighted missed opportunities to support patients to prepare physically for upcoming treatment despite their desire for help and direction. A number of interviewees recalled being given advice to wait until after their transplant before initiating exercise which was in discordance with their perceived need to get into better physical condition for their upcoming intensive treatment.

“I did ask them specifically... I had a telephone conversation with the [health professional] and I did go through my questions with her about what I could and couldn’t do... I remember her advice was cautionary and she said “I don’t really want you doing anything until you’ve got through the other end of the transplant.”
Chris, 56, Control

This was a common experience for the interviewees who had experienced spinal bracing and general lack of advice regarding exercising with myeloma related bone disease.
8.4.4  Active ingredients – participants’ experience of the intervention

Deductive coding identified elements of the intervention suggested as influential, both explicitly and implicitly, by intervention group participants. A more positivist approach was used to draw out and describe the elements of the intervention that were highlighted through quantification of number of interviewees who mentioned them as well as the frequency of which they appeared in the coded dataset.

8.4.4.1 Exercise programme and sessions

As described within the subtheme related to ongoing support (section 8.4.2.2), the role of the physiotherapist in providing regular input appeared to be the most valued part of the intervention for participants allocated to the intervention group, followed by the exercise programme itself.

Interviewees described varied expectations of what the exercise programme would entail when they enrolled on the study. Overwhelmingly, they valued the individualised, tailored approach to the programme made possible through their engagement with the physiotherapist. Some younger, previously active participants initially thought of the structured exercises specific to the trial as too basic but that with tailoring they found a level that challenged them and saw progress.

“I think the exercise given is geared towards people that are less mobile before. And so we kind of worked out something that worked well for me. But I think they were really decent exercises because they were strengthening exercises, which I would do anyway.”    Kate, 37, Intervention

Other previously active participants also shared how they benefited most from the aerobic component of the programme and working with the physiotherapist to progress their fitness. Some interviewees felt they would have preferred more frequent supervised sessions, particularly pre-ASCT, in order to benefit from the higher intensity aerobic exercise they felt they achieved more easily through use of gym equipment and supervision of the physiotherapist. Other participants found the combination of resistance and strengthening exercises to be most impactful.

Collectively interviewees recalled how seeing their own progress over time spent following the exercise programme, whether through lifting more weight or completing
more repetitions or through seeing changes to their body or fitness, was motivating and encouraged them to continue to adhere to the programme. A number of intervention participants interviewed reported to have continued elements of the programme as part of their ongoing exercise after they had completed the trial.

“For me, the aerobic side of stuff was always challenging, was always challenging for me. The strength work, yes, in the beginning I suppose [pause] the exercises themselves were fine because all the exercises can be personalised to where I was, so everything that we did I’m still doing; I’m still doing that set of exercises because they work, it’s just that now I’m able to do the sets with weights and with the extra Pilates work that I do myself. Especially in the beginning, the programme was definitely enough and definitely worked all parts of the body.”

Steve, 64, Intervention

8.4.4.2 Behaviour Change Techniques (BCTs)

The trial intervention was informed by behaviour change theory and components of the intervention were mapped according to the BCT taxonomy (BCTT v1) (Michie et al., 2013; McCourt et al., 2020). Aforementioned findings in this chapter already describe components of the intervention indicative of BCTs, such as ‘credible source’ evident from descriptions of education and guidance from a physiotherapist with expertise in myeloma. Additional BCTs were identified from the transcripts through implicit and explicit mentions by interviewees. The five most frequently coded BCTs were: 1. Goal-setting of the behaviour; 2. Graded tasks; 3. Adding objects to the environment; 4. Self-monitoring of behaviour; 5. Generalisation of behaviour.

The most common BCT referred to by most participants and mentioned most frequently throughout the transcripts was ‘goal-setting’. Most interviewees described positive experiences of setting and monitoring goals with the physiotherapist, with goals not only relating to exercise and physical activity behaviour but some described setting ‘lifestyle’ goals especially in the recovery or rehabilitation phase of the intervention. When talking about goal-setting most participants referred to the intervention log-book they received. Alongside mentions of the intervention booklet, the supply of heart-rate monitors and resistance exercise bands, as well as participants obtaining or using other exercise equipment were identified as the BCT ‘Adding objects to the environment’.
Intervention interviewees also explicitly referred to progression of the exercise programme, adaptations of exercises due to improvements in fitness and their progression in terms of ability to manage daily tasks in their recovery. These were mostly linked to discussion related to following the intervention programme and receiving support from the physiotherapist. These references were coded to the BCT ‘graded tasks’. Related to progression and referring frequently to use of the intervention booklet, participants stressed importance on ‘self-monitoring’ of exercise alongside recording goals. A small number of interviewees mentioned continued self-monitoring of their exercise behaviour using their own logs, based on the study log-books. Shared examples included keeping a written notebook and a digital spreadsheet of continued activity beyond the trial period.

8.4.4.3 Intervention Booklet

As already described, most participants were candid in their regard for the intervention booklet as a key resource to support adherence to the intervention. There was suggestion that completing the log sheets brought about accountability to the intervention. Participants varied in their opinions of what part of the intervention booklet was most important for them. Many who discussed the importance of setting goals expressed having space in the intervention booklet to record their goals as valuable. Some reported recording adherence to the exercise and being able to look back at previous weeks to self-assess and monitor their progress as fundamental to their motivation, although others recalled that they did not complete these elements of the intervention booklet and described using it solely to refer to the specific instructions for the exercise programme. One participant referred to completing the log sheets as “more of a chore” and placed greater value on the weekly discussions with the physiotherapist for motivation.

8.5 Discussion

This qualitative study investigated the experiences of people with myeloma who took part in exercise related research whilst undergoing ASCT. The study focussed on gathering deeper understanding of participants engagement with trial processes as well as issues related to physical activity since diagnosis and during their participation in the trial. The themes generated from the coded dataset cumulated around three broad
areas: common experiences related to participation in the trial irrespective of group allocation; contrasting experiences of participants related to allocation; and pre-enrolment experiences of myeloma, its early treatment and the effects on physical activity and the paucity of related support. An additional area developed described factors related to the intervention.

Reasons for participating in the exercise trial fell into both altruistic and personal motivations. Altruism is known to be an important influence in recruitment to health-related RCTs with evidence that trial participants can be motivated by a genuine wish to contribute to knowledge and improvement in care as well as a way of ‘giving back’ (Houghton et al., 2020). Most of the interviewees expressed a personal motivation for participation with a perception of the trial intervention as potentially beneficial to them, therefore consistently those allocated to the control condition conveyed a sense of disappointment and dissatisfaction with their allocation. The indication of preference and possibility of negative feelings regarding allocation perhaps illustrates an unbalanced consideration and therefore deficient equipoise prior to participation, both of which are considered important for ethical, informed consent and effective randomisation in trials (Miller & Brody, 2003; Rooshenas et al., 2016; Toye et al., 2016).

Testing complex interventions, such as rehabilitation and behavioural interventions, through traditional RCT designs is inherently undermined by an inability, in most cases, to blind participants to their allocation (Boutron et al., 2004). Participants in trials such as this are aware of the treatment arm they have been allocated to and may consider themselves neglected or abandoned especially when they are offered an ‘inactive’ control condition (Toye et al., 2016). The use of usual care as the control comparator in the PERCEPT trial was determined to be appropriate given that there is no standardised approach to offering physiotherapy or exercise therapy to people with myeloma. But what was underestimated was the response to the study in highlighting how approached and enrolled participants’ had preconceived perceptions of benefit to be gained from the intervention on offer. Interviewees associated potential benefit from taking part purely because of the physical and functional deficits they had experienced and lack of advice and ameliorative support they had been able to access since diagnosis. Other studies have documented that participant dissatisfaction with their current status or a dearth of acceptable standard of usual care drives motivation to participate in trials. A
qualitative exploration of participants from a stroke rehabilitation pilot trial described participants ‘desperation’ to do anything to help their situation as a personal motivator to take part, but this was met with feelings of ‘abandonment’ when allocated to an inactive control condition (Norris et al., 2019). Another qualitative study embedded within a rehabilitation pilot trial reported people with colorectal cancer allocated to a no rehabilitation control group felt abandonment also (Hubbard et al., 2016). The possibility of participation in the trial as potentially beneficial and probable lack of balanced consideration for outcome of allocation may have instilled therapeutic expectations within participants, quickly rescinded when informed of their allocation to control.

Actions of both control and intervention participants interviewed for this qualitative study identified areas for concern regarding the fidelity of the control condition. As already introduced, dissatisfaction of allocation to control may not only lead to negative feelings but has been seen to induce dropout and increase attrition bias in RCTs (Lindstrom et al., 2010; Higgins et al., 2011), although this was not evident in this trial. Most control group interviewees reflected a shift from disappointment because of their primarily personal motivation to take part towards a more altruistic stance that their participation was still important to benefit the research and therefore remained in the trial. Although their dissatisfaction may not have played out as attrition it did result in many seeking alternatives to the intervention outside of the trial.

Contamination bias arises when the control group participants are inadvertently exposed to or receive the intervention condition and can result in muted or completely masked effects of the intervention being trialled (Levin, 2005; Robinson et al., 2020). A systematic review of contamination, dropout and control group design in exercise oncology trials found 37% of trials reported contamination of control group (Steins Bisschop et al., 2015). It is likely that this pilot trial was victim to contamination bias in two ways. Firstly, more than half of control participants interviewed reported seeking out physiotherapy support or independently becoming more physically active during the trial period therefore it is possible that this also occurred in other control group participants in the wider trial. Secondly, intervention participants, so pleased with their experience of the trial intervention and engagement with the physiotherapist, reported encouraging other patients to seek out or request referral for physiotherapy. This
informal proclamation of benefit by the intervention group could be considered a source of contamination if directed towards control participants or other patients who were later approached for the trial (Levin, 2005).

It has been established that perceived personal gain comes before altruism as motivating factors in trial participation, but it has also been proposed that altruism becomes the primary motivator for control participants after randomisation has occurred (Harrop et al., 2016a). As people are often motivated primarily at a personal level, future trial designs where blinding of allocation is not possible may need to consider alternative methods to bring about equipoise to randomisation and reduce dissatisfaction with allocation. Improved recruitment and retention, as well as reduced contamination of control could be facilitated by using alternative designs including double consent processes such as Zelen design (Zelen, 1979; Adamson et al., 2006; Land et al., 2020) or patient preference trial designs (King et al., 2005), as well as offering control conditions that could be perceived to be as advantageous as the intervention condition.

The addition of qualitative exploration alongside quantitative testing in RCTs can provide insights into benefits not explicitly observed by the chosen quantitative tools. Although there may be indications of research participation effects, contamination bias and potential deleterious impact on trial outcomes due to participation of controls in exercise or physiotherapy, what became evident from this qualitative study is that there remained polarised experiences of physical and emotional recovery from ASCT consistent with allocation. It has been hypothesised that participation within research procedures alone may induce the behaviour change under investigation (McCambridge et al., 2014b; McCambridge et al., 2014a). However, in the case of these interviewees the probable influence of participation on eliciting some form of change in physical activity behaviour before ASCT may not have been enough to impact their trajectory of recovery following ASCT. Most control participants described both an expectation and reality of a slowly progressing recovery that they expected to go beyond the trial period, whereas intervention participants were applauding of their rate of recovery and attributed it to the intervention, in particular the regularity of support from the physiotherapist. These findings indicate that the exercise intervention induced benefit and influenced recovery following treatment as intensive as ASCT. Differences were
evident despite indications of contamination. However, these benefits may relate as much to the psychological, emotional and cognitive effects of the intervention as the physiological. Over a third of myeloma patients undergoing ASCT will experience high symptom burden up for to nine months post-ASCT (Wang et al., 2015) and qualitative literature supports the positive experience of increased physical activity resulting in proportional gains in perceived physical vigour and strength among myeloma patients undergoing ASCT (Craike et al., 2013b). A thematic synthesis of qualitative literature from this population found ‘exercise for recovery’ to be a key analytical theme of high confidence (Walpole et al., 2018).

The contrast in allocation related experiences does lend support in favour of benefit of the intervention, however what is less clear is what components or elements of the intervention were responsible for these perceived outcomes. Intervention participants placed great importance upon the regular contact with the physiotherapist and although these contacts were related to intended intervention mechanisms (e.g. BCTs such as goal setting, graded tasks) that would be facilitated through discussion with the physiotherapist, this could also have been related to the additional attention received. The additional attention received through intervention delivery alone may be sufficient to induce change in participants receiving behavioural interventions (LaFave et al., 2019). The lack of additional attention afforded to the control group may pose a confounding factor in the trial. In retrospect, little consideration was given to the general therapeutic factors at play within the invention group that may have been necessary to provide and therefore control for in the control condition (Safer & Hugo, 2006; LaFave et al., 2019). It is therefore difficult to tease out whether it was the expected mechanisms of the exercise programme or regular therapeutic engagement with the physiotherapist, or both, that influenced intervention participants experience of recovery as a more positive one than that experienced by the control participants.

Analysis of intervention participants experiences of undergoing the exercise intervention did provide insight into the possible ‘active ingredients’ or mechanisms at play. Explicit references were made to the structured exercise prescribed but overall greater significance was place upon the physiotherapist contact, particularly in the post-ASCT rehabilitation phase. Intervention materials particularly the intervention booklet were also highlighted as central to their engagement in the intervention. Descriptions
of participation in the intervention activities did provide evidence for the BCTs at play. The most frequently coded BCTs from this qualitative study include those associated with interventions that support long-term physical activity behaviour change in cancer survivors (Grimmett et al., 2019). Interviewees placed importance on goal-setting and grading of tasks facilitated by the physiotherapist using an individualised approach. The benefits of practitioner support with goal-setting, setting of graded tasks as well as reviewing progress and self-monitoring of behaviour have been highlighted as influential in other exercise interventions (Turner et al., 2018; McAuliffe et al., 2021). The BCTs reported within this qualitative study are in line with those reported in other studies, confirming these elements of the intervention as likely mechanisms of influence on exercise behaviour.

Another important finding from this study is the apparent desire from interviewees to use the phase in their treatment trajectory, between commencement of induction chemotherapy and ASCT, as a period of physical restoration and preparation. Most significantly, is the commonality of experience that seeking support or practical advice related to physical conditioning in this phase of treatment is most often met with unsatisfactory response. Poor physical functioning and perceived loss of control are associated with worse psychosocial outcomes and quality of life in people undergoing stem cell transplantation (Coolbrandt & Grypdonck, 2010; Pulewka et al., 2017). Qualitative findings among people undergoing allogeneic transplantation highlight that exercise is perceived as positively influencing recovery from treatment and can provide a sense of control and structure during transplant (Abo et al., 2022). Abo et al. (2022) also found that transplant recipients welcomed support from clinicians, resources to support exercise and measurement of physical outcomes and that these provided automatic incentives and motivation to exercise during transplant. Other qualitative literature specifically amongst myeloma ASCT recipients have also found that patients place importance on the role of exercise for enhancing recovery (Coon & Coleman, 2004; Craike et al., 2013b; Craike et al., 2017; Walpole et al., 2018). Therefore the finding that myeloma patients preparing for ASCT were seeking of physical activity advice in the context of trying to take some control in their recovery is unsurprising. However the experience of most people interviewed in this study, and those described in Chapter 4, is that there is little or no access to specialist advice or individually tailored support that
people with myeloma regard as necessary to support their confident, safe-engagement in physical activity. Participants reporting a motivation to exercise to ‘build back up’ following early consequences of treatment and ‘prepare’ for upcoming ASCT but being met with lacking or inconsistent advice indicates an obvious missed opportunity to fulfil a clear patient initiated desire to self-manage in their treatment journey. This study adds further support for embedding provision of exercise and rehabilitation support within the care pathway for myeloma, particularly in preparation for ASCT (Snowden *et al.*, 2017; Walpole *et al.*, 2018).

Haematological cancer patients may engage in more self-determining actions distal to core care decisions as a means of maintaining some control and normality during a time that is largely preoccupied with illness and treatment decisions seemingly outside of their control (Ernst *et al.*, 2013). The phase in the treatment, between early induction treatment and decision to proceed with ASCT represents a key time of contemplation for myeloma patients considering becoming more active and wishing to physically optimise themselves for future treatment. This also has implications on the evaluation of the PERCEPT trial. It is evident that the population from which the trial was sampled were likely to be motivated and contemplative of seeking out support to exercise, and regardless of their state of readiness or capability to independently engage in more physical activity, being provided with information related to the exercise trial and enrolling in the trial may have been sufficient for some to change their physical activity behaviour as well as challenge the concept of equipoise required for randomisation. This qualitative study has highlighted possible research participation effects that could occur both pre- and post-randomisation to undermine the outcome of intervention effects and will need to be considered in the design of future research in this area.

### 8.5.1 Limitations

There is no doubt that the addition of qualitative investigation alongside or embedded within RCTs is an essential component to understanding the intricacies of developing and testing complex interventions (Lewin *et al.*, 2009; Toye *et al.*, 2016; Baldeh *et al.*, 2020; Skivington *et al.*, 2021), however this method of research is not without limitation. In addition to reflections shared in Chapter 4 Section 4.3.4.2 my role as the researcher will have been influenced by my perspectives as a health professional who places high
value in rehabilitation and exercise as adjuvants to cancer treatment and these factors will have shaped the research analysis. This acknowledgment of my influence in the research, use of reflexive thematic analysis as well as the inclusion of other researchers to interview and code a selection of transcripts will have contributed to coding reliability. The contribution of different researchers, from both clinical and research backgrounds with varying interaction with myeloma patients prior to interview also resulted in interviews of varying depth of enquiry.

As was also identified in the other studies described in this thesis, a disproportionate amount of the interviewees reported good levels of physical activity or described themselves as very active people pre-diagnosis and most stressed a perceived importance on being active. It may be the case that the nature of this research attracted those interested or partaking in physical activity and therefore may not be representative of all individuals with myeloma approaching ASCT.

Although the study sample was purposefully sampled to gather experiences of participants recruited across the length of the study period, including those who were recruited to both the original face-to-face and virtual study protocols, the interview schedule was not adapted sufficiently to explore experiences of the different protocols or the impact of the COVID-19 pandemic on participation. Therefore, this study missed opportunities to provide further context to the different modes of delivery used during the two approaches to trial delivery.
Chapter 9  Physical activity awareness and provision of advice by haematological healthcare professionals in the United Kingdom: an online survey

9.1  Introduction

General promotion of positive messaging and endorsement of physical activity by healthcare professionals could be influential in encouraging more people living with haematological cancer to be physically active and engage in exercise. Health professionals have a key role in providing evidence-based information to cancer patients regarding their condition, its treatment options and promoting healthy lifestyle behaviours during and after cancer treatment (Keogh et al., 2017). Cancer survivors have reported that they would value receiving physical activity advice from their care providers, particularly clinical nurse specialists and doctors, as part of their treatment and would trust that advice to be safe and accurate (Roberts et al., 2019).

Perceived barriers to health professionals providing advice regarding lifestyle behaviours such as physical activity include lack of clear guidance, a belief that they are not the correct person to give advice and lack of time to give advice (Williams et al., 2015). It is known that among health professionals, that a lack of knowledge of guidelines related to lifestyle behaviours, including physical activity, results in reduced likelihood of providing advice or recommendations to patients. A study reporting low familiarity of physical activity guidance among 1013 UK primary care physicians also found that those unfamiliar with guidance were less confident when raising the topic of physical activity and were significantly less likely to advise physical activity, particularly to patients with comorbidities, such as cancer (Chatterjee et al., 2017). In contrast, another UK based study reported high levels of awareness of guidance and initiation of physical activity conversations among physiotherapists. When questioned on the specific content of physical activity guidelines however, their knowledge of all aspects was poor and this discrepancy in knowledge may impact on the quality of the physical activity advice delivered in practice (Lowe et al., 2017).

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Although some health professionals working within the cancer setting do recognise the importance of discussing physical activity with their patients, their advice may often not be aligned with published guidelines either. In a survey of oncology professionals in Ireland, respondents most commonly reported providing verbal physical activity advice, however less than half of respondents provided recommendations in line with current guidance (Cantwell et al., 2018). The emerging research surrounding this important topic has been carried out on samples of health professionals predominately working in the area of solid tumours, such as breast, colorectal and prostate cancer, where stronger evidence for exercise during treatment and survivorship exists. Information is lacking regarding the understanding of health professionals working principally with people living with haematological cancer diagnoses.

9.2 Aim

The aim of this study was to examine awareness of physical activity recommendations, to explore beliefs surrounding the role of physical activity during and after treatment and to understand practices in provision of advice given to patients by health professionals working in haematological cancer settings in the UK. Predictors of familiarity of physical activity guidance and provision of advice to patients were also examined.

9.3 Methods

9.3.1 Design, survey development and piloting

This study was conducted using an anonymous online survey distributed to health professionals via a weblink. The survey was based on previously published studies of health professionals conducted in the UK and Ireland (Williams et al., 2015; Pugh et al., 2017; Cantwell et al., 2018). The design of the survey and questions were based on previous survey research conducted among UK oncology health professionals (Williams et al., 2015). Questions regarding agreement/disagreement with statements related to physical activity were incorporated from other health professional survey research conducted in Ireland after discussion with the researcher (Cantwell et al., 2018). Further questions were developed specifically for this study and all questions were adapted for
haematology based workforce by me with input from my supervisors. The questionnaire is presented in Appendix L.

The survey was piloted in paper format and tested with three health professionals working at UCLH. In order to test the quality of the survey questions and reduce possible measurement error through misunderstanding or varied interpretation of the questions, the components of the survey were tested using cognitive method based on theories of survey response (Collins, 2003). These participants were asked to complete the survey questions whilst ‘thinking aloud’ to allow me to gather feedback on the appropriateness and understanding of the questions. Finally, an online version of the survey was piloted using the Opinio platform to a small and varied sample of health professionals from a UCLH and research colleagues at UCL.

9.3.2 Participants and recruitment

Health professionals working in a UK cancer setting, in roles that had direct contact with people having treatment or follow-up for a haemato-oncological diagnosis were eligible to complete the survey. Responses were sought from doctors, nurses, allied health professionals (AHPs), pharmacists, research practitioners and support/auxiliary health care staff.

Distribution and invitation to the survey was assisted by input from a number of professional organisations and networks. They were requested to share an introduction and link to the survey with their members via email lists and/or through sharing it on websites or social media accounts. Seven organisations agreed, including the British Haematology Society, the UK Oncology Nursing Society, the Association of Chartered Physiotherapists in Oncology and Palliative Care, the British Dietetic Association Oncology Group, the Society of Radiographers, the British Oncology Pharmacy Association and the European Society for Blood and Marrow Transplantation Nurses and AHPs Group. The survey link was also shared on the social media platform Twitter at three separate time intervals. Data was obtained via the anonymous online survey using the Opinio online software platform. The survey link was live and open for 200 days between April and October 2019.
9.3.3 Ethical approval

This study was approved by University College London’s Research Ethics Committee (reference 14783/001). Study approval letter in Appendix M.

9.3.4 Measures

9.3.4.1 Demographics including health professionals’ own self-reported physical activity

Demographic questions related to age, gender and professional group. Professional questions explored time in current role, haemato-oncological diagnoses of patients they care for, clinical setting type and location by region. Respondents own self-reported physical activity was assessed with the questions: ‘On average, how many days per week did you engage in moderate to strenuous physical activity (like a brisk walk or run)?’ and ‘How long is your average session of moderate to strenuous physical activity in minutes (i.e. a single running/walking/exercise session)?’. Step count questions included: ‘Do you track your step count (with e.g. a phone app, smart watch, pedometer)?’ and ‘what is your average step count per day?’.

9.3.4.2 Awareness of physical activity guidelines for cancer patients

Health professionals familiarity with guidelines was asked with the question: ‘Are you familiar with any physical activity or exercise guidelines that are relevant for cancer patients?’, with response options ‘yes, I know of relevant guidelines’, ‘I’m aware there are some, but don’t know what they are’ or ‘I am not aware of any guidelines’. If respondents selected ‘yes, I know of relevant guidelines’, they were routed to an open text question: ‘please give some details of the physical activity guidance that you know? (e.g. the name of the guidelines, who produced them or any detail you can recall)’.

9.3.4.3 Beliefs about importance of physical activity during and after treatment

Health professionals were asked to share their level of agreement or disagreement with a number of statements related to physical activity in the context of people living with haematological cancer. These statements were presented in two matrix style items; the first question asked health professionals to respond to the statements while considering
patients during treatment for haematological cancer, the second asked them to respond to the statements while considering patients after completion of treatment.

9.3.4.4 Provision of physical activity advice

In relation to health professionals giving advice to their patients, respondents were asked the question: ‘Do you give advice regarding physical activity to your patients with blood cancer?’ Response options were: ‘Yes, routinely to most of my patients’, ‘Yes, only if they request information regarding physical activity’, ‘Yes, only to patients that I think would benefit from physical activity and ‘No, I do not recommend or give advice about physical activity to my patients’. Those who responded ‘Yes, only to patients that I think would benefit from physical activity’ were routed to a follow on question asking the characteristics of patients they think benefit from physical activity advice, response options were: ‘They are older’, ‘They are younger’, ‘They appear ‘fit’ and able to undertake physical activity’, ‘They are deconditioned or frail’, ‘They have comorbidities that I know benefit from regular physical activity’, ‘They have treatment related symptoms’, and ‘They are fatigued’, with respondents prompted to choose all that apply. Proportion of patients they give advice to and timing of advice were assessed with the following questions; ‘Can you estimate how many of your patients with blood cancer you give advice about physical activity to?’ and ‘When do you commonly give advice about physical activity to your patients with blood cancer?’ The response options were response options were ‘At diagnosis, before commencing anti-cancer treatment’, ‘During treatment with anti-cancer treatment’, ‘On completion of anti-cancer treatment’, ‘During maintenance treatment’, ‘During survivorship/follow-up period after anti-cancer treatment’ and ‘None of my patients ask me for advice about physical activity or exercise’.

Health professionals were asked what proportion of their patients request physical activity advice from them, with the question ‘Could you estimate what proportion of your patients with blood cancer ask you for information about physical activity?’, with response choices ‘none’, ‘0-25%’, ‘26-50%’, ‘51-75%’,’>75%’. Timing of advice was assessed with ‘When do patients with blood cancer commonly ask you for information about physical activity?’, ticking all that apply, the response options were the same as those detailed previously for the questions related to patients requesting advice.
9.3.4.5 Examples of health professional physical activity advice/information

To gather detail on the information that health professionals provide to their patients, survey participants were asked: 'Please give an example of information or advice you give about physical activity to patients with blood cancer?'. This question had an unlimited free textbox response and could be skipped without providing a response.

9.3.5 Analysis

Survey data was downloaded from Opinio and analysed using SPSS statistical package (version 25.0. Armonk, NY: IBM Corp.). Descriptive statistics were used to describe proportions of respondents overall and by professional group, their demographics, professional setting, awareness of physical activity guidelines and provision of physical activity advice. Data from respondents who completed at least one question related to the aims of the study were included within the analysis. For survey items with missing data the number of respondents included in the analysis has been detailed. Two separate logistic regression models were carried out on responses from the three largest professional groups nursing, AHPs, medical. Predictors of health professional familiarity with guidelines was assessed using an ordinal logistic regression with professional group, time in current role, health professional familiarity with guidelines and health professionals self-reported physical activity. A binominal logistic regression was used to examine provision of advice using demographic predictors (professional group and time in role) and awareness of physical activity guidelines on reported proportion of patients given advice. For the second model the dependent variable was dichotomised into provision of advice to less or more than 50% of patients and also only included the three largest professional groups.

Open-response survey question responses were transferred into qualitative data analysis software NVivo (version 12. QSR International Pty Ltd.) and coded line by line. To map the range and nature of open text responses a process of framework analysis was followed using five key stages; familiarisation of data, identifying a thematic framework, indexing, charting and mapping and interpretation, as outlined by Ritchie and Spencer (Ritchie, 2002).
9.4 Results

9.4.1 Response rate

The exact response rate for the survey is not known as the online link was shared by distributing organisations. The survey link was accessed 244 times. 219 health professionals started the survey, 206 (94%) completed all demographics questions and 196 (90%) completed at least one question related to the aims of the study. Of these, 156 (71%) completed the whole survey.

9.4.2 Respondents

The characteristics of the respondents are shown in Table 9.1. Thirty-four per cent (n=67) of respondents were nurses and thirty-one per cent (n=61) were AHPs. Seventy-six per cent (n=150) of respondents were female and the majority were aged between 26 and 45 years (73.5%, n=144). Mean age of respondents was 38 years. The mean total self-reported moderate to strenuous physical activity per week of the survey respondents who completed the questions related to own physical activity was 150.74 (±115.42) minutes per week. 44.2% of respondents who provided an answer reported engaging in 150 minutes or more of moderate or strenuous physical activity per week on average.

Table 9.2 details the geographical location and professional settings of the respondents. The survey had at least three responses from each region of England and at least six from each of the UK home countries (England, Scotland, Wales and Northern Ireland), the greatest number of respondents were from the London region (31%, n=60). Most respondents (59%, n=115) worked in a specialist oncology/haematology centre treating haematological cancers and carrying out stem cell transplantation. The most common patient group worked with was lymphoma (81%, n=159), with 32% (n=63) reporting that they worked with patients across all common blood cancer diagnoses.
<table>
<thead>
<tr>
<th>Age</th>
<th>n=196</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤25 years</td>
<td>6.1 (9)</td>
<td></td>
</tr>
<tr>
<td>26-35 years</td>
<td>37.8 (74)</td>
<td></td>
</tr>
<tr>
<td>36-45 years</td>
<td>35.7 (70)</td>
<td></td>
</tr>
<tr>
<td>46-55 years</td>
<td>19.4 (38)</td>
<td></td>
</tr>
<tr>
<td>56-65 years</td>
<td>2.6 (5)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23.5 (46)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>76.5 (150)</td>
<td></td>
</tr>
<tr>
<td>Prefer not to say</td>
<td>0.5 (1)</td>
<td></td>
</tr>
<tr>
<td>Professional Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing</td>
<td>34.2 (67)</td>
<td></td>
</tr>
<tr>
<td>Clinical nurse specialist</td>
<td>18.9 (37)</td>
<td></td>
</tr>
<tr>
<td>Matron/lead nurse</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Inpatient/ward nurse</td>
<td>11.2 (22)</td>
<td></td>
</tr>
<tr>
<td>Outpatient/day care nurse</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Allied health professional</td>
<td>31.1 (61)</td>
<td></td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>19.4 (38)</td>
<td></td>
</tr>
<tr>
<td>Occupational Therapist</td>
<td>2.6 (5)</td>
<td></td>
</tr>
<tr>
<td>Dietitian</td>
<td>5.6 (11)</td>
<td></td>
</tr>
<tr>
<td>Therapeutic Radiographer</td>
<td>3.1 (6)</td>
<td></td>
</tr>
<tr>
<td>Speech and Language Therapist</td>
<td>0.5 (1)</td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>16.8 (33)</td>
<td></td>
</tr>
<tr>
<td>Pharmacist</td>
<td>6.6 (13)</td>
<td></td>
</tr>
<tr>
<td>Advanced clinical practitioner</td>
<td>5.6 (11)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>5.6 (11)</td>
<td></td>
</tr>
<tr>
<td>Time working in current role/career stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5 years</td>
<td>51.5 (101)</td>
<td></td>
</tr>
<tr>
<td>6 years or more</td>
<td>48.5 (95)</td>
<td></td>
</tr>
<tr>
<td>Self-reported Physical Activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting guidelines (≥150 mins/week)</td>
<td>35.2 (69)</td>
<td></td>
</tr>
<tr>
<td>Not meeting guidelines (&lt;150 mins/week)</td>
<td>44.4 (87)</td>
<td></td>
</tr>
<tr>
<td>Total self-reported moderate or strenuous physical activity per week (minutes)</td>
<td>Mean (SD) 150.74(±115.42)</td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>Median (range) 120 (0-630)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) 20.4 (40)</td>
<td></td>
</tr>
</tbody>
</table>
Table 9.2 Professional setting and patient groups

<table>
<thead>
<tr>
<th>Proportion of their patients who have a blood cancer diagnosis</th>
<th>n=196</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 50%</td>
<td>69.4 (136)</td>
</tr>
<tr>
<td>Less than 50%</td>
<td>30.6 (60)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient diagnoses cared for†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>81.1 (159)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>78.1 (153)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>77 (151)</td>
</tr>
<tr>
<td>Myelodysplastic Syndromes</td>
<td>50 (98)</td>
</tr>
<tr>
<td>Myeloproliferative Neoplasms</td>
<td>37.8 (74)</td>
</tr>
<tr>
<td>All of the above diagnoses</td>
<td>32.1 (63)</td>
</tr>
<tr>
<td>Other</td>
<td>7.1 (14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist oncology/haematology centre treating blood cancers</td>
<td>58.7 (115)</td>
</tr>
<tr>
<td>&amp; carrying out stem cell transplant</td>
<td></td>
</tr>
<tr>
<td>District general hospital treating blood cancer, that does not</td>
<td>15.8 (31)</td>
</tr>
<tr>
<td>carry out stem cell transplant</td>
<td></td>
</tr>
<tr>
<td>Hospice</td>
<td>1.5 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>3.6 (7)</td>
</tr>
<tr>
<td>missing</td>
<td>20.4 (40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Affiliation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>London</td>
<td>30.6 (60)</td>
</tr>
<tr>
<td>South East England</td>
<td>12.8 (25)</td>
</tr>
<tr>
<td>South West England</td>
<td>6.1 (12)</td>
</tr>
<tr>
<td>North West England</td>
<td>4.6 (9)</td>
</tr>
<tr>
<td>East of England</td>
<td>4.1 (8)</td>
</tr>
<tr>
<td>East Midlands</td>
<td>3.6 (7)</td>
</tr>
<tr>
<td>West Midlands</td>
<td>3.1 (6)</td>
</tr>
<tr>
<td>North East England</td>
<td>2.6 (5)</td>
</tr>
<tr>
<td>Yorkshire &amp; Humber</td>
<td>1.5 (3)</td>
</tr>
<tr>
<td>Scotland</td>
<td>4.6 (9)</td>
</tr>
<tr>
<td>Wales</td>
<td>3.1 (6)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>3.1 (6)</td>
</tr>
<tr>
<td>missing</td>
<td>20.4 (40)</td>
</tr>
</tbody>
</table>

† Respondents were instructed to select all that applied from the list
9.4.3 Awareness of physical activity guidelines

Thirty-one percent (n=60) of respondents knew relevant physical activity guidance. Thirty-seven percent (n=72) reported being aware there was guidance but did not know what it was and 33% per cent (n=64) were not aware of any. Awareness of guidelines by professional group is presented in Figure 9.1. Differences were evident between professional groups with a higher proportion of medical respondents not aware of any guidelines and no medical respondents reported knowing relevant physical activity guidelines. A high proportion of AHPs reported knowing of relevant physical activity guidance and a small number reporting they were not aware of any guidelines, whereas responses among nursing professionals were more evenly spread.

Professional group had a statistically significant effect on awareness of guidelines. AHPs were more likely to be aware of physical activity guidelines (odds ratio (OR) 32.1 [(95% CI 10.4-98.5), p<.001]) as were nurses (OR 5.9 [(95% CI 2.2-15.6), p<.001]), compared to medics. Time in role and the health professionals own self-reported physical activity were not related to knowing the guidelines (see Table 9.3). The assumption of proportional odds was met, as assessed by a full likelihood ratio test comparing the fit of the proportional odds model to a models with varying location parameters, $\chi^2(4) = 6.350, p = .174$, as was the assumption of no multicollinearity. The Pearson and deviance goodness-of-fit tests indicated that the model was a good fit to the observed data, $\chi^2(18) = 13.903, p = .735$ and $\chi^2(18) = 14.486, p = .697$ respectively. The final model statistically predicted the dependent variable over and above the intercept-only model, $\chi^2(4) = 48.871, p <.001$.

| Table 9.3 Health professionals (HP) (nursing, allied health professional (AHP), medical) predictors of familiarity with physical activity (PA) guidelines |
|---|---|---|
| **Professional group** | Odds Ratio | 95% CI | p-value |
| Medical | 1 | | |
| Nursing | 5.9 | 2.2-15.6 | <.001 |
| AHP | 32.1 | 10.4-98.5 | <.001 |
| **Time in role** | | | |
| 0-5 years | 1 | | |
| ≥6 years | 1.6 | 0.8-3.3 | 0.16 |
| **HP self-reported PA** | | | |
| <150mins PA/week | 1 | | |
| ≥150mins PA/week | 0.8 | 0.4-1.6 | 0.53 |
Figure 9.1 Awareness of physical activity guidelines by professional group (AHP, allied health professional; ACP, advanced clinical practitioner)
Of the 60 respondents who reported knowing relevant guidance, 43 (72%) provided details of the guidance they knew in their open text response. Thirty-four (57%) named a source of guidance or guideline, the most frequently named source of guidance was from charities, with Macmillan Cancer Support most commonly mentioned (19 references), followed by international sources such as the American College of Sports Medicine (ACSM) (8 references). The Chief Medical Officer/Department of Health and Social Care guidelines were mentioned by four respondents. Nineteen respondents provided details related to appropriate principles or components of physical activity guidance (e.g. “150 minutes moderate intensity per week, 2 strengthening and 2 balance sessions per week”). When comparing the three largest professions (nursing, AHP, medical), who responded to the survey, nurses more commonly made reference to charity sources of guidance but only five named a relevant physical activity guideline and three mentioned principles of physical activity guidance, whereas sixteen AHPs named a relevant physical activity guideline, fifteen mentioned principles of physical activity guidance and the most common mentioned source of guidance were international sources (e.g. American College of Sports Medicine, World Health Organisation, ESPEN - The European Society for Clinical Nutrition and Metabolism, Clinical Oncology Society of Australia (COSA) statement). There were no open text responses from medical professionals as none reported knowing relevant guidelines in the previous survey question.

9.4.4 Beliefs about the role of physical activity during and after completion of treatment

Most respondents agreed that patients with haematological cancer should be encouraged to be physically active, that regular exercise can alleviate symptoms of fatigue, can improve QOL and that structured exercise should be part of the treatment pathway for patients during treatment for haematological cancer. When questioned about confidence in making recommendations to patients, overall more than half of all respondents disagreed with not feeling confident (58%) (Figure 9.2). Among the three largest professional groups only 34% of medical professionals disagreed or strongly disagreed with the statement, compared to 72% of AHPs and 67% of nursing professionals. Professional group differences were also evident regarding knowing
where or who to refer patients who require support to become more active, 77% of nurses and 70% of AHPs agreed or strongly agreed to this statement compared to just 22% of medical professionals.

Similar patterns of agreement were seen for statements regarding the role of physical activity for patients with haematological cancer on completion of treatment (Figure 9.3). Slightly increased proportions of medical professionals disagreed with not feeling confident making recommendations to patients that ask about physical activity after treatment (45%) and more medical professionals agreed to knowing where or who to refer patients to for support to be more after treatment (32%) but these numbers remain low compared to nurses and AHPs.
Considering patients *during* treatment for blood cancer:

- Patients should be encouraged to be physically active
- Regular exercise can alleviate symptoms of fatigue for patients
- Regular exercise can improve QOL for patients
- Structured exercise should be part of the treatment pathway for patients
- There is not enough evidence for HPs to promote exercise to patients
- I do not feel confident making recommendations to patients who ask about PA
- I know where or who to refer patients who require support to become more physically active

**Figure 9.2** Statements regarding role of physical activity (PA) during treatment for blood cancer, all responses (n=165)
Figure 9.3 Statements regarding role of physical activity (PA) after completion of treatment for blood cancer, all responses (n=161)
9.4.5 Provision of physical activity advice to people living with and beyond haematological cancer

9.4.5.1 Health professional provision of advice

49% (n=85) of respondents who answered questions related provision of advice reported routinely giving advice regarding physical activity to most of their patients. 26% (n=46) respondents reported that they only provide advice if their patients request information on physical activity. A small number of respondents reported only providing physical activity advice to patients they think would benefit from it (11%, n=19) and the most commonly cited reasons were if patients were fatigued, deconditioned or frail, have comorbidities that benefit from regular physical activity and/or have treatment related symptoms (Table 9.4).

Table 9.4 Responses to question ‘Do you give advice regarding physical activity (PA) to patients with blood cancer?’

<table>
<thead>
<tr>
<th>Response</th>
<th>n=175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, routinely give advice to most patients</td>
<td>48.6 (85)</td>
</tr>
<tr>
<td>Yes, only if patients request information regarding PA</td>
<td>26.3 (46)</td>
</tr>
<tr>
<td>Yes, only to patients that they think would benefit from PA</td>
<td>10.9 (19)</td>
</tr>
<tr>
<td>Because they are fatigued†</td>
<td>57.9 (11)</td>
</tr>
<tr>
<td>Because they are deconditioned or frail†</td>
<td>57.9 (11)</td>
</tr>
<tr>
<td>Because they have comorbidities that benefit from regular PA†</td>
<td>52.6 (10)</td>
</tr>
<tr>
<td>Because they have treatment related symptoms†</td>
<td>52.6 (10)</td>
</tr>
<tr>
<td>Because they appear ‘fit’ and able to undertake PA†</td>
<td>47.4 (9)</td>
</tr>
<tr>
<td>Because they are older†</td>
<td>26.3 (5)</td>
</tr>
<tr>
<td>Because they are younger†</td>
<td>26.3 (5)</td>
</tr>
<tr>
<td>No, do not recommend or give advice about PA to patients</td>
<td>14.3 (25)</td>
</tr>
</tbody>
</table>

† Respondents were instructed to select all that applied from the list

Differences between professional groups can be seen in Figure 9.4. The majority of AHPs and nurses (60%) reported providing advice routinely to most of their patients, whereas the majority (52%) of medical respondents reported only giving advice when patients requested information regarding physical activity. Pharmacy professionals most commonly reported not giving advice to their patients (54%).
Figure 9.4 Health professional provision of physical activity advice by professional group and overall response (AHP, allied health professional; ACP, advanced clinical practitioner)
When questioned on the proportion of patients that health professionals give physical activity advice to, overall 38% (n=56) reported they provide advice to less than 25% of their patients. 30% (n=44) respondents reported giving advice to greater than 75% of their patients. When separated by professional group, half of AHPs reported giving physical activity advice to more than 75% of their patients, nursing professionals had an even spread across all responses and the majority of medical professionals (52%) reported giving advice to less than 25% of their patients. Surveyed health professionals reported that during treatment is when they most commonly provide physical activity advice to their patients (112 responses), then on completion of treatment (83 responses) and during survivorship/follow-up or during maintenance treatment (both 69 responses) (Table 9.5).

Table 9.5 Responses to question ‘When do you commonly give physical activity advice to patients with blood cancer?’

<table>
<thead>
<tr>
<th>Event</th>
<th>n=147</th>
<th>Relative frequency by choice, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis, before commencing anti-cancer treatment</td>
<td>38.8% (57)</td>
<td>14.6</td>
</tr>
<tr>
<td>During treatment with anti-cancer treatment</td>
<td>76.2% (112)</td>
<td>28.7</td>
</tr>
<tr>
<td>On completion of anti-cancer treatment</td>
<td>56.5% (83)</td>
<td>21.3</td>
</tr>
<tr>
<td>During maintenance treatment</td>
<td>46.9% (69)</td>
<td>17.7</td>
</tr>
<tr>
<td>During survivorship/follow period after anti-cancer treatment</td>
<td>46.9% (69)</td>
<td>17.7</td>
</tr>
</tbody>
</table>

† Respondents were instructed to select all that applied from the list

9.4.5.2 Predictors of provision of physical activity advice by health professionals

A binomial logistical regression model was used to examine the role of professional group, time in role and guideline awareness on provision of physical activity advice to more than 50% of patients. Respondents who reported knowing relevant physical activity guidelines for people living with and beyond cancer had higher odds of providing physical activity advice to more than 50% of their patients (OR 3.4 (95% CI 1.1-10.6), p=0.038), but there were no other significant differences among professional group (AHPs: OR 1.8 (95% CI .67-4.74), p=.250), nurses: (OR 1.6 (95% CI .47-5.39), p=.462) or time in role (OR 1.3 (95% CI .63-2.71), p=.477).
Table 9.6 Information and advice given by health professionals to patients with haematological cancer: an analysis of open text response

<table>
<thead>
<tr>
<th>Theme</th>
<th>Captured responses</th>
</tr>
</thead>
</table>
| Promotion of usual activity          | “To continue usual activities around house to keep active, not be frightened to keep active and that it will not do them harm and keep active as far as they feel able to.”  
Advanced Clinical Practitioner       |
|                                      | “Keeping active e.g. regular walks/pottering round garden, increase activity gradually and to tolerance.” Dietitian                                  |
|                                      | “I either encourage them to continue with their regular activity levels or encourage them to be more active if they currently aren't doing anything.” Dietitian |
| Sharing and emphasising benefits of recommended physical activity | “I advise them about the general benefits of exercise (CV health, bone strength, circulation, mood, balance etc) and explain that there is evidence to suggest that exercise can help improve symptoms and side effects of treatment and it is a good way of taking control of something when you are feeling out of control.” Physiotherapist |
|                                      | “It is important for your physical well-being to remain active for at least 30mins each day - this can be part of your daily household tasks, putting groceries away etc, or can be going for a short walk but remaining active, even when you feel fatigued during treatment will lessen your physical de-conditioning, help your mental well-being and recovery post treatment.” Inpatient Nurse |
| Setting and treatment phase-based advice | “My advice would then be about trying to stay as active as possible during all the treatment stages i.e. pre, during and post.” Matron/Lead Nurse |


<table>
<thead>
<tr>
<th>Theme</th>
<th>Captured responses</th>
</tr>
</thead>
</table>
| **On the haematology ward, we give advice about physical activity to every patient we treat. It's not ideal that the inpatient stay is the only opportunity to do this but we make the most of the contact we have.” Physiotherapist**

“Come for your inpatient transplant in comfortable clothes. No need for PJ’S all day everyday. Get up and move every day. The BMT unit corridor is marked in meters and patients are encouraged from Day 0 to walk the corridor every day for as long as they can, exclusions apply e.g. neutropenic fever or infections).” Clinical Nurse Specialist

| Cautious, conservative approach to types and intensity of physical activity advised | “Advice not to swim with a vascular access device in-situ. Avoid the gym and lifting heavy weights. Avoid gardening because of the infection risk etc.” Clinical Nurse Specialist

“It's good to keep active but don’t overdo it.” Doctor

“To try and maintain a regime of physical activity, even if it only involves getting out of bed once a day and stretching.” Inpatient Nurse

| Provision of resources and signposting | “[I advice] where they can access walking groups and exercise referral schemes.” Occupational Therapist

“Prior to coming in for transplant, giving them leaflets and information on physical activity and promoting exercises both before coming into hospital, and during their 4 week inpatient stay.” Clinical Nurse Specialist

“[I] direct people to the Macmillan [support and information] desk regarding exercise/rehab programmes.” Doctor
9.4.5.3 Examples of physical activity information and advice

When asked to provide an example of information or advice they give to patients regarding physical activity, 116 participants provided a response to the open text question. Themes that were concluded from the analysis of open text responses indicated health professionals focussed the advice they give around promotion of usual activities, sharing and emphasising the benefits of physical activity, using a settings (inpatient, outpatient) and/or timing in treatment-based approach to advice. There was repetition of cautious or restrictive advice regarding intensity and type of physical activity advised and an emphasis on providing resources (e.g. leaflets, booklets) and/or signposting to others or other services (e.g. walking groups, exercise referral). Examples of captured quotes are detailed in Table 9.6.

9.5 Discussion

This survey-based study explored haematology health professionals’ awareness of physical activity recommendations, their beliefs about the role of physical activity and their reported provision of advice given to people living with and beyond haematological cancer during and after treatment. At submission for publication there were no published studies investigating professional attitudes and practices of health professionals dedicated to haematological cancer. This study demonstrated that awareness of physical activity recommendations was modest with a third of respondents reporting no awareness of any physical activity guidance, which is in keeping with other cancer health professional surveys. The haematology health professionals surveyed largely held positive beliefs about the benefits and promotion of physical activity for haematological cancer patients both during and after their treatment and their reported provision of advice to their patients regarding physical activity was promising, with approximately half of respondents reporting they give advice to about half of patients in their care. However, professional groups differences were evident.

Awareness of physical activity recommendations among respondents was varied with similar proportions confirming they knew of relevant physical activity guidance, or were aware guidance existed but not what it was, or reported being unaware of any existing guidance. These findings are in keeping with lifestyle advice surveys conducted among
health professionals working in oncology settings (Williams et al., 2015) and those working with teenage and young adult cancer patients in the UK (Pugh et al., 2017). Professional differences were seen, particularly among the most represented groups. Nursing and AHP professionals were more likely to report being familiar with guidelines. As might be expected AHPs, which include professions that provide advice on physical activity and/or energy balance as part of their clinical role (e.g. physiotherapists, occupational therapists and dietitians), reported the greatest awareness of guidance related to physical activity. Conversely, most medical respondents reported not knowing of any guidance. Familiarity with lifestyle guidance has been found to influence provision of lifestyle advice (Williams et al., 2015), as was also seen in this analysis of haematology health professionals, with those who reported knowledge of physical activity guidance at greater odds of providing advice to more than half of their patients.

Recommendations for physical activity specifically related to people living with and beyond cancer have been available since 2010 when the ACSM published their roundtable recommendations. These guidelines largely follow general population guidance such as those laid out by the Chief Medical Officers’ physical activity guidelines in the UK (United Kingdom's Chief Medical Officers, 2019), encouraging adults to aim for at least 150 minutes of moderate intensity aerobic exercise per week and two of more days of resistance training (Schmitz et al., 2010). A recent update of ASCM recommendations based on the exponential growth of evidence in exercise-oncology continues to support promoting patients to engage in physical activity to a level in general public health guidance (Campbell et al., 2019). Although this review recommends regular moderate intensity aerobic training and/or resistance training (Campbell et al., 2019), it is generally agreed that any level of physical activity is better than none and that positive health benefit exists with any amount of physical activity (United Kingdom’s Chief Medical Officers, 2019).

Across professions, approximately half of health professionals surveyed reported that they give physical activity advice routinely to their patients with haematological cancer, which is similar to levels of recommendation by health professionals working with breast and prostate cancer patients (Cantwell et al., 2018). When asked to estimate proportionally how many of their patients they give physical activity advice to, most survey respondents reported giving physical activity advice to less than 25% of patients.
with professional differences again. Over half of doctors reported only giving advice regarding physical activity when patients initiated with a request for information, and therefore give advice to less of their patients. Nurses and AHPs appear to give advice regarding physical activity more often and to more patients than doctors, perhaps reflecting their being more familiar with guidelines. Williams et al. (2015) found 51% of oncology health professionals gave physical activity advice to >50% of their patients, in keeping with our findings across professions (Williams et al., 2015).

Another survey based study, published at a similar time to this survey study, investigated the attitudes and practices of clinical haematologists specifically related to promoting physical activity to myeloma patients (Nicol et al., 2022). In contrast to these findings among doctors, this study of thirty-four Australian haematologists reported large proportions of haematologists recommended physical activity (85%) and provided general physical activity advice (74%) to their patients at least occasionally (Nicol et al., 2022). However, patients perspectives differed as only 20-54% of patients surveyed by the same research group recalled receiving a recommendation from their haematologist (Nicol, 2018), indicating some mismatch between what advice health professionals perceive they provide and what patients recall receiving.

AHPs providing recommendations on physical activity to larger proportions of patients was expected. Another small survey study of cancer physiotherapists, reported figures as high as 82% of participants who recommend or use exercise specifically for people with haematological cancer (O’Hanlon & Kennedy, 2014). Clinicians at all parts of the patient pathway should enquire about their clients’ levels of physical activity, promoting physical activity for general health benefits and signposting or referring to appropriate support to become more physically active as required. Exercise professionals, such as physiotherapists, can provide effective exercise prescription tailored to individual factors including baseline functional capacity, cancer specific deficits or challenges and the patients’ own goals and preferences for exercise. Having an awareness of local physical activity guidelines, such as the UK Chief Medical Officers’ physical activity guidelines, can assist health professionals in promoting participation in physical activity for health benefits (United Kingdom’s Chief Medical Officers, 2019).
Results from this study demonstrate general positive beliefs that physical activity and exercise should be encouraged as part of treatment and follow-up for people living with and beyond haematological cancer and that nearly all respondents provide physical activity advice to at least some of their patients. Analyses of open text responses regarding what guidance health professionals were aware of and what advice they give to patients did not always align. Few respondents provided a source or details of the guidance they knew, but most responses received were appropriate, including charity sources of advice or details of principles laid out in evidenced recommendations. Themes emerging from the analysis of advice given did indicate a mostly positive approach to promoting usual activities, the benefits of physical activity and signposting to resources. However, there was also a theme of cautionary or conservative advice given often advising limiting of exercise intensity or type to people living with and beyond haematological cancer. This may be a reflection of the varied professions who responded to the survey and may indicate a need for stronger referral links or embedding of professionals trained in exercise prescription working within haematological cancer MDTs. An additional component of research related to this survey was planned to explore these themes further through a qualitative study of health professionals working in haematology, however this was not possible due to the potential burden of interviewing health professionals after the emergence of the COVID-19 pandemic.

9.5.1 Limitations

This survey is the first of its kind to focus on haematological cancer health professionals in the UK but has some limitations. Firstly, it is not possible to ascertain a response rate due to the online distribution of the survey, also it received a modest number of respondents and therefore analyses of professional groups was limited. Secondly, research of this kind may naturally attract health professionals with a positive view of the role of physical activity themselves or who are more aware of growing social desirability to promote physical activity particularly among people living with long term conditions, such as people living with and beyond cancer (Haussmann et al., 2018) and who were already keen to promote physical activity among those with haematological cancer. The high levels of self-reported weekly physical activity among our respondents
may give some indication to sample selection bias of this nature. These factors may limit the generalisability of this survey to the wider UK haematological cancer workforce.
Chapter 10  General Discussion & Conclusions

The aim of this thesis was to explore the feasibility of embedding exercise within haemato-oncology clinical pathways, using a more homogeneous approach, focussing on the autologous stem cell transplant pathway (ASCT) in multiple myeloma. The studies presented in this thesis addressed three key areas of exploration: the views and practices of health professionals regarding physical activity in the context of haematological cancer; the practical feasibility of delivering an exercise intervention, and exploring its potential effects, as part of an established clinical treatment pathway using a pilot randomised trial; and importantly, the experiences of people with myeloma being asked to consider engaging in exercise related research whilst undergoing ASCT.

In this chapter I will bring together the findings from this multi-methods research and discuss the implications they may have in forwarding the field of rehabilitation in haemato-oncology, particularly for people undergoing treatment for myeloma.

10.1 Summary of study findings and their contribution/implications

10.1.1 Assessing feasibility of an exercise prehabilitation and rehabilitation intervention for myeloma patients undergoing ASCT

The results from the PERCEPT trial indicate that it is feasible and acceptable for people with myeloma to engage in exercise before, during and after ASCT. Loss to follow-up was low and attrition was mostly due to participants relapsing, becoming ineligible for ASCT and being withdrawn. The overall uptake to the study was lower than the a priori target of 50%, which was estimated from previous published studies in transplant and myeloma where uptake was good (>60%). Given that a subsequently published study specifically investigating prehabilitation in myeloma ASCT reported an uptake of 41%, it could be considered that the recruitment target for PERCEPT was too high. The main reason for declining the original trial protocol was due to the level of travel required and a possible assumption by most that they would be randomised to the exercise group, necessitating weekly travel, made the trial undesirable for many. When separated by protocol, uptake was better for the virtual trial (52%) and did reach the a priori threshold for feasibility, possibly due to the elimination of travel and perceived time burden of visiting the centre and increased acceptability of using remote ways to access appointments and communicate with clinical services. However recruitment in this part
of the trial did not take place within a typical ASCT pathway. Recruitment to the amended protocol only took place over two months before the pandemic again paused ASCT activity, and potential participants were recruited off a list of those waiting for ASCT, some on holding chemotherapy, rather than sequentially on referral for ASCT, as would be the case with the usual pathway. These considerations may limit the generalisability of this uptake data. Prior to the pandemic, approximately ten patients per month were identified and four per month were recruited on average. The number of patients typically coming through the pathway each month does support the use of the myeloma ASCT pathway as a study population for future larger trial using a multi-centre design.

The results related to secondary outcomes indicate promise of prehabilitation and rehabilitation over the course of ASCT treatment. Unfortunately, it was the objective measures of functional capacity that were most affected by adaptation of the trial to remote delivery due to the pandemic and therefore evaluation of potential physical effects of the intervention was limited. But results from the data, albeit limited by small sample size and extrapolated scores, do indicate potential benefits on walking distance and lower limb strength. These gains may be particularly crucial for people with myeloma undergoing ASCT, given that baseline data indicated high levels of functional impairment among the trial sample. These could be important findings for justifying greater integration of rehabilitation and exercise into in haematological cancer pathways. Gait speed has been found to independently predict survival and unplanned emergency admissions in older people with haematological cancers, with the association maintained even in those with good performance status (Liu et al., 2019). Linear associations between gait speed and mortality have been evidenced in oncology patients and older adults/multiple populations (Veronese et al., 2018). Objective measures of functional capacity, such as the six minute walk and timed sit to stand tests, are rarely undertaken as part of clinical assessments in haematological cancer but may provide valuable data for identifying potential frailty that may be masked by good performance status or reasonable functional appearance in the transplant clinic setting (Jensen et al., 2022). Crucially, walking speed, lower limb strength and physical activity engagement are modifiable with physiotherapy and exercise intervention.
Pre-transplant rehabilitation has been associated with a significant reduction in post-transplant hospital length of stay (LOS) in haematological cancer patients undergoing allogeneic transplant. A retrospective observational study including records from 3,614 patients showed significant difference in LOS between those who received pre-transplant rehabilitation (mean LOS: 74.2 days, 95% CI: 72.7, 75.7) and those who did not (mean LOS: 90.2 days, 95% CI: 86.7, 93.6; p<.001) (Matsugaki et al., 2021). Findings from the PERCEPT trial related to transplant hospital admission for those who proceeded to undergo ASCT indicate no difference between groups in terms of overall LOS or ambulatory care LOS. However, differences were seen between groups in terms of proportion of participants remaining in ambulatory care for their whole admission (e.g. not admitted to full inpatient care on a ward), as well as reduced readmissions to hospital in the three months post-ASCT in favour of the intervention arm. These findings indicate promise and warrant investigation as it is likely that the small sample size of the pilot trial may limit the true interpretation of these possibly important effects. Facilitating better utilisation of ambulatory care facilities and reducing hospital readmissions could positively influence patient experience and satisfaction as well as provide potential benefit in terms of cost-effectiveness (Sive et al., 2012; Comerford & Shah, 2018) within the ASCT pathway and would support integration of rehabilitation as a component part of care.

In summary, despite the set-backs associated with the COVID-19 pandemic on completing the pilot trial according to its original design, the necessary adaptations allowed continuation of this work and provided opportunities to explore feasibility of both a face-to-face and virtually delivered intervention and study processes. There may be promising effects on a range of physical, psychometric, as well as resource related, outcomes. A future larger trial is warranted and should likely explore a virtually delivered intervention but with face-to-face study assessments to allow capture of objective measures as well as use of digital data capture for patient reported outcome measures (PROMS) and intervention adherence.
10.1.2 Exploring the experiences of people with myeloma undergoing ASCT, who were engaged with the research process

Collectively, the two qualitative studies included thirty-four people with myeloma and although analysed and reported separately in Chapter 4 and Chapter 8, commonality features across both sets of findings. No formal synthesis of the studies was undertaken, however both studies are similar in providing useful insight into the impact of a diagnosis of myeloma on physical activity engagement and subsequent effects on function and QOL. Participants in both studies found their participation in physical activity and activities of daily living were badly affected by diagnosis and early treatment, mostly due to increased levels of fatigue and a resulting inactivity cycle, but also for others related to immobilisation and pain associated with myeloma related bone disease. The impact of symptom burden as a barrier to physical activity and resultant effect on QOL among people with myeloma has been reported previously (Craike et al., 2013b; Osborne et al., 2014; Walpole et al., 2018; Land et al., 2022). Also contributing to previously reported qualitative findings in myeloma, both qualitative studies identified that participants were positive about the potential role of being more physically active or undertaking an exercise programme during treatment for restoring physical capacity lost in early treatment and preparing them for the intensive treatment they were about to undergo. Other literature has also reported that people with myeloma are open to receiving information and support to engage in exercise (Coon & Coleman, 2004; Craike et al., 2017). However, the fragility of many patients due to their bone disease and the reported absence of rehabilitation input in their treatment journey led to them experiencing a scarcity of advice related to physical activity following diagnosis and for some who did receive advice, it was perceived as either vague, restrictive, or over-cautious. Some were told not to engage in physical activity, often following diagnosis in the context of severe bone disease, but never received any rehabilitation or follow-up advice as their disease stabilised. There is little or no published literature on the lived experience of myeloma related bone disease and its consequences on engagement in physical activity or activities of daily living. Lack of support or practical advice paralleled with restrictive advice promoting little or no activity in these patients may have implications for safety in those who may need to avoid certain activities. It is possible that education or individualised input to educate patients to engage in exercise while
minimising risk of injury in the presence of bone disease would be welcomed. Individualisation and tailoring is an important component of safe and effective exercise training in people with cancer (Maddocks, 2020), and in the context of myeloma bone disease this is even more crucial.

The qualitative research in this thesis provided insight into a potentially important time in the treatment journey of transplant-eligible myeloma patients. Myeloma is known to have one of the greatest symptom burdens and impact upon QOL of all cancers (Allart-Vorelli et al., 2015; Shapiro et al., 2021), so themes from the decliners qualitative study around the participants’ expectation of symptoms in early treatment and their perception of an inevitability of experiencing symptoms were concerning but perhaps unsurprising. More troubling findings common to both qualitative studies were how this expectation or knowledge of symptoms led to little reporting of concerns or perceptions of their concerns being minimised by their clinical teams, despite clear impact on participants daily lives. Participants described clearly their self-identified loss of functional ability or an inability to engage in usual activities, as well as reporting a desire to restore or prepare physically before the next intensive phase of treatment. However, they also recall that their seeking of advice was met with inconsistent information and no practical support.

These findings indicate missed opportunities to influence self-management among people with myeloma at a time when motivation is likely high but capability is low and unaddressed. It is known that myeloma patients need more holistic care and that more comprehensive, regular assessments may promote self-management of negative consequences on their physical and psychological health (Cormican & Dowling, 2017). Drawing on the findings of the health professionals survey (Chapter 9) and as previously discussed in Section 10.1.3, these studies add to the literature that supports the role of physiotherapy within myeloma treatment pathways (Craike et al., 2017; Snowden et al., 2017; Walpole et al., 2018; Nicol et al., 2020).

The PERCEPT study was conducted to quantify the feasibility and acceptability the intervention and trial protocol procedures. Pilot studies are also recommended to assess vital trial parameters related to recruitment and loss to follow-up for determining sufficient power in any subsequent trial to determine benefit of an intervention.
However, evaluations of complex interventions, such as the PERCEPT trial exercise programme, are multi-faceted in nature and rely on numerous contextual factors. Any RCT involving a complex intervention pose methodological challenges requiring careful consideration and likely adaptation to the standard RCT design (Oakley et al., 2006). I determined early on in my doctoral research planning that collection of qualitative data would be an important part of a process evaluation of the pilot trial. I was interested in better exploring not only the experiences of people participating in the trial and their views on its processes, but I was also wanted to gain greater understanding of why people may decline the trial, beyond a short list of reasons collected during screening and recruitment.

Influences on participation in RCTs have been explored in numerous qualitative studies. Houghton et al. (2020) conducted a qualitative evidence synthesis of factors that impact recruitment to RCTs in health care. This Cochrane collaborative review of 29 studies, included seven exploring the perspectives of trial decliners and a further twelve involving both participants and decliners. This review identified three key areas of influence on decision making of potential participants of health trials: i) communication relating to trial information and its component parts; ii) personal influences including their perception of participation, influence of others and weighing up the risks of taking part; iii) impact of potential benefits of participation, both personally and altruistically to contribute to making a difference for others (Houghton et al., 2020). Three studies within this review related to physical activity or rehabilitation interventional trials. Among those approached for a trial of pulmonary rehabilitation, difficulties with travel/location, low perceived benefit, competing demands and poor or negative understanding of the research were reported as reasons for declining participation (Taylor et al., 2007). Explorations of non-participation in surgical RCTs have found that participant preference for a particular treatment arm meant they were not willing to accept randomisation, particularly when clinically, outside of the research they could choose a preferred procedure (Gopinath et al., 2013; Harrop et al., 2016b). The aforementioned literature has recommended recruitment strategies based on their findings. Although many of the these studies propose recruitment strategies that are potentially transferable to exercise oncology trials, gathering deeper understanding of why people with cancer may decide not to take part in exercise related research was felt
to be important to further facilitate improved study and/or intervention design to attract participants who may be considered harder to recruit.

My own prior experience recruiting and delivering the intervention for the MASCOT trial (an exercise intervention in myeloma survivors not receiving active treatment) principally informed my decision to interview study decliners for the PERCEPT study. MASCOT used a double-consent, adapted Zelen design, meaning those randomised to the exercise intervention had originally consented to participate in an observational cohort study but were then asked to take part in the intervention arm (Land et al., 2020). Uptake to the intervention was lower than expected with 57% of those allocated agreeing to take part, but most continued to take part in the follow-up assessments for the cohort study. Reasons for declining the intervention included travel and time constraints (Koutoukidis et al., 2020). These participants were not interviewed and anecdotally whilst delivering the intervention I noticed that some of the participants that did take part were undertaking long journeys to the centre, that took up much of their day and that it was not a barrier to participation for them. Therefore, I felt deeper exploration of non-participation, as well as participation, in the PERCEPT study was important, particularly given that the trial would be delivered to myeloma patients who would be much closer to diagnosis and during a period of intensive treatment.

Both qualitative studies in this thesis, but particularly the study of trial completers, provided insights into the timing of approach for the PERCEPT trial being at a key stage of contemplation in the participants’ treatment journey. Most participants demonstrated an understanding or belief that the exercise intervention on offer in the trial would be beneficial and would help them prepare for upcoming intensive treatment. As discussed in detail in Chapter 8, it is likely that allocation to the ‘non-exercise’ control group would cause disappointment and could be enough to induce behaviour change related to physical activity and question the equipoise of randomisation (McCambridge et al., 2014b; McCambridge et al., 2014a). This study also provided signal of contamination of the control group and there may be an indication of other factors that could have impacted on the internal validity of the pilot trial but a more conclusive process evaluation would be required. More implications related to the research in this thesis and future research are discussed in Section 10.3.
Exploring the views of haematology health professionals regarding physical activity for patients with haematological cancer

The survey of health professionals working with people with haematological cancer (Chapter 9) found that most respondents were supportive of the role of physical activity during and after cancer treatment. There was good understanding that exercise can alleviate cancer-related fatigue and improve quality of life (QOL) among people with haematological cancer. Indeed the majority of respondents agreed that structured exercise should be part of the treatment pathway for patients. However, there was a discrepancy between beliefs about the positive role of physical activity and the practices and knowledge of survey respondents regarding advice given and clear differences between professional groups. Overall, only 30% reported giving advice regarding physical activity to more than 75% of their patients, with more allied health professionals (AHPs) providing advice compared to nurses, and most medical professionals reporting provision of advice to less than a quarter of their patients (McCourt et al., 2021).

Professional group was not a significant predictor of provision of physical activity advice to more than half of patients, but reported knowledge of relevant guidelines related to physical activity was. The survey found similar levels of awareness of physical activity guidelines among haematological professionals as reported for professionals in oncology (Williams et al., 2015) and teenage and young adult cancer (Pugh et al., 2017). Approximately a third of survey respondents reported knowing of relevant guidelines for physical activity among cancer survivors. The survey highlighted the possible differences in awareness of physical activity guidelines among the three largest professional groups (medical professionals, nurses and AHPs) and although the model for prediction of provision of advice did not find professional group to have a significant effect, it did find reported knowledge of guidelines to be a significant predictor (McCourt et al., 2021).

In the delivery of cancer care, health professionals are recognised as crucial to endorsement and promotion of physical activity and lifestyle advice (Berra et al., 2015), particularly medical and nursing clinicians (Jones et al., 2004a; Murphy & Girot, 2013). Malalur et al. (2021) found that patients with haematological cancer consider access to
educational material and physician counselling as important elements for positive behaviour change but this study did not specifically investigate if counselling and advice had been received by participants. Similar findings regarding the important role of health professionals in providing or signposting patients to information regarding healthy lifestyle behaviours following a cancer diagnosis have been found among women with endometrial cancer (Koutoukidis et al., 2017), breast, prostate and colorectal cancer survivors (Roberts et al., 2019) and teenager and young adults with cancer (Pugh et al., 2018). People living with and beyond cancer are open to receiving physical activity advice from health professionals but report lack of advice given in their care setting (Smith et al., 2017). Delivery of recommendations from the core care delivery team can be effective (Jones et al., 2004a) and is associated with greater physical activity participation in people living with and beyond cancer (Fisher et al., 2015). Prior to this thesis there had been no published research specifically exploring the views or practices of health professionals working with haematological cancer patients regarding their delivery of physical activity advice and their views on the role of exercise during and after treatment.

Given that most patients routinely encounter medical and nursing health professionals, they may have the most potential influence in encouraging physical activity participation among all people living with and beyond haematological cancer. However, despite high levels of positive support for the role of physical activity, haematologists have also reported low confidence in prescribing specific exercises or recommending physical activity for myeloma patients who are less well or have spinal fractures. In addition, less than half refer their patients to exercise specialists for specific support (Nicol et al., 2022). Given the variable evidence of knowledge of appropriate physical activity guidance among health professionals (Maddocks, 2020), there is an identified need for greater education that considers professional tailoring and additional barriers to providing physical activity advice and appropriate onward referral of patients requiring specialist support (Murphy & Girot, 2013; Williams et al., 2015; Haussmann et al., 2018).

This study demonstrated that AHPs were most likely to report knowing physical activity guidelines and reported giving advice to greater proportions of their patients. These findings were not unexpected given the high proportion of physiotherapists in this professional group, as well as other AHPs professions for which energy balance plays a
key role their therapeutic interventions (e.g. dietitians and occupational therapists). There is a recognised requirement to have access to nutritional and rehabilitation services delivered by AHPs in haematological cancer services in the UK (National Institute for Health and Clinical Excellence, 2016; Snowden et al., 2017) however, the incorporation of specialist AHPs embedded within multidisciplinary teams is limited, even in tertiary cancer centres (Miller, 2008; Robb & Davis, 2015). Therefore the number of people living with and beyond haematological cancer who access AHPs, particularly physiotherapists, as part of their care pathway and receive physical activity input from them is likely to be limited. As well as targeting education and knowledge of haematology medical and nursing professionals, as they are currently most likely to engage with most people with haematological cancer under their care and have a key role in positively influencing healthy behaviours, there is perhaps a growing need to diversify haematology multidisciplinary teams to include AHPs. As evidenced by this survey study, AHPs working with people with haematological cancer are more likely to deliver advice and support to engage in physical activity and therefore their specific role, particularly that of physiotherapists, within haematology multidisciplinary teams warrants further exploration.

10.2 Limitations

Limitations related to each study in this thesis have been discussed within the relevant chapters. In this section, the limitations common to one or more studies or that should be considered as part of the overall interpretation of thesis findings are described.

10.2.1 Impact of COVID-19 pandemic

It is likely that few research studies conducted during the COVID-19 pandemic were unaffected by the huge societal disruption it caused. Our working lives, clinically and academically required review and revision in order to continue and the work in this thesis was no exception. A number of adaptations and sacrifices to the original research plans were necessary and resulted in both opportunity and loss from the overall work.

Firstly, the health professionals survey study (Chapter 9) was originally designed as a two-part study. The first part, the survey was anonymous but allowed participants to provide contact details and consent to being contacted to take part in part two of the
study, a qualitative interview study. The aim of this second stage of the study would have been to explore health professionals’ opinions in-depth on timing of exercise information and their thoughts on the role of exercise as part of treatment pathways in haemato-oncology and when, and who by, it would be best delivered. Over 80 survey respondents provided their contact details, expressing an interest in participating in the interview study. Email communication to approach health professionals for the second part of the study commenced at the end of February 2020, just as the pandemic was taking hold. With the pressures ensuing within our health system from that point on, and I myself redeployed back into full-time clinical work, the decision was made, with my supervisors, to cease recruitment to the interview study.

As has been discussed in more depth in the chapters related to the PERCEPT trial, major adaptations were required to continue the study through the pandemic. This was welcomed by participants already enrolled in the trial and the new, virtual format was acceptable to those approached after the substantial amendment was approved in August 2020. Although the continuation of trial feasibility data and self-reported measures using questionnaires was largely unaffected, the collection of objectives measures of function were. Changes to the protocol lead to uncomplete follow-up data for a number of participants.

Another important consideration related to the use of PROMs in the trial was their use within the context of the pandemic. The COVID-19 pandemic compounded the existing social, psychological and economic impact of living with cancer principally due to the adaptations required at an individual, health-system and wider economic levels (Kirby et al., 2022). The EQ-5D-5L dimensions reported in Chapter 7 Section 7.3.1 Table 7.3 indicate interesting patterns of change for the domain related to usual activities. This dimension showed the most variability across levels at all timepoints in both groups. It may be the case that this item was answered by participants with respect to living through the COVID-19 pandemic whereby shielding due to infection risk had a significant effect on all participants’ abilities to partake in usual activities, particularly where social activities outside their homes were not possible. Indeed a number of PROMs measures were returned completed by participants with annotations or notes next to items related to usual or social activities in which some highlighted that their score was due to the pandemic or shielding. Survey research conducted among myeloma patients
during the pandemic found almost all were at least partially shielding through both waves of the pandemic, resulting in variable impact on lifestyle and social activities of respondents and that one in five were at risk of social isolation (Ramasamy et al., 2022). In addition, qualitative research carried out at our centre highlighted how myeloma ASCT recipients who had their transplants delayed or deferred, reported being hugely affected by shielding and that reduced social activities had a negative impact on their mental well-being (Camilleri et al., 2022). Therefore, there may have been undetectable contextual influence on capture of QOL measures used within the trial, as all included items related to usual or social activities, engaging with others or undertaking activities outside of the home. It may be possible that the influence of the pandemic on social activities as well as disruption to routine ASCT timeline for many participants could have dampened potential effects of the intervention on some domains of PROMs.

Further, the impact of living and undergoing ASCT during the pandemic was not specifically explored in the two qualitative interview studies. The first study of trial decliners (Chapter 4) had completed recruitment prior to the pandemic as the trial had been recruiting well and the number of declining participants willing to be interviewed allowed obtainment of sufficient interview data by January 2020. However, in retrospect it would have been advantageous to interview a number of participants approached for and declining the virtual trial protocol to ascertain what the different or similar challenges to participation may have been. The second qualitative study of completers did include participants who experienced the virtual protocol and those who’s participation spanned from before the pandemic was declared to completion during the virtual protocol. Participants did make reference to their experiences in relation to living through the pandemic but the interview schedule was not adequately adapted to capture enough content to ascertain findings specific to the two different trial protocols. Lack of adaptation of the qualitative studies was a missed opportunity, particularly in relation to informing a future remotely delivered trial protocol. I did however contribute to the forementioned study conducted separately to this thesis exploring the lived experiences of myeloma patients who had their ASCT delayed or deferred indefinitely (Camilleri et al., 2022).
10.2.2 Volunteer bias and social desirability

Research studies seek to use information obtained from sample populations to extrapolate or deduce information about a whole population, in the expectation that the sample population is representative of the whole. Volunteer, or self-selection, bias arises when the sample population differs from the general population. It can include but is not restricted to differences in socio-demographic or disease characteristics, motivations to participate or not in a study as well as any perceived advantages or disadvantages in participation (Catalogue of Bias Collaboration, 2017). Each of the studies in this thesis may be limited by volunteer bias of varying degrees. The health professionals survey was likely to attract participants who were already engaged and aware of the benefits of exercise for their patients. As seen in the sample characteristics, levels of physical activity participation among the sample was higher than general population levels and more active participants may be more likely to endorse physical activity participation among patients. The trial and related qualitative studies may well have attracted participants who were supportive of rehabilitation or exercise interventions, who were seeking and therefore more motivated to take part, in a study related to exercise or rehabilitation support. Importantly, the requirement to travel or exercise for those who were more frail or lacked confidence to engage in the trial may have resulted in a sample that was not representative of transplant eligible myeloma patients generally.

Social desirability refers to a phenomenon in which research participants tend to report or provide responses that they perceive to more socially acceptable or more favourable to the researcher (Callegaro, 2008). Social desirability may have been at play in the health professionals survey in reporting of proportions of physical activity advice given. Social desirability bias can also commonly occur within qualitative research and therefore may be have factored into participants responses in the two interview studies detailed in this thesis. This work was informed by my professional and personal beliefs and perspectives as the researcher and this will have shaped the whole qualitative research process. Development of the questions and double coding and discussion with supervisors as part of the analysis process were methods used to ensure data captured was as ‘true’ as possible, but social desirability related to attributes of either the participants or the researcher cannot be fully eliminated. It is possible, with all
participants in each of the studies, that their participation and/or their responses were shaped by their own perceptions of themselves, of the importance of the research topic, or by their interactions with me or the study physiotherapists.

10.2.3 Study design – adaptation to virtual delivery

Discussions in Chapter 4 and Chapter 8 identified some of the challenges that ensue when using quantitative research to evaluate complex interventions. Barriers to recruitment and participation, accessibility of the intervention on offer, awareness and reaction to allocation, are all elements of the research process that may induce research participation effects conducive of eliciting the behaviour under investigation.

The adaptation of protocol and the different stages that participants were at between follow-up timepoints when the protocol was amended resulted in small numbers of participants who were recruited and proceeded through the trial only experiencing the face-to-face or virtual version. Differentiating between recruitment strategies was possible for some measures of feasibility and was thought to be useful for informing future trial design but many participants were exposed to both ‘modes’ of delivery and an intention to treat approach was necessary for subsequent analysis of secondary outcomes. Therefore it was not possible to tell if one mode or the other showed more or less promise.

Another element of importance when changing to remote delivery and relying on self-completion of outcomes measures, was the completion and return rates of questionnaires. A number of those lost to follow-up was due to not returning their questionnaires despite contact to prompts to participate. Some participants reported losing questionnaires, particularly the T2 hospital discharge pack. This could have been limited if digital strategies had been used to capture questionnaire-based outcomes. The trial was original designed for assessments to coincide with clinical attendance and therefore relied heavily on use of paper-based tools. Rapid adaption to virtual delivery did not allow adequate time to modify existing questionnaires into electronic versions and so postal return was used.

Another area where reliance on manual data capture was detrimental was the dependence on participants to record their adherence to the programme on paper-
based resources which resulted in poor completeness of data. Less than a third of intervention participants returned the intervention booklets, and only three returned a booklet for each phase of the intervention. This limited analysis of adherence to home-based sessions in particular. Although attendance of supervised sessions provided useful information for planning of future studies or clinical services, it is not adequate to determine the fidelity of the trial intervention, its delivery as intended and most importantly, its tolerability for participants across the continuum of ASCT. Exercise intensity and duration, alongside individual tailoring, are likely to be the most important components of prescribed exercise training in cancer patients and therefore better reporting of the intervention related to frequency, intensity, time and type is essential (Slade et al., 2016; Christensen et al., 2018; Mazzoni et al., 2020). Provision of heart rate monitors and activity trackers can provide data regarding intervention fidelity for remote exercise interventions (Ibegazene et al., 2021), but for remote delivery to be assessed as successful then more automatic capture of digital data will be required in future trial design.

### 10.3 Implications for future research and clinical practice

Research within this thesis indicates that health professionals working within haematology think physical activity is important for their patients, that they hold largely positive beliefs and support for exercise as part of clinical pathways. Qualitative research among people living with myeloma undergoing ASCT indicate that they are open to receiving and often seeking of greater advice and practical support to become more active or regain lost function. These studies also highlight that patients with myeloma are not receiving adequate physical activity advice in early treatment and at times are even discouraged from engaging in physical activity. There were also unexpected findings from this work that indicate that people with myeloma may be underreporting symptoms and side-effects of their treatment, despite leading to difficulties or an inability to fulfil activities of daily living or social engagement. This research supports the role of greater integration of physiotherapy within myeloma clinical services in particular. Internally, data from this thesis has been included in a business case for specialist physiotherapy provision for the myeloma clinical service locally.
The interest in these studies from people with myeloma in particular is supportive of greater provision of specialist rehabilitation and exercise advice, tailored to the specific needs of living with this disease. The work in thesis strongly supports the development of further interventional studies. The limitations imposed by the COVID-19 pandemic provided opportunity to gather feasibility findings of two modes of delivery of exercise during ASCT, face-to-face and remotely supervised. However, the trial was not originally designed to be delivered remotely and although it was acceptable to participants further development work is required to refine the resources required to enhance virtual delivery, and in particular to allow testing of the effects of the intervention. Work has commenced to explore the utilisation of a digital platform to support virtual delivery of the intervention as well as provide automatic capture of data that will inform its fidelity, including physical activity and heart rate tracking, and digital logging of independent exercise.

It is likely that a future trial would benefit from a more hybrid approach than was possible in this pilot. Patients and health professionals are supportive of remotely delivered exercise support during haematological cancer treatment. Future intervention design should focus on designing and testing remotely supervised exercise with testing of its effects through evaluation using objective measures of functional capacity, and for this face-to-face study assessments would be more advantageous. It was acceptable for patients undergoing ASCT to participate in research assessments at times when they were attending the centre for other appointments related to their treatment and so in a future model of face-to-face research assessments but virtual delivery of an intervention would allow for more rigorous testing of efficacy. This approach would allow for optimisation of data collection and minimise non-participation.

The design of a future randomised controlled trial (RCT) is likely to differ from the pilot study in this thesis and will be informed by findings for the qualitative studies, as well as future patient and public involvement. RCTs provide the strongest methodology for intervention testing, however the traditional RCT design may not always be the most appropriate method for evaluating rehabilitation interventions. It has been argued that some areas of rehabilitation, such as for neurological conditions, where established standards of rehabilitation care exist that improvement in interventions may best be gained through interrogation of existing practice and components of interventions at
play through mixed-methods (Kersten et al., 2010). In the field of cancer rehabilitation and exercise-oncology, where there is no established standard of provision within usual care (Robb & Davis, 2015) then comparison to a no-rehabilitation or no-exercise control group may in itself be flawed. Indeed, as there is growing appreciation by people with cancer of the benefits of exercise during treatment and recognised gaps in standard of care, then a trial that offers an intervention that appears advantageous and compares to no intervention could even be considered unethical (Aycock et al., 2018). Therefore, given the established evidence for the benefit of physical activity participation for cancer patients it could be considered that some form of physical activity advice as a comparable attention control group is warranted. Designing a trial with a more ‘active’ control group in which those allocated still perceive some benefit of participation may also facilitate recruitment and minimise dropout. Contamination and dropout is lower in exercise oncology trials that offer control participants the intervention activity after the study period, or an alternative to the study exercise intervention (lower dose or different type of exercise) if provided during or after the trial period (Steins Bisschop et al., 2015).

In addition to the considerations for designing future research studies discussed previously, the use of an attention control as part of a ‘non-exercise’ control condition could be an option for reducing potential confounding related to additional contact received during intervention delivery. Attention control groups can enhance internal validity in RCTs, especially in evaluation of behavioural interventions (Aycock et al., 2018). The therapeutic factors that could be influencing outcomes, such as regular remote appointments or physiotherapist telephone calls, could be replicated in a control condition and as such could be experienced by both groups. The effectiveness of the intended intervention would be tested through the addition of the ‘active ingredient’ (the exercise prescription or programme) being tested (Safer & Hugo, 2006). However, careful design of comparison conditions is needed. Considerations for implementation of an attention control design include ensuring factors common to both conditions are mapped and reliably measured (Safer & Hugo, 2006) and that control conditions are interesting, acceptable and evaluated to ensure common factors are not associated with the intended study outcomes (Aycock et al., 2018). As discussed, a placebo or ‘non-exercise’ control group may be assumed to offer the best comparison for assessing
efficacy through a RCT design but an attention control group that allows mimicking of common therapeutic factors that may be at play in addition to the central component of the intervention – the exercise prescription – may offer a more useful comparator in complex interventions such as this. This is particularly relevant to consider in pathway-based interventions such as prehabilitation before surgery or transplant, where a crossover or wait list design offering the intervention condition to both groups prior to the procedure is not feasible.

Despite the research in this thesis not focussing on living with myeloma related bone disease, it is a prominent feature of the disease and participants with significant bone disease were not excluded, therefore it is not surprising that the impact of living with bone disease has featured in both qualitative studies. These patients are likely to have specific needs in terms of education, support and rehabilitation input and therefore, greater exploration of the consequences of living with significant myeloma related bone disease warrants further investigation. Bone disease is a unique disease feature which causes most concern among clinicians providing physical activity promotion to myeloma patients, particularly among those with spinal disease and high risk of pathological fracture. The only published study investigating practices of haematologists promoting exercise to myeloma patients found over half would not recommend exercise to patients with spinal fractures (Nicol et al., 2022). Early studies of exercise in myeloma excluded people with significant bone disease (Coleman et al., 2003; Coleman et al., 2008). Some recent studies have not reported whether those with bone disease were excluded or the proportion, if any, of participants with bone disease (Mawson et al., 2021; Hacker et al., 2022).

Obesity is a leading cause of cancer, including myeloma and significant positive association has been found between mortality rate and increasing body mass index (BMI) among people with myeloma (Calle et al., 2003). Prevalence of sarcopenic-obesity is high among intensively treated myeloma patients, and its presence is likely to affect clinical outcomes as well as having significant implications on health outcomes into survivorship (Greenfield et al., 2014). One study of 142 post-ASCT myeloma patients reported similar prevalence of overweight or obese patients as this trial and identified 23% as having sarcopenic-obesity and 51% had sarcopenia. The authors found sarcopenia was associated with increased cardiovascular complications (12% versus 3%,
p=0.03) and reduced overall survival (hazard ratio: 1.11, 95% confidence interval: 1.02–1.22, p=0.02) (Williams et al., 2021). Incidence of BMI-related myeloma diagnoses have increased annually over last 30 years and the proportion of age-standardised deaths and disability adjusted life years attributable to high BMI in myeloma is also rising (Zhou et al., 2021). As literature suggests that obesity may impact survival among those with myeloma, BMI may be a potentially modifiable factor in improving survival rates (Shapiro et al., 2021). Findings from both qualitative studies in this thesis and other literature provide insight into the negative impact of diagnosis and early treatment on physical activity engagement in people with myeloma. Deconditioning from inactivity, as well as significant intake of corticosteroids required to manage the disease make patients vulnerable not only to weight gain and increased adiposity, but also loss of lean muscle mass (Shapiro et al., 2021). However, assessment of body composition by BMI or body mass alone is not without limitation. Given the proportion of participants in the pilot trial with high BMI, a future exercise study design may be enhanced by including more robust measurement of body composition with a nutritional intervention component. Therefore, there is a need to work with nutritional colleagues to develop lifestyle interventions in survivorship. Future research into the identification and management of sarcopenia and sarcopenic-obesity in myeloma needs to utilise valid and reliable assessment of body composition, integration of nutritional assessment and interventions in conjunction with exercise. The combination of physical activity support, nutritional support and psychological support (including behaviour change support) would also align better with the recommended approach for prehabilitation delivery in cancer (Macmillan Cancer Support, 2019).

Mawson et al. (2021), who conducted a single-arm study of prehabilitation before ASCT in myeloma in the UK, calculated a suggested sample size for a future RCT based on group difference in six minute walk test distance (MD 30m [SD: 80m]) and estimated 336 participants would be required (equivalent to standardised effect size 0.38, 10% attrition, 90% power and 5% two-side significance). Their feasibility study recruited only two participants per month and therefore using a conservative calculation, they recommended more than 7 centres would be required to recruit two participants per centre per month over 24 months (Mawson et al., 2021). If this sample size calculation is adjusted for higher attrition (20%), and higher recruitment rate seen in the PERCEPT
trial, then 362 participants would be required but could be recruited over 24 months from 4 centres of equivalent size to UCLH. A multi-centre trial design, perhaps using cluster randomisation by centre may be a suitable approach to reduce some of challenges with contamination of control group. Given the findings from this thesis and the opportunity to further develop learnings from two modes of intervention delivery, further patient and public involvement work will be essential to ascertain suitable approaches to allocation and control conditions so as not to induce the disappointment reported by participants and their resultant behaviour that may threaten the internal validity of a trial through contamination.

10.4 Final conclusions

This thesis has explored the feasibility of embedding an exercise intervention within a clinical pathway in haematological cancer, from the viewpoint of health-professionals, people living with myeloma and pilot testing of face-to-face and remote delivery of an exercise intervention during stem cell transplantation. This work demonstrates that people with myeloma are impacted by their early treatment and that physical inactivity precipitates loss of QOL and slower trajectory of recovery following treatment. This patient population are largely supportive of physiotherapy provision during ASCT and highlight the pre-ASCT phase as period of opportunity to restore function lost in early treatment and enhance their physical and mental condition before further intensive treatment. A number of methodological challenges due to adaptation of the research during the COVID-19 pandemic limited completeness of data collection. However, despite these challenges this work has demonstrated acceptability of a remotely delivery exercise intervention and indications of promise in terms of improving functional capacity, physical activity engagement, levels of fatigue and QOL before and after ASCT.
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Appendix A. Publication of original protocol for PERCEPT pilot randomised controlled trial

**BMJ Open**

**PERCEPT myeloma: a protocol for a pilot randomised controlled trial of exercise prehabilitation before and during autologous stem cell transplantation in patients with multiple myeloma**

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**ABSTRACT**

Introduction: Myeloma, a blood cancer originating from plasma cells, is the most common indication for autologous stem cell transplantation (ASCIT). Patients with myeloma undergoing autologous ASCIT (ASCIT) experience treatment-related morbidity and reduction in function and well-being for many months post-treatment. Interventions targeting physical functioning delivered prior to and during ASCIT have shown promising results in mixed haematological populations and may offer a non-pharmacological solution to post-treatment fatigue and preparing patients for ASCIT. The aim of this study is to investigate the feasibility of a physiotherapist-led exercise intervention as an integral part of the myeloma ASCIT pathway at a UK tertiary centre.

Methods and analysis: PERCEPT is a single-site, pilot randomised controlled trial of an exercise intervention embedded within the myeloma ASCIT pathway, compared with usual care. The primary study end points will be feasibility measures of study and intervention delivery including recruitment rates, acceptability of intervention, study completion rate and any adverse events. Secondary end points will evaluate differences between the exercise intervention group and the usual care control group in cancer-related fatigue, quality of life, functional capacity (6min walk test; hand-held dynamometry; timed sit-to-stand test) and objective and self-reported physical activity. Outcomes will be assessed at four time points, approximately 8–12 weeks prior to ASCIT, on discharge from ASCIT hospital admission and 12 weeks post-discharge. The exercise intervention comprises of partly supervised physiotherapist-led aerobic and resistance exercise including behaviour change techniques to promote change in exercise behaviour. The primary outcomes from the trial will be summarised as percentages or mean values with 95% CI. Group differences for secondary outcomes at each time point will be analysed using appropriate statistical models.

**Strengths and limitations of this study**

- This study features a pragmatic trial design integrated into the existing autologous transplant treatment pathway and the use of partly supervised exercise intervention, which will incorporate behaviour change techniques (BCTs), in myeloma patients before, during and after stem cell transplantation.
- It is the first study of a prehabilitation and rehabilitation exercise intervention in myeloma transplant recipients in the UK to incorporate a control arm.
- Although the intervention includes exercise and integrated BCTs, it does not include nutritional assessment and/or dietary intervention, as recommended in guidance for prehabilitation interventions.
- This study is a single-site pilot trial and is not statistically powered.

**PRESENTATION**

- Presentation at haematology and rehabilitation-related meetings.
- Trial registration number: ISRCTN13763759.

**INTRODUCTION**

Myeloma, also known as multiple myeloma, is an incurable blood cancer of plasma cells in the bone marrow and accounts for 10% of all haematological cancers. The incidence is approximately 22 cases per 100 000 people in the UK. Although incurable, improved understanding of disease mechanisms and advances in treatments means that survival in myeloma is increasing at the fastest rate among all cancer types. Median estimated survival time for myeloma has quadrupled over the last four decades and 5-year survival is now around 47%.

Myeloma patients are treated with autologous stem cell transplantation (ASCIT) if eligible...
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(based on age and performance status).\textsuperscript{2} Autologous SCT (ASCT) involves harvesting the individual's own stem cells and re-infusing them after high-dose chemotherapy.\textsuperscript{3} ASCT has been shown in multiple randomised controlled trials (RCTs) to prolong progression-free survival, and in some studies overall survival in myeloma.\textsuperscript{4} In the UK, the total numbers of ASCTs carried out each year have been increasing by 5\% each year.\textsuperscript{5} Data from the British Society of Blood and Marrow Transplant register shows that myeloma is the most common indication for ASCT in the UK, with 1411 procedures taking place in 2016.\textsuperscript{6} However ASCT has a number of side effects,\textsuperscript{7} including repeated infections, cachexia, anorexia and fatigue and patients can suffer a reduction in their functionality and well-being for 6 to 12 months post-transplantation.\textsuperscript{8} There is a need to develop supportive interventions for patients undergoing ASCT aimed at optimising patient fitness before and during ASCT in order to mitigate or minimise the negative effects of treatment on physical and psychological outcomes.\textsuperscript{9} Prehabilitation and rehabilitation, targeting physical function and fitness, have been suggested as an integral component of myeloma treatment pathways in guidance for managing the consequences of the disease and its treatment; however, further research is required to better understand the potential impact of prehabilitation/rehabilitation before and after treatment for myeloma.\textsuperscript{10} Given the prevalence of myeloma-related bone destruction, it is important that exercise, to develop and test tailored exercise interventions that are safe and effective at enhancing physical capacity in the presence of disease-related skeletal deformity and pain, common symptoms that limit patients with myeloma being physically active during and after treatment.\textsuperscript{11}

There is emerging evidence that exercise during or after SCT may be beneficial. However, existing studies have generally been small, with methodological limitations, particularly the heterogeneity of the interventions and mixed haematological cancer populations studied.\textsuperscript{12} Two systematic reviews, of 8 and 11 RCTs, respectively, have shown that exercise is safe and feasible for people being treated for different types of blood cancer during hospital admission and that the best results are seen when exercise is introduced before or during treatment, when compared with usual care. The majority of the studies included in these reviews were carried out with patients undergoing autologous SCT or mixed samples of both autologous SCT and ASCT recipients using varied interventions.\textsuperscript{13} There is acknowledged variation in symptoms and consequences of treatment experienced by patients with different blood cancers, and between undergoing allogeneic SCT and ASCT.\textsuperscript{14} Studies among allogeneic SCT recipients highlight the intensive nature of the medical intervention and its associated symptom burden and consequences, most notably graft versus host disease (GvHD) and an increased risk of treatment-associated mortality.\textsuperscript{15} In contrast, with autologous transplantation the mortality is considerably lower and there is no risk of GvHD, with its attendant risk of infections and short-term and long-term morbidity.\textsuperscript{16} These variations in clinical features support the need to study rehabilitation interventions in uniform blood cancer patient populations.

Only two small trials have explored the use of a pre-transplant exercise in a myeloma only population undergoing ASCT, with mixed results.\textsuperscript{17} In the first study, a feasibility study of 24 participants showed a significant increase in lean muscle mass in the exercise group.\textsuperscript{18} The second study of 166 patients reported a decline in aerobic capacity and increased fatigue in both the experimental and control group, with no difference between groups after SCT. This study, reported in two papers was also using the effect of prophylactic ankin alfa therapy, a medical product that raises haemoglobin levels, alongside exercise and was therefore not solely assessing the efficacy of the prescribed exercise.\textsuperscript{19} Additional limitations to these studies include provision of an unsupervised home-based exercise intervention and that the control groups were also advised to walk 20 min/day,\textsuperscript{20} which may have diluted the effect size. These studies, however, have demonstrated that it is safe for myeloma patients to exercise while undergoing ASCT.

Limited published literature exists regarding physical activity (PA) or exercise interventions in patients undergoing SCT originating in the UK. A single-arm pilot study of a physiotherapist-led, tailor-made exercise intervention conducted 24 h post-transplant showed that exercise was associated with improvements in quality of life (QoL), cancer-related fatigue and muscle strength, and was extremely well received by patients.\textsuperscript{21} A single-arm study to test feasibility of delivering exercise during ASCT among people with myeloma in a centre in Sheffield has completed recruitment but the results are yet to be published.\textsuperscript{22}

Objectives

This primary aim of this pilot, single-centre, RCT is to investigate the feasibility of a physiotherapist-led exercise intervention as an integral part of the ASCT pathway for patients with myeloma. It is hypothesised that this intervention, delivered before and during ASCT treatment for myeloma, will be feasible in terms of recruitment rate and willingness of the participants to be randomised, intervention adherence, compliance to the exercise prescription and attrition due to the intervention.

Primary objectives of the pilot study are to measure eligibility and recruitment rates from potential participants screened on referral to myeloma outpatient clinics for consideration for ASCT, acceptability of the intervention, including adherence to exercise sessions and deviations from exercise protocol; study completion rate and any adverse events.

Secondary objectives are to collect preliminary data on the intended primary/secondary outcomes of a future fully powered RCT to obtain mean and SD estimates to inform a sample size calculation. These outcomes include: cancer-related fatigue; QoL; levels of PA and
sedentary time: functional capacity and muscle strength; hospital length of stay, rates of readmission and health service utilisation and if the trial/exercise intervention is delivered as intended.

Exploratory objectives are to investigate any effect on immune parameters (including immunoglobulins, T cells, B cells, natural killer cells).

METHODS AND ANALYSIS

Participants

All patients with a diagnosis of myeloma referred to University College London Hospitals NHS Foundation Trust (UCLH) for consideration for ASCT will be identified through discussion with the haematology consultants, CNSs and MDT. All adult patients with myeloma referred to UCLH for consideration for ASCT who are clinically able to carry out an exercise training programme on a regular basis and willing and able to provide written informed consent will be deemed eligible to approach. Patients must have a good command of written and spoken English.

Patients will be excluded if they have known spinal instability, spinal cord compression or neurological deficits, have had recent (within 6 weeks) spinal surgery or other surgeries for pathological fractures, have an abnormal result on a RCCS and/or unstable angiogram. Patients will also be excluded if they are unable or unwilling to undertake an exercise programme on a regular basis or are unable or unwilling to provide informed consent.

The initial aims of this study were developed with input from participants with myeloma survivorship research conducted at our centre. The study has been further developed through involvement of the UCLH Cancer Patient and Public Advisory Group (CPPAG) during the preparation of the grant application and development of the study protocol. The CPPAG will continue to be provided with updates on the progress of the study and its results.

Setting

UCLH is an acute NHS trust in London, England and tertiary referral centre for SCT. Recruitment and outcome assessments will take place at the University College London Hospital (UCLH) Macmillan Cancer Centre. Weekly visits to assess the feasibility of an exercise intervention will take place at UCLH in a gym setting. Exercise assessments during admission for autologous transplant will take place either in the UCLH Macmillan Cancer Centre or on the haematology inpatient wards at UCLH.

Recruitment procedures

A participant information sheet (PIS) detailing the study will be provided in a clinical information pack routinely posed to patients prior to their first routine transplant clinic appointment. Potential participants will be contacted by the principle researcher or study physiotherapist, with a follow-up telephone call to allow patients to ask questions about the study. Those who wish to proceed will be asked to provide informed consent and this will be recorded on the participant consent form. Those approached to take part in the study who are subsequently found to be ineligible or decline to take part will be recorded in a screening log by the principle investigator.

It is conservatively estimated that approximately 60–75 patients will be recruited over a 15–18-month period, with completion of follow-ups within 18–21 months. Approximately 100 myeloma patients undergo ASCT at UCLH each year.

Randomisation procedures and blinding

Participants randomisation will be undertaken centrally by a researcher not involved in outcome assessment or intervention delivery, using minimisation, with age and gender as the stratification factors using MinimPy, a free, open-source, desktop programme (https://sourceforge.net/projects/minimpy/). This researcher will communicate their allocation of participants to the physiotherapist who will inform participants of the allocation and deliver the intervention to those in the intervention arm. The principle investigator will attempt to remain blinded to group allocation and will conduct follow-up outcome assessments.

Intervention

The intervention will involve a partly supervised exercise intervention incorporating behaviour change techniques (BCIs), delivered by a physiotherapist and individually tailored to the ability of each participant. The intervention will involve aerobic and resistance exercise during three phases of the ASCT pathways:

• Phase 1 (6–8 weeks before hospital admission for ASCT): Participants will receive one exercise session per week, supervised by a physiotherapist, at a UCLH gym. Participants will be requested to complete two further sessions per week, independently.
• Phase 2 (during hospital admission): Participants will be offered supervised exercise sessions with a physiotherapist in the hospital setting three times per week.
• Phase 3 (12 weeks after hospital discharge): Participants will be asked to continue exercising independently three times per week and will receive a weekly phone call from a physiotherapist for support and guidance.


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Supervised aerobic exercise will comprise of treadmill walking or stationary cycling. Participants will be encouraged to use walking as their aerobic exercise activity, or a stationary bike or elliptical trainer if they have access to one, for independent exercise sessions. In phase 1, prior to transplant admission, aerobic exercise intensity will be targeted between 60% and 80% of heart rate reserve (or Karvonen formula), in which target HR = [ (max HR – resting HR) × % intensity] – resting HR, where maximum HR-220 – age. Duration will be started at 15 min and progressed by 5 min/week to achieve a minimum of 30 min by week 3–4. This will be further progressed to 40 min by week 5. Target HR will be monitored using HR belts and participants will also use a Rating of Perceived Exertion (RPE) Scale. The participants will be given a scale in their exercise log book, instructed in its use and advised to work to levels of exertion as determined under supervision. Participants will be encouraged to reach the target duration in one bout but in the presence of discomfort or wish to change exercise machine/method then participants will be required to complete the target duration in bouts of 15 min or more.

Resistance exercises will be prescribed to target all major muscle groups (depending on individual health and contraindications). Resistance training will be performed using body weight, progressed with weights or using elastic resistance bands of various strengths. These bands will be supplied to participants to allow convenient independent resistance training. Starting resistance and repetitions of the exercises will be informed by a 10-repetition maximum assessment carried out by the physiotherapist during the first session. Individual tailoring and gradual progression in resistance training will be prescribed as deemed appropriate at each exercise session by the physiotherapist according to published principles. Participants will be provided with exercise log books and asked to record what exercise they do in the book, as well as document how they feel after exercising and any reasons for not carrying out the exercise as prescribed.

In phase 2, when participants are admitted to hospital for their ASCT, they will be offered supervised exercise with the physiotherapist three times per week in the ambulatory care or hospital ward setting (depending on each participant’s clinical location), which they can decline if they wish to do so. It is anticipated that participants will be symptomatic from the effects of their ASCT, which may include nausea, gastrointestinal complaints and fatigue. They may also experience bleeding and infection as a result of thrombocytopenia and low white cell counts. Therefore, the exercise intervention will be highly individualised and tailored according to participant’s capacity to carry out the exercises. Aerobic exercise will be carried out, as able, on a stationary bike in bouts of 10 min, up to a total duration of 30 min. HR will be monitored throughout and participants will be guided to exercise at a RPE (determined by RPE scale) they are comfortable with. Any exercise undertaken, declined or not possible due to clinical indication will be recorded by the physiotherapist in the participants’ log book.

In phase 3, when the participants have been discharged from hospital they will be advised by the physiotherapist to continue the independent exercise programme, tailored to their fitness on discharge, until they are 12 weeks post-ASCT. During these 12 weeks, they will be contacted once per week via telephone by the physiotherapist to provide support and guidance with continuing to exercise regularly during their recovery and to assist them in progressing their exercise programme. The participants will be encouraged to meet recommended guidance for levels of PA and requested to record any exercise undertaken in their log books.

Previous systematic reviews and meta-analyses have shown that BCTs from exercise interventions that are associated with improved adherence to exercise by cancer survivors include ‘goal setting (behaviour)’, setting ‘graded tasks’, and ‘instruction of how to perform behaviour’.”

Usual care (control) group

Participants randomised to usual care will receive the usual advice provided by haematology CNSs. Participants who specifically ask the research team for exercise advice will be signposted to generic PA advice offered for people undergoing cancer treatment on the Macmillan Cancer support website or from the information and support service within UCLH.

During hospital admission, patients undergoing SCT are routinely screened by a hospital physiotherapist and receive input for any functional or mobility-related deficits that may prevent or delay hospital discharge. All patients within the study who require physiotherapy or occupational therapy during their hospital admission will receive input as indicated. The indication for and details of input required will be obtained from participants’ hospital records and recorded in the study file for enrolled participants who require additional therapy input. Control group participants will not be asked to monitor their activity or receive log books.

Outcome assessment

The primary end points of this pilot study will be study feasibility. A target recruitment rate of >50% of potential participants screened as eligible and approached for this
Table 1: BCT coded to BCT taxonomy (BCTT V1) (Michie et al., 2013)

<table>
<thead>
<tr>
<th>BCT label</th>
<th>BCT no. (BCTT v1)</th>
<th>Component of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal setting (behaviour)</td>
<td>1.1</td>
<td>Overarching goal of exercise programme for all participants is to exercise three times per week. Participants are also supported to define their own personal subgoals, which are recorded in log book.</td>
</tr>
<tr>
<td>Problem-solving</td>
<td>1.2</td>
<td>Enables, barriers and solutions to barriers completed with physiotherapist and recorded in log book. Problem-solving with physiotherapist if discrepancy between current behaviour and goal is identified.</td>
</tr>
<tr>
<td>Action planning</td>
<td>1.4</td>
<td>Attendance at supervised exercise sessions in gym planned for specific day each week. Participants are also supported to plan independent exercise sessions (e.g., time/day of the week) with physiotherapist. These plans are recorded in log book prior to planned execution.</td>
</tr>
<tr>
<td>Review behaviour goal</td>
<td>1.5</td>
<td>Participants review performance of exercise sessions recorded in log book against planned goals and consider modifying goals accordingly with physiotherapist in supervised exercise sessions.</td>
</tr>
<tr>
<td>Discrepancy between current behaviour and goal</td>
<td>1.6</td>
<td>Physiotherapist informs participant if there is a discrepancy between current behaviour and goal.</td>
</tr>
<tr>
<td>Feedback on behaviour</td>
<td>2.2</td>
<td>Feedback on performance of exercise programme delivered by physiotherapist during supervised exercise sessions (phases 1 and 2) and telephone calls (phase 3).</td>
</tr>
<tr>
<td>Self-monitoring of behaviour</td>
<td>2.3</td>
<td>Participants asked to record exercises carried out each week in log book. Heart rate monitoring used in supervised and independent exercise sessions to monitor behaviour being carried out at target intensity.</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>2.4</td>
<td>Heart rate monitoring of aerobic exercise effort.</td>
</tr>
<tr>
<td>Instruction on how to perform the behaviour</td>
<td>4.1</td>
<td>Supervised exercise sessions with physiotherapist who instructs/teaches participant how to perform behaviour.</td>
</tr>
<tr>
<td>Information about health consequences</td>
<td>5.1</td>
<td>Physiotherapist and log book provide information about effects of exercise for health in context of myeloma.</td>
</tr>
<tr>
<td>Monitoring of emotional consequences</td>
<td>5.4</td>
<td>Participants encouraged to complete weekly reflectors in log book.</td>
</tr>
<tr>
<td>Information about emotional consequences</td>
<td>5.5</td>
<td>Physiotherapist and log book provide information about effects of exercise on emotional well-being.</td>
</tr>
<tr>
<td>Demonstration of the behaviour</td>
<td>6.1</td>
<td>Physiotherapist demonstration and teaching of exercise programme in supervised sessions.</td>
</tr>
<tr>
<td>Behavioral practice/rehearsal</td>
<td>6.2</td>
<td>Exercises taught/demonstrated in supervised sessions are practised within those sessions and independent sessions (phases 1 and 2).</td>
</tr>
<tr>
<td>Generalisation of target behaviour</td>
<td>6.5</td>
<td>Advice to perform exercise programmes, learn in supervised session, in independent sessions, during hospital admission and post-discharge.</td>
</tr>
<tr>
<td>Graded tasks</td>
<td>8.1</td>
<td>Progression of exercise sessions throughout exercise period.</td>
</tr>
<tr>
<td>Feedback source</td>
<td>9.1</td>
<td>Education and prompting from a physiotherapist with expertise in myeloma/haematology and provided in log book.</td>
</tr>
<tr>
<td>Prompts and core</td>
<td>9.2</td>
<td>Prompt to consider advantages and disadvantages of exercising through discussion with physiotherapist and recorded in log book.</td>
</tr>
<tr>
<td>Adding objects to the environment</td>
<td>12.1</td>
<td>Provision of heart rate monitors, resistance exercise bands and exercise programme sheets/log book for use in independent sessions.</td>
</tr>
<tr>
<td>Verbal persuasion about capability</td>
<td>15.1</td>
<td>Verbal support and supervision of physiotherapist to encourage exercise sessions before, during and after transplant treatment.</td>
</tr>
</tbody>
</table>

BCT, behaviour change techniques.
study will be a primary indication of feasibility. Feasibility of delivering the intervention protocol will be assessed by evaluating adherence to the intervention and acceptability of receiving the intervention (including deviations from exercise protocol). Attrition due to the intervention, loss to follow-up and adverse events will also be assessed.

A number of secondary end points will also evaluate any between group differences and determine intended primary and secondary end points for a full powered trial. Fatigue will be assessed using the Functional Assessment of Chronic Illness Therapy (FACIT-F) questionnaire. QOL will be measured with two complementary instruments, the European Organisation for Research and Treatment of Cancer QOL Questionnaire (EORTC QLQ-C30) and myeloma-specific module QLQ-MY20, and the Functional Assessment of Cancer Therapy Bone Marrow Transplantation (FACT-BMT) scale questionnaires. The EORTC QLQ-C30 has a focus on physical and functioning dimensions of QOL whereas FACT-BMT can assess impact of treatment and side effects on QOL. Comparison analysis indicates that both instruments should be used together rather than in place of each other when assessing QOL in patients undergoing SCT. Functional capacity will be assessed with a 6 min walk test (6MWT), handgrip dynamometry and a timed stand test. PA and sedentary time will be recorded over 5–7 days using an ActiPele accelerometer (PAL Technologies, Glasgow, UK). Additional measures of self-reported PA behaviour will be captured using the self-complete short form International Physical Activity Questionnaire and the Exercise Self-Efficacy Scale. All these measures will be recorded at baseline and three time points during the ASCIT pathway. At the final time point, as adapted Checkliste fuer Rehabilitation (CfR) Inventory questionnaire will be used to assess health and social care usage in the time following hospital discharge.

The outcomes measures and time points for data collection are summarised in Table 2.

Qualitative data

Semi-structured interviews will be conducted with a purposeful sample of participants at two time points. Study ‘decliners’ deemed eligible for the study, who have received a study offer but declined to enrol in the study, will be asked if they would participate in a short interview. These interviews will take place either face to face in the clinic setting or via telephone (based on participant’s preference) and will be conducted to explore the patients’ experiences of being approached for the exercise study and the process and outcome of their decision-making process in relation to the exercise study.

Additional semi-structured interviews from approximately 12 participants who enrol and take part in the study will take place at final follow-up, approximately 3 months post-transplant, and will be conducted to explore the participants’ experiences of ASCIT treatment and their experiences of being enrolled in the study.

Participants will be purposively sampled to include participants from both the intervention arm and the control arm.

Anticipated dates of trial commencement and completion

Recruitment commenced in June 2019, with data collection for all follow-up assessments estimated to be completed by December 2020.

Statistical analysis including sample size calculations

This is a pilot study with no formal power calculation. There is limited available data on the application of an exercise intervention delivered prior to ASCT in people with myeloma. This study will provide estimates of means/SD for the intended outcomes of a full powered RCT to support a sample size calculation for a larger trial. Meaningful clinically important differences are known for a number of the secondary end points, including the FACIT, EORTC-QLQ-C30 and MY20 module and 6MWT and will be used to inform future sample size calculations. For a pilot study, including 230 participants in each arm is considered to be an acceptable number.

Data analysis

The primary outcomes (intervention recruitment rate and intervention adherence) from the trial will be summarised as percentages or mean values for each item, with 95% CIs. Data on the acceptability of the randomisation through its effect on dropout rates, completion rates of the outcome assessments and reported use and satisfaction with the intervention materials will also be analysed descriptively. Group differences in fatigue, QOL, functional capacity, PA and sedentary time, self-efficacy at each time point will be analysed using linear regression for continuous factors (eg, fatigue) and frequency tables, text and logistic regression for categorical factors. Gender and age will be included within the models as covariates. Repeated measures analyses (eg, mixed models) will be used to analyse the baseline and follow-up scores of all measures together. Assessments for each outcome will be made to determine whether the data are normally distributed. For outcomes that are not, even after appropriate transformations, non-parametric methods will be used for data analyses at specific time points.

Qualitative data derived from the interviews of patients will be analysed thematically using an approach that is both deductive and inductive to ensure that the full range of participants’ responses are represented. Codes generated from the data will be assigned to portions of the text to develop an initial coding framework, which will be used by another researcher familiar with the sample population to independently double-code a proportion of the interview transcripts. The framework will be revised to ensure that the codes accurately reflect the data and any discrepancies will be resolved via discussion. The final codes will be applied to the data and incorporated into appropriate themes/subthemes.
<table>
<thead>
<tr>
<th>Visit no.</th>
<th>Screening</th>
<th>Baseline assessment (T0)</th>
<th>Follow-up 1 (T1)</th>
<th>Follow-up 2 (T2)</th>
<th>Follow-up 3 (T3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On referral to UCLH ASCT MDT</td>
<td>On day of first transplant clinic appointment</td>
<td>Day of transplant</td>
<td>Day of discharge from hospital</td>
<td>Post-transplant follow-up clinic at 3 months</td>
</tr>
<tr>
<td>Qualitative interview (~20 patients who X decline study)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Window of flexibility for timing of visits</td>
<td>+2 days</td>
<td>0±1 day</td>
<td>0±1 day</td>
<td>+6 days</td>
<td></td>
</tr>
<tr>
<td>Screening eligibility</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics and clinical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fatigue: FACT-F</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL: EORTC QLQ C-30-MY20</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL: FACT-BMT</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise behaviour: IPAQ-SF</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise Self-efficacy Scale</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional capacity: 6MWT</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional capacity: 30 s STS</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Functional capacity: handheld dynamometry</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting BP and HR</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height and weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accelerometry (3–7 days)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qualitative interview (20 participants)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health and social care service use: CRSI</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood counts</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levels of immune function (blood)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; BP, blood pressure; EORTC QLQ C-30-MY20, European Organisation for Research and Treatment of Cancer QOL Questionnaire and myeloma specific module; CRSI, Client Service Receipt Inventory; FACT-BMT, Functional Assessment of Cancer Therapy Bone Marrow Transplantation; FACT-F, Functional Assessment of Chronic Illness Therapy Fatigue questionnaire; HR, heart rate; IPAQ-SF, International Physical Activity Questionnaire short form; MDT, multidisciplinary team; 6MWT, 6 min walk test; QOL, quality of life; STS, sit to stand; UCLH, University College London Hospitals NHS Foundation Trust.

**ETHICS AND DISSEMINATION**

All participants will provide informed written consent to take part and can withdraw at any time.

Results of this study will be written up as part of a doctoral thesis and disseminated through publication in peer-reviewed journals, presentation at haematology and rehabilitation-related meetings and shared locally. A lay summary of the study results will be provided to participants who request to receive one after the study has completed.

**DISCUSSION**

The study described in this protocol will evaluate the feasibility of carrying out an exercise intervention among people with myeloma before, during and after ASCT at a UK centre. There is no standardised or accepted approach to using lead-time before SCT to prepare and physically optimise patients and the importance of carrying out research of this kind is particularly pertinent in this population for whom SCT currently offers the best possibility of longer progression-free survival, yet carries the risk of considerable morbidity.

The strengths of this study include the use of a pragmatic intervention using BCTs and designed to integrate into the existing ASCT treatment pathway at our centre and the use of a partly supervised exercise intervention among myeloma patients preparing for transplant. This study is also the first of its kind in the UK to incorporate a control arm. If the feasibility criteria for trial is met and this single-site, pilot trial is deemed to be successful, it
is anticipated to be an easily replicable trial design for future evaluation as a fully powered multicentre trial. Recent guidance for prehabilitation in cancer advocates for a multimodal intervention, comprising of exercise, nutrition and psychological/behaviour change assessment and support. There is no nutritional assessment or dietary intervention included in the study which may be considered a limitation of this exercise-focused intervention. It is expected that this pilot study will be acceptable and feasible as an important step in developing the field of exercise prehabilitation and rehabilitation within haematological cancer treatment in the UK. Dissemination of study results is expected in early 2021.

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Contributors CM drafted the manuscript, CM, KC, AV and GB designed the study and secured funding and ethical approval. AL, JL and NR provided intellectual input to the final study protocol according to their area of expertise. All authors contributed to writing and final approval of the submitted manuscript.

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Conflict of Interest None declared.

Patient consent for publication Not required.

Ethics approval This study has been approved by the Nhs Health Authority Research Ethics committee—Camden and Kings Union—Reference 16/LO/0304. (Protocol version 1.0, 14 December 2016).

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix B. Publication of protocol amendments in response to COVID-19 pandemic for the PERCEPT trial
of myeloma, who were willing to and clinically able to undertake an exercise training programme and had good command of written and spoken English were eligible and approached. The trial assessments included a range of objective measures of functional capacity (6min walk test, 30s timed sit to stand test, hand grip strength test, levels of physical activity) as well as patient-reported outcome measures assessing quality of life (Functional Assessment of Cancer Therapy (FACT) bone marrow transplant and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30), fatigue (FACT fatigue subscale) and physical activity intention (International Physical Activity Questionnaire and exercise self-efficacy scale). Assessments were initially designed to be conducted face to face at established touchpoints within the clinical pathway that usually coincided with patient attendance at transplant clinic appointments. The intervention involved an exercise intervention with incorporated behaviour change techniques, delivered in part through weekly face to face, group-based exercise sessions at a UCLH gym supervised by a physiotherapist and through unsupervised home exercise sessions with telephone support in the post-ASCT rehabilitation phase. Participants were asked to exercise three times per week, at moderate to high intensity, for 30 min of aerobic exercise and complete a programme of resistance exercises. Exercise was individually advised and progressed by the physiotherapist. In the prehabilitation phase before ASCT patients were expected to attend weekly supervised gym sessions and exercise independently twice per week. During hospitalisation and following discharge from hospital participants were supported to continue three unsupervised exercise sessions per week with weekly telephone guidance from a physiotherapist. The original trial was registered (ISRCTN15873250) and the protocol is described in detail elsewhere.2

TRIAL RECRUITMENT PRIOR TO THE PANDEMIC

Trial recruitment was progressing as planned and between June 2019 and end of February 2020 90 potential participants had been identified and screened for eligibility. Of those, n=56 (40%) consented to take part and were randomised, n=8 (5%) were ineligible and n=46 (31%) declined. The main reasons for declining for to take part were travel or distance to take part in the intervention, poor mobility/inability to use public transport and already having too many hospital appointments. Many of those who declined had a favourable opinion of the trial and would have taken part if it had been closer to their home. It had been anticipated that target recruitment (n=50-75) would be reached by December 2020.

Face-to-face recruitment was paused in March 2020, due to the COVID-19 pandemic, when all but essential NHS research activity was instructed to cease and research physiotherapists were redeployed to clinical services. In addition, the myeloma ASCT service was also paused due to resource limitations, lack of critical care provision and increased risk of COVID-19 infection in transplant recipients.

RESUMING RECRUITMENT AND ADAPTATION TO VIRTUAL INTERVENTION DELIVERY

Between March and June 2020, all participants already enrolled within the trial expressed their wish to continue in the trial while awaiting their delayed ASCT. All participants were placed on hold pending chemotherapy by their clinical teams. A minor ethics amendment was granted to allow participants to remain in the trial longer than in the original protocol, to continue delivery of the home-based component of the exercise intervention via telephone support and to collect follow-up assessment data via postal delivery of trial questionnaires.

Following resumption of the myeloma ASCT clinical service in June 2020, elements of the clinical pathway on which the trial procedures were designed had changed significantly in response to the ongoing threat of the pandemic. Namely, patients were no longer attending UCLH clinics in person in the lead up to their ASCT and were instead receiving telephone contact for clinical appointments. It was therefore necessary to adapt the trial to accommodate these changes to the clinical pathway.

Patient and public involvement

Participants who had remained in the study during the first national lockdown were consulted on how best to proceed with the trial. These participants were asked to consider their acceptability of receiving study assessments/questionnaires via post, and importantly, how they would feel about having access to a physiotherapist and exercise intervention via video platform. Overwhelmingly, they supported adapting the trial to virtual delivery and reported that having regular contact with the study physiotherapist was supportive, especially as they were no longer attending their clinical services in person. Some reported that the exercise intervention was something positive to focus on while feeling apprehensive about having their ASCT delayed and remaining isolated in their social activities due to shielding. These participants were consulted on the proposed substantial amendment and gave their approval to the changes described in this manuscript.

Following review of leading literature for adapting pulmonary rehabilitation services to virtual delivery17-19 and liaising with other cancer rehabilitation services delivering exercise virtually, the trial design was substantially amended.

Virtual recruitment, consenting and baseline assessments

- Identifying potential participants from a list of patients awaiting consideration for ASCT, rather than from weekly clinic lists of expected clinic attendance.
- An additional inclusion criterion was added to require patients to have access to and the ability to
Participants were sent trial consent forms, self-complete questionnaire measures until a pre-programmed ActiPulse accelerometer by post and a Zoom video call appointment was arranged for approximately 3 days later. Completion of consent forms, baseline questionnaires and fitting of accelerometer occurred and conducted virtually over Zoom appointment.

Addition of the Activities-Specific Balance Confidence Scale to assess risk of falling, used to screen those randomised to the intervention for any necessary actions required to reduce risk of exercising at home as no longer objectively assessed by the physiotherapist face to face. If any participant scored <85% on the scale they were deemed high risk of falling and their assessment and participation in the group sessions would be adapted to minimise risk.

Objective measure of functional capacity changed to a remotely delivered 1 min timed sit to stand test, which has been demonstrated to produce comparable cardiovascular and lower limb muscle fatigue as the 6 min walk test.

Virtual delivery of the partly supervised exercise intervention

The intervention delivery was changed to be completely online out following the principles of the original protocol in terms of frequency, intensity, time and type of exercise. Each new participant had an initial one to one session to introduce the programme and tailor to their individual abilities, including any symptoms of bone disease or balance deficits. Each participant was then asked to attend a weekly virtual group-based exercise class via Zoom until they were admitted for their ASCT.

RECRUITMENT TO VIRTUAL TRIAL TO DATE

Recruitment restarted after the first wave of the pandemic in August 2020. Up to October 2020 a further 33 potential participants were identified and screened for eligibility. Of those, 14 (43%) agreed and consented to take part, 0 (18%) were ineligible and 15 (45%) declined. This indicates that uptake to the virtual part of the trial was similar to the original face to face design. Despite fewer people declining the virtual trial, more people were ineligible. The main reason for increased proportion of ineligibility was related to some potential participants already having a date to be admitted for ASC at the line in the current follow-up trial. Further, in the original study schedule. Further, a small number of participants were withdrawn from the trial after strong evidence of ASC and therefore were not recruited.

CONCLUSION

The emergence of the COVID-19 pandemic required significant adaptation for the continuation of this pilot RCT. Our sample population being clinically extremely vulnerable were advised to shield, as well as the requirement to reduce all but clinically necessary face to face contact altered how potential ASC recipients accessed the clinical service and consequently the planned trial delivery. We have briefly described how the trial protocol was amended and continued virtually delivering a rehabilitation intervention virtually. Adaptation to virtual delivery was deemed important to participants already enrolled within the trial and appears to have been acceptable for the adapted virtual trial of the trial while this was possible.

The original trial design relied heavily on participant attendance at face-to-face clinical contact as part of the routine ASC pathway as it exists pre-pandemic. This was a strength in terms of increasing likelihood of follow-up study assessments and ensuring completeness of data capture as participants would be present in the centre at the planned follow-up time points. However, assumptions that all assessments would be conducted face to face resulted in reliance on paper-based questionnaires and because study resources did not allow for transformation to electronic data capture, postal follow-up assessment was required. On reflection, the original study would have been somewhat future proofed as electronic questionnaires and intervention materials were incorporated at design and should certainly be a requirement of future work.

As ASC recipients with myeloma are generally older, with high incidence of bone disease, deconditioned by induction chemotherapy with possible impairments to mobility and function, adapting the trial to explore feasibility of a virtually delivered physiotherapy intervention was an important opportunity arising from the threat posed by the pandemic. Considering the possible increased risk from not assessing participants face to face, required implementation of a remotely delivered
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An alternate objective measure of functional capacity suitable for remote assessment and on-line adaptation of intervention delivery to include a virtual group-based exercise class was all important steps. Development of effective, remotely delivered rehabilitation and physical activity programmes are likely to be increasingly valuable to people living with myeloma for whom shielding during clinically vulnerable periods of treatment and recovery, and travel to their specialist treatment centres will be continuing challenges in the post-pandemic era.

Twitter Ona McCourt @ona.mccourt

Acknowledgments The authors wish to thank the people living with myeloma who provided input into the original and amended study designs.

Contributors GM drafted the manuscript, with input and final approval from KY, AC, CDR, JG, J, KRI and NJS, GM, KY and AC designed and obtained ethical approval for the original and amended study protocols. AC, JG, J, KRI provided intellectual input to the study protocols according to their area of expertise. All authors contributed to the design of the study, conduct of the study and are accountable for all aspects of the work.

Funding This communication relates to independent research supported by the National Institute for Health Research (HS/19/118/156). Structural Clinical Doctoral Research Fellowship, NRS). McCourt, IC (CICD-2017-03-06).

Disclaimer The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Competing Interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by NRES Committee London - Camden & Kings Cross (18/LO/1804). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

Ms Orla McCourt
HEE/NHR Clinical Doctoral Research Fellow
University College London Hospitals NHS Foundation Trust
University College Hospital
235 Euston Road
London
NW1 2BU

26 March 2019

Dear Ms McCourt

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title: Pilot randomised controlled trial of a physiotherapist-led exercise intervention delivered prior to and during stem cell transplant in patients with myeloma
IRAS project ID: 258814
REC reference: 19/LO/0204
Sponsor: University College London

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales? You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

This is a single site study with joint management arrangements with the site. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.

It is important 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 of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland? HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.
If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
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.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Nikkayla Dixon
E-mail uch.randd@nhs.net
Telephone 020 3447 2177

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is 254814. Please quote this on all correspondence.

Yours sincerely
Catherine Adams
Senior Assessor

Email: hra.approval@nhs.net

Copy to: Miss Nikkayla Dixon, Sponsor's Representative
List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

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<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
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Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

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<td>3.1</td>
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<td>Yes</td>
<td>There is a joint management arrangement in place between the Sponsor and site, no agreement is required.</td>
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### Section 6.2

CTIMPS – Clinical Trials Authorisation (CTA) letter received

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### Section 6.3

Devices – MHRA notice of no objection received

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### Section 6.4

Other regulatory approvals and authorisations received

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#### Participating NHS Organisations in England and Wales

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.

If this study is subsequently extended to other NHS organisation(s) in England or Wales, an amendment should be submitted, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England or Wales.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

#### 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 Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).

A Principal Investigator is expected at the research site.

GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA 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.

No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list...
checks, and occupational health clearance.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.

The applicant has indicated that they intend to apply for inclusion on the NH/CRN Portfolio.
Appendix D. NHS Health Research Authority approval letter for substantial amendment to the PERCEPT pilot trial

Dear Ms McCourt,

Study title: Pilot randomised controlled trial of a physiotherapist-led exercise intervention delivered prior to and during stem cell transplant in patients with myeloma

REC reference: 19/LO/0204
Amendment number: Project ID: 19/0552 Amendment: SA1
Amendment date: 17 July 2020
IRAS project ID: 254814

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.

Approved documents
The documents reviewed and approved at the meeting were:

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20 August 2020

Ms Orla McCourt
Membership of the Committee
The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations
Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19
We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

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.

HRA Learning
We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities—see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 254814: Please quote this number on all correspondence

Yours sincerely

Mrs Julia King
Alternate Vice Chair

E-mail: CamdenandKingsCross.REC@hra.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms Orla McCourt
Physio-led ExeRCisE Prior to & during Transplant for myeloma
The PERCEPT Myeloma study

REC Reference: 19/LO/0204

Pre Transplant Exercise Diary

Name: ______________________

Contact details
Research Physiotherapist:

If you have any concerns or are unclear about your exercise programme then please contact the research physiotherapist. It may be possible to resolve difficulties over the telephone or they can help you adapt the exercises in the next gym visit.

If you have become unwell or suffered an injury then in the first place please contact your GP or go to your local accident and emergency if you require urgent assistance.
You should also phone the trial physiotherapist, Joanne Sowter (0207 679 1914) to inform the research team and for non-urgent telephone advice.

When to contact the hospital
Always carry the 24-hour hospital telephone numbers that you have been given by the myeloma transplant team at UCLH. If you are worried about anything, contact them on the numbers provided at any time of day or night. The doctors and nurses in your team always prefer you speak to them rather than risk being unwell at home.
Exercise Programme

For the first part of the study, before your transplant, we would like you to exercise **three days per week**, with at ideally one day rest between sessions. It is important that you perform the sessions as instructed by the research physiotherapist.

The aim for this part of the study is to work on increasing your **aerobic fitness** and **muscular strength** in preparation for your upcoming stem cell transplant.

The exercises will be introduced by the physiotherapist at a level that suits your abilities, adjusted for any pain or other symptoms you may have. This part of the exercise programme will feel quite challenging but you will start to feel benefits from the exercise over the next number of weeks.

The research physiotherapist will assist you to set goals and record your efforts each week, to map your progress.

**Aerobic exercise**, such as brisk walking or cycling, should start with a 5 minute warm up, before gradually increasing effort until your heart rate is within the target range set out by the research team. In the first week you will start with 15 minutes aerobic exercise and you will work towards cycling for 40 minutes at your target heart rate by week 5-8. You will then reduce your effort at the end of the session for a 5 to 10 minute cool down period.

Your target training heart rate is written at the top of the page on each of your training weeks. You will be provided with a heart rate monitor during the supervised sessions, this will give you feedback on your heart rate and you will record this during your exercise sessions.

Don’t worry if you find it difficult to carry out the full 40 minutes training. It is possible that some people will need to do 2 or 3 shorter bouts rather than 40 minutes all in one go, the research physiotherapist will guide you.

**Strengthening** or **resistance exercises** are detailed in the back of this book and you will aim to do with 10-15 repetitions of each at a level of resistance or weight advised by the research physiotherapist. You should do 3 sets of each exercise. The physiotherapist will advise you when to increase the number of repetitions or the level of resistance or weight you need to progress the exercises each week.

If you are struggling to complete a full exercise session as planned then just complete as much as you can manage and record what you have done accurately in your diary.

Part of this study is about exploring the best exercise regime for people with myeloma preparing for and undergoing a transplant and so it is important to capture your experience in these diaries.

If you feel unwell then it is best to leave the exercise sessions until you feel better. It is important to make a note in this diary if you are unable to do your exercise session, for whatever reason as this will be helpful for planning future services for people with myeloma.
How do I fill out the exercise diary?

Aim to complete the diary during or immediately after the session so that you are able to record your exercise activities easily.

Record the date of the session at the top of the page. In the **aerobic exercise** table record the total time you were walking/cycling for (not including your warm up and cool down periods), in the next column record the average and maximum heart rate you were able to achieve during the session as recorded by the heart rate monitor watch (this might not be the same as the target heart rate).

The “**Borg score**” column should be used to record how hard you felt you worked when doing each of the exercises using the Borg scale. Use the instructions on page 11 to decide upon your Borg score. In the ‘description’ section you can give detail of what you actually did e.g. one block of 30 minutes walking, or 3 blocks of 10 minutes cycling etc.

The **strengthening exercises** are listed in the first column of the table, followed by number of repetitions and sets you completed. In the gym session, write down the number of reps and sets you achieved with the physiotherapist and a BORG rate for how difficult you found the exercise. During the home sessions, you should simply tick the boxes when you complete the reps/sets detailed in your log book.

There is a comment section where you can tell us any other information you think we should know. At the end of the week there is space for the research physiotherapist to add any comments and also for you to reflect on the week’s training and tell us how you are feeling.

**Using the Heart Rate Monitor Watch**

Attach the chest strap as shown. Adjust the length of the belt such that the belt is snug, but neither too loose nor too tight. Position the belt around the chest such that the logo is facing outwards and in the correct position directly over the breast bone. For men, the chest belt should be located directly below the pectoral muscles, for women, directly below the breast.

It may take some time until the heart rate is measured and displayed on the watch. Put on the chest strap a few minutes before starting exercise in order to warm it up to body temperature and establish optimal contact. It can be helpful to wet the contact points on the inside of the chest strap with a little water before putting it on.

Once in place and picking up your heart rate, the watch display will show your heart rate at the top of the display above the time.

**To record your aerobic training session:**

Ensure the watch is picking up your heart rate. Press the ‘Menu’ button (top right) two times, until it reads ‘training’. Then press ‘Start/Stop’ button (top left) once to start recording. You should see your heart rate and a stop watch timer, with the word ‘Run’ underneath.

When you have finished your aerobic training, press ‘Start/Stop’ button (top left) again to stop recording the session.

To obtain the hear rate recordings for your logbook, press the ‘Menu’ button (top right) to get to ‘Result’ - the reading for Average HR will appear first as a number with ‘bpm avg’ underneath. Then press ‘Option/Set’ button (bottom left) once to display your maximum heart rate recording, a number with ‘bpm HRmax’ underneath it.

To reset the watch before your next session, press the ‘Menu’ button (top right) until ‘Training’ is displayed. Then press and hold the ‘Start/Stop’ button (top left) until a 0:00 clock appears. The watch is ready for the next recording.
What do I do if I experience pain?

Some people experience soreness and tenderness of the muscles one or two days after starting a new exercise program. This is known as delayed onset of muscle soreness (DOMS). DOMS is a normal response to new exercise that should settle over 4 to 5 days. DOMS will usually settle and stop happening as you continue to train.

However, if you are concerned about any pain that you experience or it is making it difficult to exercise then you should contact the research physiotherapist who will advise you on the best course of action.

What if my pain does not feel like DOMS?

It is important that if you have any concerns or issues that make it difficult to perform the exercises you contact the research physiotherapist as soon as possible.

If you experience a new pain that does not feel like DOMS (for instance it is a sharp pain or isn’t located in the muscles that you are exercising), you should contact the research physiotherapist for advice. You should also call for advice if you normally have some pain but the exercise aggravates it.

If you experience very severe pain that does not settle, then you should stop performing the exercises and contact your myeloma medical team for advice as soon as possible.

What if I want to carry on doing the exercises during the stem cell transplant admission phase of the study?

These exercises will form the basis of the exercises you will be asked to complete in hospital during your transplant admission. We hope that the 6-8 weeks that you do this exercise programme before your transplant will help you feel more confident about exercising during your hospital admission for your transplant. Depending on how you are feeling, your blood counts and any other symptoms your exercise programme may be adapted or tailored with input from the physiotherapist.

During the admission phase, the research physiotherapist will offer to supervise you exercising three times per week in hospital or ambulatory care, adapting the programme to suit your symptoms as needed. We will record how many of these sessions you feel you can complete. You will receive a new exercise diary for the transplant admission phase of the study.

Remember that, at the end of the study the research physiotherapist will advise and support you to review your activity and continue to exercise independently during your recovery. You will receive weekly telephone or online contact to support your exercise at home and for further guidance.

It is important to remind you that you are free to withdraw from the study at any point without giving a reason. This will not affect your future medical care.
How to work out your Borg score

We want you to rate your feeling of effort. This feeling should reflect how heavy and tiring the exercise feels to you, combining all feelings of physical stress, effort, and fatigue. Do not concern yourself with any one factor such as pain or shortness of breath, but try to focus on your total feeling of effort.

Look at the rating scale on the page opposite and try to recall how you felt; it ranges from 6 to 20, where 6 means "no effort at all" and 20 means "maximal effort".

Try to recall how you felt when you were doing the exercises most recently. Look at the scale and the descriptions and then give a number that best describes your level of effort during last session.

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<tr>
<td>6</td>
</tr>
<tr>
<td>7           Very, Very Light</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9           Very Light</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11         Fairly Light</td>
</tr>
<tr>
<td>12</td>
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<tr>
<td>13         Somewhat Hard</td>
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<td>18</td>
</tr>
<tr>
<td>19         Very, Very Hard</td>
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<tr>
<td>20</td>
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Advantages & Disadvantages

Starting out on a new exercise programme can feel daunting, especially during cancer treatment. It can be helpful to think about the possible advantages of taking part, for example you may feel stronger after a few weeks of exercise. But there may be disadvantages too, such as time taken to do your exercises may mean less time to watch TV or do other leisure activities.

Have a think about the advantages and disadvantages that are personal to you and list them here:

<table>
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<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>

Goal Setting

The main goal of taking part in this exercise programme is:

To exercise on 3 days each week

You may find it helpful to set your own specific goals, that will help you achieve this main goal. For example you could set a goal to carry out your exercises on a particular day of the week, or time of day.

My personal goals are:

1. 
2. 

Enablers & Barriers

Taking part in a new exercise programme can be a challenge. There are some things that can make it more likely that you will carry out your exercises and enable you to stick to your exercise programme. An example might be encouragement from your friends or family.

Think about you and your situation, what are the possible enablers that will help you to exercise 3 times per week?

Factors that I think will help me to stick to the exercise programme are:

There are also some factors that make it difficult to exercise and are barriers to keeping up your exercise programme. For example you may find it difficult to find the time each week.

Think about you and your situation, what are the possible barriers for you?

Factors that I think will prevent me keeping to the exercise programme are:

Solutions

Now you have identified some potential barriers that may make it more difficult for you to carry out the exercise programme 3 times per week, what is a possible solution to over coming those barriers?

A solution to forgetting might be to set a reminder on your phone, or ask a friend to do the exercises with you.

I will overcome my barriers by:
### Week 1: Physio Session

<table>
<thead>
<tr>
<th>Aerobic Exercise (eg walking, cycling)</th>
<th>Total time</th>
<th>BORG score</th>
<th>Max HR</th>
<th>Avg HR/ sess</th>
<th>Description</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Strengthening Exercise</th>
<th>Reps</th>
<th>Sets</th>
<th>Weight</th>
<th>BORG</th>
<th>Comments/adaptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder Press</td>
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<tr>
<td>Wall Press</td>
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<tr>
<td>Seated Row</td>
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<tr>
<td>Squats</td>
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<tr>
<td>Lunges</td>
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<tr>
<td>Step Ups</td>
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<tr>
<td>Trunk: Bridge</td>
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<tr>
<td>Trunk: Scissors</td>
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<tr>
<td>Trunk: Hip Twist</td>
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</tr>
</tbody>
</table>

**Physio session comments:**

**Date:**

**Time:**

---

### Week 1: Home Exercise Sessions

**Session 1 Date:**

<table>
<thead>
<tr>
<th>Session 1 Aerobic Exercise (eg walking, cycling)</th>
<th>Total time</th>
<th>BORG score</th>
<th>Description</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Strengthening Exercise</th>
<th>Reps</th>
<th>Sets</th>
<th>Weight / resistance</th>
<th>Home sess 1</th>
<th>Home sess 2</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder Press</td>
<td></td>
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<td>Wall Press</td>
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<td>Seated Row</td>
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<td>Squats</td>
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<td>Lunges</td>
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<td>Step Ups</td>
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<tr>
<td>Trunk: Bridge</td>
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<tr>
<td>Trunk: Scissors</td>
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<tr>
<td>Trunk: Hip Twist</td>
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</tr>
</tbody>
</table>

**Session 2 Date:**

<table>
<thead>
<tr>
<th>Session 1 Aerobic Exercise (eg walking, cycling)</th>
<th>Total time</th>
<th>BORG score</th>
<th>Description</th>
</tr>
</thead>
</table>

**Your reflections or points to note about this week** (tell us how training is going and how you are feeling)
**Strengthening Exercises: Upper Limbs**

**Shoulder Press**
- Stand tall. Hold weights at shoulder height with your elbows pointing to the sides.
- Press the weights up to straight arms. Return to the starting position in a controlled manner.
- **Note:**
  - Try not to shrug your shoulders.
  - Keep abdominals tight to avoid excessively extending your lower back.
- Repeat and record as instructed in your log book.

**Wall Press Up**
- Stand facing a wall with your arms straight and hands on the wall.
- Do push-ups against the wall keeping your body in a straight line.
- Repeat and record as instructed in your log book.

**Seated Row**
- Extend your legs and wrap middle of band around feet. Be sure band is secure around feet and won’t slip. Grasp both ends of band with elbows straight. Pull band upward and back, bending elbows. Slowly return to starting position.
- **TIP:** Keep your knees and back straight.
- Repeat and record as instructed in your log book.

**Strengthening Exercises: Lower Limbs**

**Squat**
- Slowly bend your knees, keeping your back straight and weight back on your heels. Hold then push through both legs, using your bottom muscles to return to standing.
- Repeat and record repetitions/sets in your logbook.

**Lunge**
- Stand straight.
- Take a step forward and bend your knees, lowering your back knee towards the floor. Keep your weight back onto your back leg and your front knee behind your toes. Push through both legs to return to the starting position.
- Repeat and record repetitions/sets in your logbook.

**Step ups**
- Hold on to a rail for stability if needed.
- Push through your front leg on the step to step up with one leg leading and then repeat with the other leg leading.
- Repeat and record repetitions/sets in your logbook.
**Strengthening Exercises: Trunk**

**Bridge**
Starting position: Rest position. Centre engaged.
**Level 1**
- INHALE to prepare
- EXHALE, gently roll your lower back into mat, scoop your tailbone upwards and continue to peel your spine off the mat, bone by bone until you are resting on your shoulder blades
- INHALE and hold the shoulder bridge position
- EXHALE, lower the shoulder bridge by lowering one bone at a time to the mat, beginning with the highest vertebræ of your bridge and finishing with your tailbone to return to neutral position.
- Reps: 10

**Scissors**
Starting position: Rest position. Centre engaged.
**Level 1**
- INHALE to prepare
- EXHALE, slide your right foot inwards towards your sitting bone and float this leg into tabletop
- INHALE and hold the tabletop position
- EXHALE, lower your right leg to the mat
- Repeat alternating legs Reps: 10

**Hip Twist**
Starting position: Rest position. Centre engaged.
**Level 1**
- INHALE to prepare
- EXHALE, roll your left leg outwards from your body
- INHALE, roll your left leg back inwards until your left knee is in line with the left hip
- Repeat alternating leg
Appendix F. Consent form for PERCEPT pilot randomised controlled trial and decliners interview study

CONSENT FORM

Title of Project: Pilot randomised controlled trial of physiotherapist-led exercise prior to and during stem cell transplant in patients with Myeloma

Name of Researcher: Ms Orla McCourt

1. I confirm that I have read the information sheet dated 05/08/2020 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

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

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

4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

5. I agree to my General Practitioner being informed of my participation in the study.

6. I agree to take part in the above study.

To inform the wider evaluation of this research, we would like to gather information from patients who have been approached to take part in this study but choose not to participate about the reasons for their choice.

7. I do not agree to take part in the above study but I agree to share my reasons for declining in a short interview with a researcher.

Name of Participant __________________________________________ Date ________________ Signature ________________

Name of Person taking consent __________________________________ Date ________________ Signature ________________

PERCEPT - Myeloma Study Consent Form, IRAS: 254814, Version 3.0 15/08/2020

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.
Appendix G. Interview schedule for decliners interview study

Myeloma Transplant Exercise Study
Interview Schedule v2 – People who decline to take part in trial

This guide is to ensure key aspects are covered during the interview. However a respondent-sensitive approach should be taken, allowing deviation from question order and raising additional issues if desired.

Interviewers should be mindful of the sensitive subject of the interview.

Introduction
Introduce yourself and explain purpose of the interview: to explore the participant’s experience of being approached to be a participant in the trial and the reasons for deciding not to take part. Ask permission to record the conversation. Assure confidentiality and ask participant to be as open and honest as they can be.

1. I understand some time has passed since you were sent the letter about the research study. If I can ask you to think about the study, do you remember what it involved?
   - Can you recall what the study assessments involved?
   - What was the study intervention?
   - Can you recall anything about allocation of a group...

2. Can you give some detail [for the recording] about your reason for deciding not to take part in this study?
   - Probe: If distance/journey is given as reason – asking them to explain their journey to UCLH, what does it involve, how long does it take etc
   - If symptoms/side effects of myeloma/treatment given – explore how they experience these symptoms, how they make travelling/doing things/life difficult, how do these changes make them feel?
   - Have you sought advice from anyone regarding these symptoms/changes to activities

3. If you can think back, what do you remember about your experience of being approached about the study and being asked to take part?
   - Probe: Do you recall who approached you? What was their manner? Did you receive adequate information?

We would like to know more about the process people go through when they are asked to take part in a study like this one. I am going to ask a few questions and I would like to know your thoughts or feeling about these different parts of the process of being asked to take part in this research study.

4. Did you read the information leaflet in full?
   - Probe: What did you think about the length of it? About the language? Was it easy to read/follow/understand?
   - If not, what put you off reading it in full?

5. What did the information in the leaflet make you think about?

6. Did you weigh up any positives and negatives about taking part?
   - Probe: What were the negatives/positives for you?
   - Person may already have given negatives in earlier questions, so perhaps explore positives if not yet discussed

PERCEPT – Decliners Sub study Interview Schedule, IRAS: 254814, Version 1.0 14/12/2018  Page 1 of 2
7. Did you discuss it with anyone else?
   - **Probe:** if so, with whom? What did they say? Did their opinions/thoughts affect your decision or thinking?

8. Do you have any experience of taking part in research before?
   - **If yes, PROBE**

9. How did you feel about being contacted about the study by the research team rather than by the consultant or clinical nurse specialist?
   - Would being sent information about this study through your clinical team changed your decision?

10. Have you received any information about physical activity since your diagnosis?
    - **Prompt:** if no, would they have liked advice during treatment
    - If mentions previous activity now reduced, explore why they do less – were they advised to reduce/stop their activity/exercise or did they arrive at the decision to stop themselves and why?

11. Has being approached about this research study changed your thoughts or opinions on physical activity or exercises?
    - **Prompt:** will you do anything differently in preparation for your transplant?

12. Is there anything else you would like to say about the trial, that we've not already talked about?

**Concluding comments and thanks**
Thank the participant for their time today and ongoing and let them know where they can contact you in the future if they do have any additional comments.
Appendix H. Chapter 7 additional results tables and figures: functional capacity

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>N</th>
<th>Control Mean ±SD Median (IQR)</th>
<th>95% CI Range</th>
<th>N</th>
<th>Intervention Mean ±SD Median (IQR)</th>
<th>95% CI Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timed 30 second sit to stand (repetitions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>20</td>
<td>13 ± 3.7 (11,15.3)</td>
<td>11.4, 14.6</td>
<td>6-21</td>
<td>10.1 ± 5.1 (6.5,13.5)</td>
<td>7.6, 12.7</td>
</tr>
<tr>
<td>T1</td>
<td>15</td>
<td>12.7 ± 3.4 (11,14)</td>
<td>11, 14.4</td>
<td>7-21</td>
<td>16.7 ± 4.6 (15.3,18.3)</td>
<td>13, 20.4</td>
</tr>
<tr>
<td>T2</td>
<td>9</td>
<td>11 ± 3.9 (8,14)</td>
<td>8.4, 13.6</td>
<td>6-17</td>
<td>15.8 ± 2.8 (13.8,17.5)</td>
<td>13-19</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>12.6 ± 3.2 (10.8,14)</td>
<td>10.4, 14.8</td>
<td>8-17</td>
<td>19 ± 3.2 (17.3,21.3)</td>
<td>15.9, 22.1</td>
</tr>
<tr>
<td><strong>Timed 1 minute sit to stand (repetitions)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>6</td>
<td>22.5 ± 4.9 (19.3,22.8)</td>
<td>18.6,26.4</td>
<td>19-32</td>
<td>20.8 ± 9 (16.3,21)</td>
<td>14.5, 27</td>
</tr>
<tr>
<td>T1</td>
<td>2</td>
<td>26 ± 8.5 (23,29)</td>
<td>14.2, 37.8</td>
<td>20-32</td>
<td>23.4 ± 8.2 (19.8,25.8)</td>
<td>17.7, 29</td>
</tr>
<tr>
<td>T2</td>
<td>2</td>
<td>27.5 ± 6.4 (25.3,29.8)</td>
<td>18.7, 36.3</td>
<td>23-32</td>
<td>16.5 ± 9.4 (15,20.5)</td>
<td>7.3, 25.8</td>
</tr>
<tr>
<td>T3</td>
<td>3</td>
<td>24 ± 5.3 (22,27)</td>
<td>10, 30</td>
<td>18-28</td>
<td>28.9 ± 9.6 (21,37)</td>
<td>22.6, 35.2</td>
</tr>
<tr>
<td><strong>Calculated 1 minute sit to stand (repetitions)</strong></td>
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</tr>
<tr>
<td>T0</td>
<td>26</td>
<td>25.7 ± 7.3 (20.5,31)</td>
<td>22.8, 28.5</td>
<td>12-43</td>
<td>20.7 ± 9.8 (15,25.5)</td>
<td>16.6, 24.7</td>
</tr>
<tr>
<td>T1</td>
<td>17</td>
<td>25.8 ± 7 (22,29)</td>
<td>22.5, 29.1</td>
<td>14-43</td>
<td>28.1 ± 10.3 (20.3,33)</td>
<td>22.7, 33.4</td>
</tr>
<tr>
<td>T2</td>
<td>11</td>
<td>23.3 ± 8 (17,30.5)</td>
<td>22, 28.3</td>
<td>12-35</td>
<td>24.5 ± 11.2 (19,30.5)</td>
<td>16.8, 32.2</td>
</tr>
<tr>
<td>T3</td>
<td>11</td>
<td>25.3 ± 6.2 (21,27.5)</td>
<td>21.6, 28.9</td>
<td>16-35</td>
<td>32.1 ± 9.9 (23,37)</td>
<td>26.7, 37.4</td>
</tr>
</tbody>
</table>

Appendix H Table 1 Raw scores for 30 second and 1 minute timed sit to stand test protocols and calculated 1 minute sit to stand per group at each timepoint
| Timepoint  | Control |  |  | Intervention |  |  |
|------------|---------|  |  |  |  |  |
|            | Mean estimate ± SE | 95% CI | Mean estimate ± SE | 95% CI | Between group difference ± SE (Intervention-Control) |
| Calculated 1 minute sit to stand (repetitions) | T0 | 25.7 ± 1.6 | 22.5, 28.9 | 20.7 ± 1.7 | 17.2, 24.1 | -5 ± 2.4 |
|            | T1 | 26 ± 1.8 | 22.4, 29.5 | 26.5 ± 1.9 | 22.7, 30.4 | 0.6 ± 2.7 |
|            | T2 | 22.2 ± 2 | 18.3, 26.2 | 21.6 ± 2.2 | 17.2, 26.1 | -0.6 ± 3.1 |
|            | T3 | 26.6 ± 2 | 22.6, 30.5 | 30.4 ± 2 | 26.5, 34.3 | 3.8 ± 2.9 |

Appendix H Table 2 [Unadjusted model] Mean estimates ± standard error (SE) and between-group contrasts for calculated 1 minute sit to stand scores (excluding time from baseline to ASCT as a covariate)

| Timepoint  | Control (n=8) |  |  | Intervention (n=4) |  |  |
|------------|---------------|  |  |  |  |  |
|            | Mean ±SD | Median (IQR) | 95% CI | Range | Mean ±SD | Median (IQR) | 95% CI | Range |
| Hand grip strength (kg) | T0 | 29.5 ± 8.7 | 29.3 (23.6,36.6) | 23.5, 35.5 | 17.3-40.7 | 26.3 ± 13.2 | 27.8 (22.2,31.9) | 13.3, 39.2 | 8.7-40.7 |
|            | T1 | 27.7 ± 7.9 | 28.7 (21.3,32.1) | 22.2, 33.2 | 17-38.3 | 26.4 ± 9.7 | 23 (21.8,27.7) | 16.9, 35.9 | 19-40.7 |
|            | T2 | 26 ±8.1 | 24.7 (21.8,30) | 20.4, 31.7 | 16.3-38.7 | 30.1 ± 9.6 | 29.5 (24.8,34.8) | 20.7, 39.5 | 19.3-42 |
|            | T3 | 28.5 ± 7.3 | 28.5 (26.2,34) | 23.4, 33.6 | 15.3-37.7 | 27.9 ± 8.9 | 24.7 (23.6,29) | 19.2, 36.6 | 21.3-41 |

Appendix H Table 3 Sub analysis of hand grip strength (dominant hand) of participants who completed an assessment at all timepoints
### Appendix H Table 4 Average daily sit to stands taken and overall activity score in metabolic equivalent task hours per day from activPAL accelerometers

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Control N</th>
<th>Median (IQR)</th>
<th>Range</th>
<th>Intervention N</th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sit to stands (counts)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>23</td>
<td>42 (39,51)</td>
<td>24-81</td>
<td>20</td>
<td>45 (41-53.8)</td>
<td>21-73</td>
</tr>
<tr>
<td>T1</td>
<td>11</td>
<td>45 (39.5,51.5)</td>
<td>29-62</td>
<td>8</td>
<td>50 (40,60.5)</td>
<td>34-79</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
<td>45.5 (38.3,50)</td>
<td>31-65</td>
<td>5</td>
<td>49 (32,57)</td>
<td>32-67</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>49 (43,54.3)</td>
<td>31-58</td>
<td>4</td>
<td>53.5 (50,56.8)</td>
<td>41-65</td>
</tr>
</tbody>
</table>

| **Activity score (MET.hours)** | | | | | | |
| T0 | 23 | 33.4 (32.6,34.4) | 31.6-36.4 | 20 | 32.5 (31.6,33.6) | 30.6-38.9 |
| T1 | 11 | 31.5 (30.9,32) | 30.6-32.5 | 8 | 32.2 (31.3,32.9) | 31.3-33.4 |
| T2 | 10 | 31.6 (31.1,31.8) | 30.6-32.7 | 5 | 32.4 (31.3,32.4) | 30.4-34 |
| T3 | 8 | 32.9 (32.5,33.6) | 31.1-35.1 | 4 | 34.1 (33.1,35.6) | 31.4-38.6 |

### Appendix H Table 5 Sub analysis step count and time in stepping from activPAL accelerometers for participants who provided data at both T0 and T3 timepoints

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Control N</th>
<th>Median (IQR)</th>
<th>Range</th>
<th>Intervention N</th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step count</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T0</td>
<td>8</td>
<td>9089.5 (7466.8,10108.8)</td>
<td>3406-12634</td>
<td>4</td>
<td>8432 (6362,12428.8)</td>
<td>2876-21695</td>
</tr>
<tr>
<td>T1</td>
<td>7</td>
<td>3379 (2573.5,4130)</td>
<td>1403-4798</td>
<td>4</td>
<td>6700 (5492.8,7557.3)</td>
<td>3506-8491</td>
</tr>
<tr>
<td>T2</td>
<td>5</td>
<td>3096 (1167,3578)</td>
<td>1050-4682</td>
<td>4</td>
<td>5346 (4034.8,6545.3)</td>
<td>710-9534</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>6200.5 (5151.8,8150.5)</td>
<td>3575-10807</td>
<td>4</td>
<td>8923.5 (7020,12331.8)</td>
<td>2856-21010</td>
</tr>
</tbody>
</table>

| **Stepping time (minutes)** | | | | | | |
| T0 | 8 | 105.1 (90.7,113) | 56.6-137.1 | 4 | 119.4 (86,159.6) | 40.3-225.6 |
| T1 | 7 | 40.5 (32.9,50.1) | 17.1-56.5 | 4 | 86.2 (67.6,99.9) | 44.2-108.6 |
| T2 | 5 | 39.4 (17.1,46.8) | 16.2-66.6 | 4 | 79.7 (59.7,89) | 11.1-105.3 |
| T3 | 8 | 77.5 (71,88.9) | 44.9-119 | 4 | 124.9 (92.1,157.4) | 37.4-211.9 |
Appendix H Figure 1 Scatterplot of time between baseline and ASCT in days (x-axis) and change in self-efficacy exercise score between T0 and T1 for each group

Appendix H Table 6 Raw scores for SEE outcome measure of self-efficacy for exercise at each timepoint (all participants)
### Appendix H Table 7 [Unadjusted model] Mean estimates ± standard error (SE) and between-group contrasts for SEE outcome measure of self-efficacy for exercise (excluding time from baseline to ASCT as a covariate)

<table>
<thead>
<tr>
<th>Self-efficacy exercise score</th>
<th>Control Mean estimate ± SE</th>
<th>95% CI</th>
<th>Intervenion Mean estimate ± SE</th>
<th>95% CI</th>
<th>Between group difference ± SE (Intervention-Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>6.6 ± 0.5</td>
<td>5.6, 7.6</td>
<td>5.7 ± 0.5</td>
<td>4.6, 6.8</td>
<td>-0.9 ± 0.8</td>
</tr>
<tr>
<td>T1</td>
<td>6.0 ± 0.6</td>
<td>4.9, 7.2</td>
<td>6.7 ± 0.6</td>
<td>5.4, 7.9</td>
<td>+0.6 ± 0.9</td>
</tr>
<tr>
<td>T2</td>
<td>5.3 ± 0.6</td>
<td>4.2, 6.5</td>
<td>4.1 ± 0.7</td>
<td>2.7, 5.6</td>
<td>-1.2 ± 1.0</td>
</tr>
<tr>
<td>T3</td>
<td>5.8 ± 0.6</td>
<td>4.6, 6.9</td>
<td>6.4 ± 0.6</td>
<td>5.1, 7.6</td>
<td>+0.6 ± 0.9</td>
</tr>
</tbody>
</table>
Appendix I. Chapter 8 additional results tables and figures: patient reported outcome measures

Appendix I Figure 1 Scatterplot of time between baseline and ASCT in days (x-axis) and change in FACT-F fatigue score between T0 and T1 for each group.

Appendix I Table 1 [Raw scores] Group means, standard deviation (SD) with 95% confidence intervals (CI) for the means, and medians (IQR) with range for FACT-F outcome measure of cancer-related fatigue at each timepoint (all participants)
### Appendix I Table 2 [Unadjusted model] Mean estimates ± standard error (SE) and between-group contrasts for FACT-F outcome measure of cancer-related fatigue (excluding time from baseline to ASCT as a covariate)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Between group difference ± SE (Intervention-Control)</th>
</tr>
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<tbody>
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<td>Mean estimate ± SE</td>
<td>95% CI</td>
<td>Mean estimate ± SE</td>
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<td>Fatigue FACT-F (0-52)</td>
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<td>14.4, 24.2</td>
<td>19.0 ± 2.9</td>
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<tr>
<td>T3</td>
<td>39.8 ± 2.4</td>
<td>35.4, 44.6</td>
<td>40.2 ± 2.7</td>
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### Appendix I Figure 2 Scatterplot of time between baseline and ASCT in days (x-axis) and change in EQ5D Visual Analogue Scale (VAS) score between T0 and T1 for each group
### Unadjusted models

Mean estimates ± standard error (SE) and between-group contrasts quality of life outcome measures (model excluded time from T0 to ASCT as a covariate)

<table>
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<tr>
<th></th>
<th>Control Mean estimate ± SE</th>
<th>95% CI</th>
<th>Intervention Mean estimate ± SE</th>
<th>95% CI</th>
<th>Between group difference ± SE (Intervention-Control)</th>
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<tr>
<td><strong>EQ-5D-5L Visual Analogue Scale (VAS) (0-100)</strong></td>
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</tr>
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<td>60, 73.5</td>
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<tr>
<td>T1</td>
<td>67.8 ± 3.6</td>
<td>60.7, 74.9</td>
<td>69.3 ± 4.1</td>
<td>61.1, 77.5</td>
<td>1.5 ± 5.6</td>
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<td>52.3 ± 4.6</td>
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<td>67.6, 82.5</td>
<td>78 ± 4.1</td>
<td>69.8, 86.1</td>
<td>2.9 ± 5.8</td>
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<td>68.8, 79.3</td>
<td>72.4 ± 2.9</td>
<td>66.6, 78.1</td>
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Continued next page
Appendix I Table 4 [Raw scores] Group means, standard deviation (SD) with 95% confidence intervals (CI) for the means, and medians (IQR) with range for quality of life outcome measures at each timepoint (all participants)

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<th>T3</th>
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<td>EORTC QLQ-C30 Global QOL (0-100)</td>
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<td>15</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>68.8 ± 21.6</td>
<td>73.3 ± 12.7</td>
<td>33.8 ± 17.3</td>
<td>69.0 ± 17.3</td>
</tr>
<tr>
<td></td>
<td>75 (64.6,83.3)</td>
<td>75 (66.7,83.3)</td>
<td>33.3 (16.7,47.9)</td>
<td>66.7 (58.3,83.3)</td>
</tr>
<tr>
<td></td>
<td>59.3, 78.2</td>
<td>66.9, 79.8</td>
<td>25.8, 41.8</td>
<td>61.0, 77.0</td>
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<td></td>
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<td>16.7-75</td>
<td>33.3-100</td>
</tr>
<tr>
<td>T2</td>
<td>18</td>
<td>12</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>33.8 ± 17.3</td>
<td>28.5 ± 17.6</td>
<td>33.8 ± 17.3</td>
<td>69.0 ± 17.3</td>
</tr>
<tr>
<td></td>
<td>33.3 (16.7,47.9)</td>
<td>25 (22.9,33.3)</td>
<td>33.3 (16.7,47.9)</td>
<td>66.7 (58.3,83.3)</td>
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<td>25.8, 41.8</td>
<td>61.0, 77.0</td>
</tr>
<tr>
<td></td>
<td>16.7-75</td>
<td>0.0-66.7</td>
<td>16.7-75</td>
<td>33.3-100</td>
</tr>
<tr>
<td>T3</td>
<td>18</td>
<td>15</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>69.0 ± 17.3</td>
<td>70 ± 18.0</td>
<td>69.0 ± 17.3</td>
<td>82.5 ± 11.2</td>
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<td>66.7 (58.3,83.3)</td>
<td>75 (54.2,83.3)</td>
<td>66.7 (58.3,83.3)</td>
<td>84.7 (78,88.6)</td>
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<tr>
<td></td>
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<td>61.0, 77.0</td>
<td>77.3, 87.7</td>
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<tr>
<td></td>
<td>33.3-100</td>
<td>41.7-100</td>
<td>33.3-100</td>
<td>56.4-97.9</td>
</tr>
</tbody>
</table>

Appendix I Figure 3 Scatterplot of time between baseline and ASCT in days (x-axis) and change in EORTC QLQ-C30 summary score between T0 and T1 for each group
Appendix J. Interview schedule for completers interview study

Myeloma Transplant Exercise Study
Interview Schedule – T3 Trial Participants

This guide is to ensure key aspects are covered during the interview. However a respondent-sensitive approach should be taken, allowing deviation from question order and raising additional issues if desired.

Interviewers should be mindful of the sensitive subject of the interview.

Introduction
Introduce yourself and explain purpose of the interview: to explore the participant’s experience of the myeloma intervention and their experience of being a participant in the trial. Ask permission to record the conversation. Assure confidentiality and ask participant to be as open and honest as they can.

Motivational factors
• What was your main reason for taking part in this research?
  o Probe: to improve wellbeing or fitness/to help contribute to research/to receive additional monitoring by Health Professionals?

Demotivating factors
• Was there anything that made you think twice about taking part in the research?
  o Probe: personal concerns – practicalities/factors relating to your illness or stem cell transplant treatment?
  o Probe: Trial concerns – factors relating to the research itself?

General trial feedback
• How did you feel about being asked to take part in this research initially, i.e. on referral for stem cell transplant treatment?
  o Prompt: pleased/confused/surprised/annoyed/excited

Physical Activity Prior to and during Myeloma Treatment
• Can you tell me about your physical activity levels before you started your treatment for myeloma and how this has changed during treatment?
  o Probe: occupational/recreational/sporting activities
  o Probe: How often, how long
  o Probe: What caused the person to change, if change mentioned

• Did you receive any advice or support to maintain your physical activity when you started your treatment for myeloma?
  o Probe: from whom? What advice? Did you follow it?

• Thinking specifically about preparing for your stem cell transplant. Did you receive any information, other than from the researchers, about physical activity or exercise while undergoing a transplant?
  o Probe: Did the Clinical Nurse Specialists or doctors provide support and information?
  o Probe: Did you seek or look for information?
Usual Care Group Participant:
- You have already spoken about how you felt about your allocation (above), now can you tell me about your physical activity behaviour after enrolling in the study and learning you were in the usual care group?
  - How did you feel physically during your transplant admission and did you require any rehabilitation or physical support in hospital?
    - Probe: did your symptoms affect your daily routine or function?
    - Probe: How did what you described affect you, how did you feel?
- How has your recovery been since leaving hospital after your transplant?
  - Probe: levels of symptoms/function/physical activity
  - Probe: accessing support/advice/input for any concerns raised

Exercise Group Participant:
- Before your transplant, was the travel to your gym sessions ok?
- How did you feel about the frequency of gym sessions?
  - Prompt: was it useful to attend the gym as often as you did? Or were the session too frequent for your liking?
  - If so how often would you have liked to have them?
- What did you think of the exercise you were prescribed?
  - Probe: did you feel they were either too arduous, or not arduous enough?
  - did you have any concerns or worries?
- Were you able to carry out the prescribed exercises ok in the gym?
- How about in hospital?
- How about at home?
  - Probe: Were you able to exercise to the same intensity/level as in the gym?
  - If not, why do you think this would be?
- When you weren’t able to carry out the exercises at any stage, why was this?
- How did you feel about the level of contact you had with the Physio during your hospital admission and after discharge?
  - Prompt: would you have liked any more or less contact? If so why?
- How did doing the exercise make you feel while you were awaiting your transplant?
- How did doing the exercise make you feel on the whole?
  - Prompt: enjoyable/happy/energised/tired/increased levels of pain
- How did you find being in a group with other Myeloma patients, when in the gym?
  - Prompt: did it result in extra support/reduce contact time with the Physio?
- What did you think of the behaviour change support provided?
- **Probe:** have you used any of them?

- How useful would you say the behaviour change support was in terms of helping you change your behaviours?
  - **Probe:** which elements were most helpful. E.g. log book, goal setting, rewards? which were least helpful?

- What did you think of the log books?
  - **Probe:** did you fill it out?
    - did you use it to reflect on how you’d done over the weeks?
    - was there anything about it you would change?

- Overall, do you think exercising and having support to be active before and during your transplant affected your recovery after discharge?
  - **Probe:** What do you think was most important? How did it make you feel?
  - **Probe:** Was the recovery period after hospital what you expected?

**Assessments**

- How were the assessments?
  - How did you find the length of assessments?
  - What did you think of the questionnaires?

- Were you happy with the tests and measures that were carried out (e.g. walking test, muscle strength, wearing the accelerometer)?
  - **Probe:** was there anything you felt should have been done differently?
    - was there anything you were uncomfortable with?

- How did you perceive the skills and knowledge of the researcher/s who saw you for your baseline and follow-up assessments?
  - **Probe:** did you like their approach?
    - how was their manner?

**General**

- Can you tell me about the support you received before and during and after your transplant?
  - From health professionals
  - From family/friends
  - **Prompt:** was the support practical, emotional or both?
  - **Probe:** if yes, how important was that to you?
    - if no, do you think this could have helped?

- Can you tell me how you felt, overall, about being a participant in this research?
  - **Probe:** what were the benefits of taking part?
    - What were the disadvantages?

- Do you think that you have learned anything as a result of taking part in the trial?
  - **Probe:** do you think you have gained anything?

- Would you recommend taking part to other people who have myeloma or are having a transplant?
• Is there anything you think we should have done differently?

• Is there anything else you would like to say about the trial, that we’ve not already talked about?

Concluding comments and thanks
Thank the participant for their time today and ongoing and let them know where they can contact you in the future if they do have any additional comments.
Physical Activity During and After Haematological Cancer Treatment: A Cross-Sectional Survey of Haematology Healthcare Professionals in the United Kingdom

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Kwee Yong3
Gita Ramdharry2
Abigail Fisher4

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2Research Department of Haematology, Cancer Institute, University College London, London, UK;
3Queen Square Centre for Neurovascular Disease, University College London, London, UK;
4Research Department of Behavioural Science and Health, University College London, London, UK.

Purpose: Health professionals’ (HPs) knowledge of recommended guidelines for physical activity (PA) is thought to influence the advice they provide to their patients. Little is known about the knowledge or provision of PA advice by HPs working with haematological cancer patients. This study examined awareness of PA guidance, beliefs and practices in provision of advice given by UK HPs working with haematological cancer patients.

Methods: Online survey including questions on awareness of PA guidance, levels of agreement/disagreement with statements related to PA in haematological cancer and reported provision of advice in practice. Open text responses sought detail regarding guidance knowledge and examples of advice given by respondents. Predictors of familiarity with guidance and provision of advice were examined.

Results: Complete responses were received from 156 professionals, mostly nurses, allied HPs and doctors. Many (37%) reported knowing relevant guidance and nearly half (48.6%) reported routinely giving PA advice. Nurses and allied HPs give advice to more patients than doctors and knowledge of guidelines among doctors was poor.

Conclusion: Beliefs of haematology professionals regarding the role of PA during and after treatment for haematological cancers were generally positive. Those reporting familiarity with guidance were more likely to give advice. Mismatch exists between guidelines and advice given by professionals to their patients. Increasing knowledge of guidelines among HPs, including nurses, may lead to increased provision of PA advice and promotion of PA to more of their patients. HPs education in haematology on PA guidance tailored to professional group is needed.

Keywords: physical activity, haematological cancer, health professional, guidelines, survey

Introduction
Five-year survival rates for haematological cancers are estimated to be 69% and 250,000 people are currently living with haematological cancer in the United Kingdom (UK). Management can include surveillance only, chemotherapy, immunotherapy, stem cell transplantation and radiotherapy. Many patients require prolonged treatment with phases of therapy using a combination of different modalities, resulting in an array of morbidity and side-effects perpetuated by toxicities and deconditioning. Therefore, there is urgent need for supportive strategies adjacent to anti-cancer treatments to assist improvements in treatment.
responses. The positive role of physical activity (PA) interventions across the cancer continuum has been demonstrated. **Meta-analyses of randomised controlled trials have concluded that exercise interventions are safe, feasible and beneficial for haematological cancer patients receiving intensive systemic treatment and may improve QOL, physical function and reduce fatigue, particularly for allo-genic SCT recipients at discharge from hospital when exercise was introduced before or during admission.** Despite this PA levels among people living with and beyond cancer during and after treatment are known to remain below recommended levels.** General promotion of positive messaging and endorsement of PA by healthcare professionals (HCPs) could be influential in encouraging more people living with haematological cancer to be physically active. HCPs have a key role in providing evidence-based information to people living with and beyond cancer regarding their condition, treatment options and promoting healthy lifestyles during and after cancer treatment.** Individuals living with and beyond cancer have reported that they would value receiving PA advice from their HCPs, particularly clinical nurse specialists and doctors as part of treatment and would trust that advice to be safe and accurate.** Perceived barriers for HCPs to provide advice regarding lifestyle behaviours such as PA include lack of clear guidance, a belief that they are not the correct person to give advice and lack of time.** However, HCPs may lack knowledge of public health recommendations for positive lifestyle behaviours, resulting in a reduced likelihood of providing such advice or recommendations to patients.** A study of 1013 UK primary care physicians found low familiarity with PA guidance and that those unfamiliar with the guidance were less confident when raising the topic of PA and significantly less likely to advise PA, particularly to patients with comorbidities, such as cancer.** In contrast, another UK-based study reported high levels of awareness of guidance and initiation of PA conversations among physiotherapists. When questioned on the specific content of PA guidelines however, their knowledge of all aspects was poor and this discrepancy in knowledge may impact on the quality of advice delivered in practice.** Although some HCPs working within the cancer setting do recognise the importance of discussing PA with their patients, their advice may often not be aligned with published guidelines either. In a survey of Irish oncology professionals, respondents most commonly reported providing PA advice verbally, however less than half of respondents provided recommendations in line with current guidance.** The emerging research surrounding this important topic has been carried out on samples of HCPs predominately working in the areas of solid tumours, such as breast, colorectal and prostate cancer, where stronger evidence for exercise during treatment and survivorship exists. Information is lacking regarding the understanding of HCPs working in haematological cancer.

Therefore, the purpose of this study was threefold; i) to examine awareness of PA recommendations, ii) explore beliefs surrounding the role of PA during and after treatment and iii) to understand practices in provision of advice given to patients by HCPs working with people living with and beyond haematological cancer in the UK. Predictors of familiarity with PA guidance and provision of advice to patients were also examined.

**Materials and Methods**

**Participants and Recruitment**

Data was obtained via an anonymous online survey using the Opinio platform. HCPs working in a UK cancer setting in roles that had direct contact with patients with a haematological cancer diagnosis were eligible. Responses were sought from doctors, nurses, allied health professionals (AHPs), pharmacists, research practitioners and support/auxiliary health care staff. The study was approved by the University College London (UCL) Research Ethics Committee (reference 17/E3/001) and conducted in accordance with the principles stated in the Declaration of Helsinki. Participants were informed of the aims of the study and that they could participate anonymously, prior to providing informed consent and accessing the survey.

A number of professional organisations were approached to distribute the survey to their members. Seven agreed, including the British Haematology Society, the UK Oncology Nursing Society, the Association of Chartered Physiotherapists in Oncology and Palliative Care, the British Dietetic Association Oncology Group, the Society of Radiographers, the British Oncology Pharmacy Association and the European Society for Blood and Marrow Transplantation Nurses and AHPs Group. An introduction and online link to the survey was sent to each
organisation, who either forwarded the survey to their members via email, placed it on their websites or shared it on social media. The survey link was also shared by the research team on social media platforms. The survey link was open for 200 days between April and October 2019.

Survey Development and Piloting
The survey was based on previously published studies of HPs conducted in the UK and Ireland, with incorporation of questions regarding agreement/disagreement with statements regarding PA from another HP’s survey. Further questions were developed specifically for this study and all questions were adapted for haematology-based workforce by the authors.

The survey was piloted in paper format and tested on three HPs working at a local NHS hospital. These participants were asked to complete the survey questions whilst “thinking aloud” to gather feedback on the appropriateness and understanding of the questions. Finally, an online version of the survey was piloted using the Opinio platform with a small varied sample of HPs from a local NHS hospital, including AHPs, a doctor, and a nurse, and research colleagues.

Measures
Demographics
Demographic questions related to age, gender and professional group. Professional questions explored time in current role, haematological cancer diagnoses of patients in their care, clinical setting type and location by region. Respondent’s own self-reported PA was assessed with the questions: “On average, how many days per week did you engage in moderate to strenuous PA (like a brisk walk or run)?” and “How long is your average session of moderate to strenuous PA in minutes (i.e., a single running/walking/exercise session)?”

Awareness of PA Guidelines for People Living with and Beyond Cancer
HPs familiarity with guidelines was asked with the question: “Are you familiar with any PA or exercise guidelines that are relevant for cancer patients?” If respondents selected “yes, I know of relevant guidelines,” they were routed to an open text question: “Please give some details of the PA guidance that you know? (eg. the name of the guidelines, who produced them or any detail you can recall).”

Beliefs About Importance of PA During and After Treatment
HPs were asked to share their level of agreement or disagreement with a number of statements related to PA in the context of people living with haematological cancer. These statements were presented in two matrix style questions: one asking HPs to respond to the statements while considering patients during treatment for haematological cancer, the second asked them to respond to the statements while considering patients after completion of treatment for their haematological cancer.

Provision of PA Advice
In relation to HPs giving advice to their patients, HPs were asked the question: “Do you give advice regarding PA to your patients with blood cancer?” The proportion of patients they give advice to and the timing of advice were assessed with the following questions: “Can you estimate how many of your patients with blood cancer you give advice about PA to?” “When do you commonly give advice about PA to your patients with blood cancer?”

Examples of HP PA Advice/information
To gather detail on the information that HPs provide to their patients, survey participants were asked, “Please give an example of information or advice you give about PA to patients with blood cancer?”. This open text question had an unlimited free textbox response and could be skipped without providing a response.

Analyses
Survey data was downloaded from Opinio into the statistical package SPSS (version 25.0. Armonk, NY: IBM Corp.) for analysis. Descriptive statistics were generated to describe proportions of respondents overall and by professional group, demographics, professional setting, awareness of PA guidelines and provision of PA advice. Due to the limited numbers of respondents across professions, some underrepresented groups were categorised as “other” (including research staff, support workers) and statistical analyses focused on the three largest professional groups who responded, nurses, AHPs and medical professions.

Predictors of familiarity of PA guidance were examined using an ordinal logistic regression including HP familiarity with guidelines, professional group, time in current role and HPs self-reported PA. Provision of advice to patients were explored using a binomial odds ratio.
logistic regression examining demographic predictors (professional group and time in role) and awareness of PA guidelines on reported proportion of patients given PA advice. For the second model the dependent variable was dichotomised into provision of advice to less or more than 50% of patients and also only included the three largest professional groups.

Responses to the open text survey questions were transferred into NVivo (version 12. QSR International Pty Ltd.) and coded line by line. To map the range and nature of open text responses a process of framework analysis was followed using five key stages: familiarisation of data, identifying a thematic framework, indexing, charting and mapping and interpretation, as outlined by Ritchie and Spencer (2002).21

Results
Respondents
The exact response rate for the survey is not known as the online link was shared by distributing organisations. The survey link was accessed 244 times. Two hundred and six (94%) completed all demographics questions and 105 (89.5%) completed at least one question related to the aims of the study. Of these, 156 (71%) completed the whole survey. The survey had at least three responses from each region of England and at least six from each of the UK home countries (England, Scotland, Wales and Northern Ireland), the greatest number of respondents were from the London region (31%, n=60). Most respondents (59%, n=115) worked in a specialist oncology/hematology centre treating haematological cancers and carrying out stem cell transplantation. The characteristics of the respondents are shown in Tables 1 and 2. Thirty-four per cent (n=67) of respondents were nurses and thirty-one per cent (n=61) were AHPs. The mean total self-reported moderate to strenuous PA per week of the survey respondents who completed the questions related to own PA was 150.74 (±115.42) minutes per week. 44.2% of respondents who provided an answer reported engaging in 150 minutes or more of moderate or strenuous PA per week on average.

Awareness of PA Guidelines
Thirty-one per cent (n=60) of respondents know relevant PA guidance. Thirty-seven per cent (n=72) reported being aware there was guidance but did not know what it was and 33% (n=64) were not aware of any. Awareness of guidelines by professional group is presented in Figure 1. Differences were evident between professional groups with a higher proportion of medical respondents not aware of any guidelines and no medical respondents reported knowing relevant PA guidelines. A high proportion of AHPs reported knowing of relevant PA guidance.

<table>
<thead>
<tr>
<th>Table 1 Respondent Characteristics (n=196)</th>
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<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>≤25 years</td>
</tr>
<tr>
<td>26-35 years</td>
</tr>
<tr>
<td>36-45 years</td>
</tr>
<tr>
<td>46-55 years</td>
</tr>
<tr>
<td>56-65 years</td>
</tr>
<tr>
<td>% (n), n=196</td>
</tr>
<tr>
<td>6.1 (7)</td>
</tr>
<tr>
<td>17.8 (24)</td>
</tr>
<tr>
<td>37.5 (57)</td>
</tr>
<tr>
<td>19.4 (20)</td>
</tr>
<tr>
<td>2.6 (5)</td>
</tr>
</tbody>
</table>

| Sex                                      |
| Male                                     |
| Female                                   |
| Prefer not to say                        |
| % (n), n=196                              |
| 22.3 (46)                                 |
| 77.7 (150)                                |
| 0.5 (1)                                   |

| Professional Group                      |
| Nurse                                    |
| Clinical nurse specialist                |
| Matron/Lead nurse                       |
| Inpatient/ward nurse                     |
| Outpatient/day care nurse                |
| Allied health professional               |
| Physiotherapist                          |
| Occupational Therapist                   |
| Dietitian                                |
| Therapeutic Radiographer                 |
| Speech and Language Therapist            |
| Medical                                  |
| Pharmacist                               |
| Advanced clinical practitioner           |
| Others                                   |
| % (n), n=196                              |
| 34.2 (67)                                 |
| 18.3 (37)                                 |
| 1 (2)                                     |
| 11.2 (27)                                 |
| 3 (6)                                     |
| 31.1 (61)                                 |
| 19.4 (38)                                 |
| 2.6 (5)                                   |
| 5.6 (11)                                  |
| 3.1 (6)                                   |
| 0.5 (1)                                   |
| 16.9 (33)                                 |
| 6.6 (13)                                  |
| 5.6 (11)                                  |
| 5.6 (11)                                  |

| Time working in current role/career stage|
| 0-5 years                                 |
| 6 years or more                          |
| % (n), n=196                              |
| 51.5 (101)                                |
| 48.5 (95)                                 |

| Self-reported Physical Activity           |
| Meeting guideline (>150 mins/week)       |
| Not meeting guideline (<50 mins/week)    |
| Total self-reported moderate or strenuous physical activity per weak (minutes) |
| Missing                                  |
| % (n), n=196                              |
| 35.2 (69)                                 |
| 44.8 (87)                                 |
| 150.74 (±115.42)                          |
| 20.4 (40)                                 |
Table 2: Professional Setting and Patient Groups (%=96)

<table>
<thead>
<tr>
<th>Professional Setting</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of their patients who have a blood cancer diagnosis</td>
<td>63.4 (116)</td>
</tr>
<tr>
<td>More than 50%</td>
<td>30.6 (60)</td>
</tr>
<tr>
<td>Less than 50%</td>
<td>6.1 (12)</td>
</tr>
<tr>
<td>Patient diagnosed care for</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>81.1 (139)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>78.3 (133)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>77.0 (51)</td>
</tr>
<tr>
<td>Myelodysplastic Syndromes</td>
<td>30.9 (8)</td>
</tr>
<tr>
<td>Myelodysplastic Neoplasms</td>
<td>37.8 (74)</td>
</tr>
<tr>
<td>All of the above diagnoses</td>
<td>32.1 (63)</td>
</tr>
<tr>
<td>Other</td>
<td>7.4 (14)</td>
</tr>
<tr>
<td>Clinical Setting</td>
<td></td>
</tr>
<tr>
<td>Specialist oncology/haematology centre treating blood cancer &amp; carrying out stem cell transplant</td>
<td>38.7 (115)</td>
</tr>
<tr>
<td>District general hospital treating blood cancer that does not carry out stem cell transplant</td>
<td>15.8 (31)</td>
</tr>
<tr>
<td>Hospita</td>
<td>1.5 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>3.6 (7)</td>
</tr>
<tr>
<td>Missing</td>
<td>30.4 (48)</td>
</tr>
<tr>
<td>Regional Affiliation</td>
<td></td>
</tr>
<tr>
<td>London</td>
<td>30.4 (60)</td>
</tr>
<tr>
<td>South East England</td>
<td>2.9 (5)</td>
</tr>
<tr>
<td>South West England</td>
<td>6.1 (12)</td>
</tr>
<tr>
<td>North West England</td>
<td>6.6 (9)</td>
</tr>
<tr>
<td>East of England</td>
<td>6.1 (9)</td>
</tr>
<tr>
<td>East Midlands</td>
<td>3.6 (7)</td>
</tr>
<tr>
<td>West Midlands</td>
<td>3.1 (6)</td>
</tr>
<tr>
<td>North East England</td>
<td>3.6 (5)</td>
</tr>
<tr>
<td>Yorkshire &amp; Humbershire</td>
<td>1.5 (3)</td>
</tr>
<tr>
<td>Scotland</td>
<td>4.6 (9)</td>
</tr>
<tr>
<td>Wales</td>
<td>3.1 (6)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>3.1 (6)</td>
</tr>
<tr>
<td>Missing</td>
<td>30.4 (48)</td>
</tr>
</tbody>
</table>

Notes: Respondents were instructed to select all that applied from the list.

Beliefs About Role of PA During and After Completion of Treatment

Most respondents agreed that patients with haematological cancer should be encouraged to be physically active, that regular exercise can alleviate symptoms of fatigue, can improve QoL and that structured exercise should be part of the treatment pathway for patients during treatment for haematological cancer. When questioned about confidence in making recommendations to patients, overall more than half of all respondents disagreed with not feeling confident (57.6%) (Figure 2). Among the three largest professional groups only 34.4% of medical professionals disagreed or strongly disagreed with the statement, compared to 71.7% of AHPs and 60.7% of nursing professionals. Professional group differences were also evident regarding knowing where or who to refer patients who require support to become more active, 71.2% of nurses and 69.6% of AHPs agreed or strongly agreed to this statement compared to 21.5% of medical professionals.

Similar patterns of agreement were seen for statements regarding the role of PA for patients with haematological cancer on completion of treatment (Figure 3). Slightly increased proportions of medical
professionals disagreed with not feeling confident making recommendations to patients that asked about PA after treatment (45.2%) and more medical professionals agreed to knowing where or who to refer patients to for support to be more active after treatment (32.3%) but these numbers remain low compared to nurses and AHPs.

Table 3: Health Professionals (Nursing, AHIP, Medical) Predictors of Familiarity with Physical Activity Guidelines (n=120)

<table>
<thead>
<tr>
<th>Professional group</th>
<th>OR (95% CI)</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nursing</td>
<td>5.04 (2.20-11.62)</td>
<td>0.001</td>
</tr>
<tr>
<td>AHIP</td>
<td>22.00 (6.41-70.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time in role</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6-12 years</td>
<td>1.64 (0.52-5.31)</td>
<td>0.114</td>
</tr>
<tr>
<td>13+ years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HP self-reported PA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;1500 min PA/week</td>
<td>0.00 (0.00-1.42)</td>
<td>0.551</td>
</tr>
<tr>
<td>&gt;1500 min PA/week</td>
<td>1.00 (0.79-1.26)</td>
<td>0.991</td>
</tr>
</tbody>
</table>

Abbreviations: AHIP, allied health professional; CI, confidence interval; HP, health professional; PA, physical activity.

Provision of PA Advice to People Living with and Beyond Haematological Cancer
HP Provision of Advice
48.9% (n=65) of respondents who answered questions related to provision of advice reported routinely giving advice regarding PA to most of their patients. 26.3% (n=46) respondents reported that they only provide advice if their patients request information on PA. A small number of respondents reported only providing PA advice to patients they think would benefit from it (10.9%, n=19) and the most commonly cited reasons were if patients were fatigued, deconditioned or frail, have comorbidities that affect regular PA and/or have treatment-related symptoms (Table 4).

Differences between professional groups can be seen in Figure 4. Majority of AHIPs and nurses (50%) reported providing advice routinely to most of their patients, whereas the majority (51.5%) of medical respondents reported only giving advice when patients requested information about PA. Pharmacy professionals most commonly reported not giving advice to their patients (51.8%).

When questioned on the proportion of patients that HPs give PA advice to, overall 37.9% (n=65) reported they provide advice to less than 25% of their patients. 20.9% (n=44) respondents reported giving advice to greater than
Considering patients during treatment for blood cancer:

- Patients should be encouraged to be physically active
- Regular exercise can alleviate symptoms of fatigue for patients
- Regular exercise can improve QOL for patients
- Structured exercise should be part of the treatment pathway for patients
- There is not enough evidence for HPs to promote exercise to patients
- I do not feel confident making recommendations to patients who ask about PA
- I know whom or whom to refer patients who require support to become more physically active...

Strongly Disagree or Disagree □ Neither disagree or agree □ Strongly Agree or Agree □ I don't know

Figure 2: Statements regarding role of PA during treatment for blood cancer; all responses N=165.

75% of their patients. When separated by professional group, half of AHPs reported giving PA advice to more than 75% of their patients, nursing professionals had an even spread across all responses and the majority of medical professionals (31.7%) reported giving advice to less than 25% of their patients. Surveyed HPs reported that during treatment is when they most commonly provide PA advice to their patients (112 responses), then on completion of treatment (83 responses) and during survivorship/follow up or during maintenance treatment (both 69 responses) (Table 5).

Predictors of Provision of PA Advice by HPs

A binomial logistical regression model was used to examine the role of professional group, time in role and guideline awareness on provision of PA advice to more than 50% of patients. Respondents who reported knowing relevant PA guidelines for people living with and beyond cancer had higher odds of providing PA advice to more than 50% of their patients (OR 3.4 (95% CI 1.1–10.6), p=0.038), but there were no other significant differences among professional group (AHPs: OR 1.8 (95% CI 0.57–4.74), p=0.250), nurses: (OR 1.6 (95% CI 0.47–5.10), p=0.462) or time in role (OR 1.3 (95% CI 0.63–2.71), p=0.477).

Examples of PA Information and Advice

When asked to provide an example of information or advice they give to patients regarding PA, 116 participants provided a response to the open text question. Themes that were concluded from the analysis of open text responses indicated HPs focussed the advice they give around promotion of usual activities, sharing and emphasising the benefits of PA, using settings (inpatient, outpatient) and/or timing in treatment-based approach to advice. There was repetition of cautious or restrictive advice regarding intensity and type of PA advised and an emphasis on providing resources (eg. leaflets, booklets) and or signposting to others or other services (eg. walking groups, exercise referral). Examples of captured quotes are detailed in Table 6.

Discussion

This survey-based study explored haematology HPs’ awareness of PA recommendations, their beliefs about the role of PA and their reported provision of advice given to people...
Considering patients after completion of treatment for blood cancer:

<table>
<thead>
<tr>
<th>Statement</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients should be encouraged to be physically active</td>
<td>88.6%</td>
</tr>
<tr>
<td>Regular exercise can alleviate symptoms of fatigue for patients</td>
<td>77.9%</td>
</tr>
<tr>
<td>Regular exercise can improve QoL for patients</td>
<td>88.6%</td>
</tr>
<tr>
<td>Structured exercise should be part of survivorship/hospital care for patients</td>
<td>90.4%</td>
</tr>
<tr>
<td>There is not enough evidence for HPs to promote exercise to patients</td>
<td>22.9%</td>
</tr>
<tr>
<td>I do not feel confident making recommendations to patient who ask about PA</td>
<td>63.9%</td>
</tr>
<tr>
<td>I know where or who to refer patients who require support to become more physically active</td>
<td>74.1%</td>
</tr>
</tbody>
</table>

Table 4: "Do You Give Advice Regarding PA to Patients with Blood Cancer?"

<table>
<thead>
<tr>
<th>Advice Provided</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, routinely give advice to most patients</td>
<td>88.6%</td>
</tr>
<tr>
<td>Yes, only if patients request information regarding PA</td>
<td>26.7%</td>
</tr>
<tr>
<td>Yes, only to patients that they think would benefit from PA</td>
<td>105%</td>
</tr>
<tr>
<td>Because they are elderly</td>
<td>12%</td>
</tr>
<tr>
<td>Because they are older</td>
<td>10%</td>
</tr>
<tr>
<td>Because they have motor problems because they are frail</td>
<td>10%</td>
</tr>
<tr>
<td>Yes, only to patients that they think would benefit from regular PA</td>
<td>10%</td>
</tr>
<tr>
<td>Because they have motor problems because they are frail</td>
<td>3%</td>
</tr>
<tr>
<td>Because they are able to undertake PA</td>
<td>3%</td>
</tr>
<tr>
<td>No, do not recommend or give advice about PA to patients</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

Note: These percentages are calculated based on the number of responses.
Health Professional Provision of Advice

- No, I do not recommend or give advice about physical activity to my patients
- Yes, only if they request information regarding physical activity
- Yes, only to patients that I think would benefit from physical activity
- Yes, routinely to most of my patients

![Chart showing percentage of health professionals who provide advice about physical activity](chart)

Figure 4: Health professional provision of advice on physical activity to professional groups and sources.

Expected AHPs, which include professions that provide advice on PA and/or energy balance as part of their clinical role (eg, physiotherapists, occupational therapists, and dietitians), reported the greatest awareness of guidance related to PA. Conversely, most medical respondents reported not knowing of any guidance. Familiarity with lifestyle guidance has been found to influence provision of lifestyle advice, as was also seen in this analysis of haematology HPs, with those who reported knowledge of PA guidance at greater odds of providing advice to more than half of their patients.

Table 5: “When Do You Typically Give PA Advice to Patients with Blood Cancer?”

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>n (%)</th>
<th>Relative Frequency by Choice, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis, before commencing anti-cancer treatment</td>
<td>20.0 (37)</td>
<td>1.46</td>
</tr>
<tr>
<td>During treatment with anti-cancer treatment</td>
<td>74.2 (112)</td>
<td>28.7</td>
</tr>
<tr>
<td>On completion of anti-cancer treatment</td>
<td>56.5 (83)</td>
<td>21.3</td>
</tr>
<tr>
<td>During maintenance treatment</td>
<td>41.9 (49)</td>
<td>17.7</td>
</tr>
<tr>
<td>During survivorship/follow-up</td>
<td>41.9 (49)</td>
<td>17.7</td>
</tr>
<tr>
<td>Other anti-cancer treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Respondents were instructed to select all that applied from the list.

Although this review recommends regular moderate intensity aerobic training and/or

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Table 4: Information and Advice Given by HPs to Patients with Blood Cancer: An Analysis of Open Text Response

<table>
<thead>
<tr>
<th>Theme</th>
<th>Captured Responses</th>
</tr>
</thead>
</table>
| Promotion of usual activity                | "To continue usual activities around house to keep active, not be frightened to keep active and that it will not do them harm and keep active as far as they feel able to." Advanced Clinical Practitioner  
"Keeping active eg regular walks/pottering round garden, increase activity gradually and to tolerance." Diattan  
"I either encourage them to continue with their regular activity levels or encourage them to be more active if they currently aren’t doing anything." Diattan |
| Sharing and emphasizing benefits of recommended physical activity | "I advise them about the general benefits of exercise (CV health, bone strength, circulation, mood, balance etc.) and explain that there is evidence to suggest that exercise can help improve symptoms and side effects of treatment and it is a good way of taking control of something when you are feeling out of control." Physiotherapist  
"It is important for your physical well-being to remain active for at least 30mins each day – this can be part of your daily household tasks, putting groceries away etc. or can be a short walk but remaining active, even when you feel tired during treatment will lessen your physical de-conditioning, help your mental well-being and recovery post treatment." Inpatient Nurse |
| Setting and treatment phase-based advice    | "My advice would then be about trying to stay as active as possible during all the treatment stages to pre, during post." Matron/Lead Nurse  
"On the haematology ward, we give advice about physical activity to every patient we treat. It is not ideal that the inpatient stay is the only opportunity to do this but we make the most of the contact we have." Physiotherapist  
"Comes for your inpatient transplant in comfortable clothes. No need for JJs all day every day. Get up and move every day. The BMT unit corridor is marked in metres and patients are encouraged from Day 9 to walk the corridor every day for as long as they can, exclusions apply eg neutropenic fever or infections." Clinical Nurse Specialist |
| Caution, conservative approach to types and intensity of physical activity advised | "Advice not to swim with a vascular access device in site. Avoid the gym and lifting heavy weights. Avoid gardening because of the infection risk etc." Clinical Nurse Specialist  
"It’s good to keep active but don’t overload it." Doctor  
"To try and maintain a regime of physical activity, even if it only involves getting out of bed once a day and stretching." Inpatient Nurse |
| Provision of resources and signposting      | "I advise where they can access walking groups and exercise referral schemes." Occupational Therapist  
"Prior to coming in for transplant, giving them leaflets and information on physical activity and promoting exercise both before coming into hospital, and during their 4 week inpatient stay." Clinical Nurse Specialist  
"Direct people to the Macmillan [support and information] desk regarding exercise/rehab programmes." Doctor |

resistance training. It is generally agreed that any level of PA is better than none and that positive health benefits exist with any amount of PA. Across professions, approximately half of HPs surveyed reported that they give PA advice routinely to their patients with haematological cancer, which is similar to levels of recommendation by HPs working with breast and prostate cancer patients. When asked to estimate proportionally how many of their patients they give PA advice to, most survey respondents reported giving PA advice to less than 25% of patients with professional differences again. Over half of doctors reported only giving advice regarding PA when patients initiated with a request for information and therefore give advice to less of their patients. Nurses and AHPs appear to give advice regarding PA more often and to more patients than doctors, perhaps reflecting their being more familiar with guidelines. Williams et al found 51% of oncology HPs gave PA advice to >50% of
their patients, in keeping with our findings across professions.18 In contrast to our findings among doctors, survey research on haematologists, preliminary presented as conference proceedings by Nicol et al, reported large proportions of haematologists recommending PA to their patients at least occasionally. However, patients perspectives differed as only 20–54% of patients surveyed in the same study actually recalled receiving a recommendation from their haematologists,19 indicating some mismatch between what advice HPs perceive they provide and what patients recall receiving.

AHPs providing recommendations on PA to larger proportions of patients was expected. Another small survey study of cancer physiotherapists, reported figures as high as 62% of participants who recommend or use exercise specifically for people with haematological cancer.20 Clinicians at all parts of the patient pathway should ensure that their patients’ levels of PA, promoting PA for general health benefits and signposting or referring to appropriate support to become more physically active as required. Exercise professionals, such as physiotherapists, can provide effective exercise prescription tailored to individual factors including baseline functional capacity, cancer-specific deficits or challenges and the patients goals and preferences for exercise. Having an awareness of local PA guidelines, such as the UK Chief Medical Officers’ PA guidelines, can assist HPs in promoting participation in PA for health benefits.21

Results from this study demonstrate general positive beliefs that PA and exercise should be encouraged as part of treatment and follow-up for people living with and beyond haematological cancer and that nearly all respondents provide PA advice to at least some of their patients. Analyses of open text responses regarding what guidance HPs were aware of and what advice they give to patients did not always align. Few respondents provided a source or details of the guidance they knew, but most responses received were appropriate, including charity sources of advice or details of principles laid out in evidenced recommendations. Themes emerging from the analysis of advice given did indicate a mostly positive approach to promoting usual activities, the benefit of PA and signposting to resources. However, there was also a theme of cautionary or conservative advice given often advising limiting of exercise intensity or type to people living with and beyond haematological cancer. This may be a reflection of the varied professions who responded to the survey and may indicate a need for stronger referral links or embedding of professionals trained in exercise prescription working within haematological cancer MDTs. Future research related to this survey intends to explore these themes further through a qualitative study of HPs working in haematology.

In the delivery of cancer care, HPs are recognised as crucial to the promotion of PA and lifestyle advice,21 particularly medical and nursing clinicians.22,23 People living with and beyond cancer are often receiving PA advice from HPs and report lack of advice given in the cancer setting.22 Delivery of recommendations from care teams can be effective22 and is associated with greater PA participation in people living with and beyond cancer.23 Although there is a recognised requirement to have access to nutritional and rehabilitation services delivered by AHPs in haematological cancer services in the UK,24,25 the incorporation of specialist AHPs embedded within multidisciplinary teams is limited, even in tertiary cancer centres.24 Therefore, the number of people living with and beyond haematological cancer who access AHPs, particularly physiotherapists, as part of their care pathway and receive PA input from them may be limited. Given that most patients routinely encounter medical and nursing HPs, they have the most potential influence in encouraging PA participation among all people living with and beyond haematological cancer. Given the variable evidence of knowledge of appropriate PA guidance among HPs, there is an identified need for greater education that considers professional utilising and additional barriers to providing PA advice.25,26,27

This survey is the first of its kind to focus on haematological cancer HPs in the UK but has some limitations. Firstly, it is not possible to ascertain a response rate due to the online distribution of the survey, also it received a modest number of respondents and therefore analyses of professional groups was limited. Secondly, research of this kind may naturally attract HPs with a positive view of the role of PA themselves or who are more aware of growing social desirability to promote PA particularly among people living with long-term conditions, such as people living with and beyond cancer28 and who were already keen to promote PA among these with haematological cancer. The high levels of self-reported weekly PA among our respondents may give some indication to sample selection bias of this nature. These factors may limit the generalisability of this survey to the wider UK haematological cancer workforce.
Ethical Approval
This study was approved by University College London’s Research Ethics Committee (reference 14/0753/001).

Acknowledgments
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Disclosure
The authors have no conflicts of interest to disclose. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

References

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Physical Activity during and after treatment for blood cancer: 
perspectives of haematology healthcare professionals

Introduction to the study

We would like to invite you to participate in this research study about physical activity and exercise for people diagnosed with blood cancer. There is limited information on the opinions of Health Professionals working in haematological oncology on physical activity and exercise for patients undergoing active treatment for blood cancers. We are interested in gathering information on the views of health professionals working with people with a diagnosis of blood cancer via this brief online questionnaire.

The questionnaire will take approximately 10 minutes to complete. You are free to withdraw at any time without giving a reason.

To be eligible to take part in this questionnaire you should be:

1. A health professional working in a clinical setting (including medical doctors, nurses, allied health professionals and support/auxiliary health care staff)
2. Currently be in a position where you are working directly with people having treatment or follow up for a diagnosis of blood cancer (leukaemia, myeloma, lymphoma, myelodysplastic syndromes or myeloproliferative neoplasms)
3. Working in the United Kingdom (UK)

Consent

Thank you for your interest in taking part in this research. If you have any questions arising from the information on the previous page, please contact Orla McCourt at orla.mccourt.18@ucl.ac.uk

We need to request formal consent so please read the following statements and check the box below if you agree to take part

1. I have read the study information on the previous page and understand what it involves.
2. I consent to the processing of my personal information for the purposes of this research study conducted under the new General Data Protection Regulation (GDPR) 2018
3. I understand that such information will be treated as strictly confidential and that the information collected from me will be used to support other research in the future, and may be shared anonymously with other researchers
4. I understand that if I decide at anytime that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately
5. I agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.

☐ I have read the above statements and I agree to complete the survey
☐ I do not agree
First, here are some questions about you, your professional experience and the patients you work with. Please choose the options you identify most closely with.

2. What is your gender?
   - Female
   - Male
   - Other
   - Prefer not to say

3. How old are you?
   - [ ] years

4. How long have you been in your current role/career stage?
   - 0-5 years
   - 6-10 years
   - More than 10 years

5. What is your profession?
   - Medical doctor
   - Advanced Clinical Practitioner (Advanced Nurse Practitioner)
   - Clinical Nurse Specialist
   - Inpatient/ward Nurse
   - Outpatient/day care Nurse
   - Allied Health Professional
   - Pharmacist
   - Support worker/unregistered health care worker
   - Other

About your patients

6. What proportion of the patients you usually care for have a blood cancer diagnosis?
   - Up to 50%
   - More than 50%
   - I do not care for haematology cancer patients

7. Which groups of blood cancer do you work with predominately? (select all that apply)
   - Myeloma
   - Lymphoma
   - Leukaemia
   - Myelodysplastic Syndromes (MDS)
   - Myeloproliferative Neoplasms
   - Other

8. Do you care for patients undergoing haematopoietic stem cell transplant?
   - Yes, frequently (at least one patient per week)
   - Yes, occasionally (at least one patient per month)
   - Yes, infrequently (less than one patient per month)
   - No
Physical Activity Guidelines

Now we are going to ask you about your awareness of guidance on physical activity and advice you discuss with your patients, if any.

It may be helpful to provide a definition or what we mean by physical activity:

“Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. Exercise, is a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective.

Physical activity includes exercise as well as other activities which involve bodily movement and are done as part of playing, working, active transportation, house chores and recreational activities.”

(NHSG, 2018)

For all of our questions we will use the term ‘physical activity’, which includes exercise.

Select an answer to the questions that applies most to you and your experience.

10. Are you familiar with any physical activity or exercise guidelines that are relevant for cancer patients?
   - Yes, I know of relevant guidelines
   - I’m aware there are some, but don’t know what they are
   - I am not aware of any guidelines

Guidance Details

11. Please give some details of the physical activity guidance that you know? (e.g. the name of the guidelines, who produced them or any detail you can recall)

Physical Activity Advice

12. Could you estimate what proportion of your patients with blood cancer ask you for information about physical activity?
   - None
   - 0-25%
   - 26-50%
   - 51-75%
   - >75%

13. When do patients with blood cancer commonly ask you for information about physical activity? (tick all that apply)
   - At diagnosis, BEFORE commencing anti-cancer treatment
   - DURING treatment with anti-cancer treatment
   - On COMPLETION of anti-cancer treatment
   - During maintenance treatment
   - During survivorship/follow up period AFTER anti-cancer treatment
   - None of my patients ask me for advice about physical activity or exercise
Physical Activity Advice

14. Do you give advice regarding physical activity to your patients with blood cancer?
   - ○ Yes, routinely to most of my patients
   - ○ Yes, only if they request information regarding physical activity
   - ○ Yes, only to patients that I think would benefit from physical activity
   - ○ No, I do not recommend or give advice about physical activity to my patients

15. Can you estimate how many of your patients with blood cancer you give advice about physical activity to?
   - ○ 0-25%
   - ○ 26-50%
   - ○ 51-75%
   - ○ >75%

16. When do you commonly give advice about physical activity to your patients with blood cancer? (Tick all that apply)
   - ○ At diagnosis, BEFORE commencing anti-cancer treatment
   - ○ DURING treatment with anti-cancer treatment
   - ○ On COMPLETION of anti-cancer treatment
   - ○ During maintenance treatment
   - ○ During survivorship/follow up period AFTER anti-cancer treatment

17. Please give an example of information or advice you give about physical activity to patients with blood cancer?

---

Physical Activity During Treatment

Please select the appropriate box that best represents your level of agreement or disagreement with the following statements.

18. Considering patients DURING TREATMENT for blood cancer

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Neither disagree or agree</th>
<th>Agree</th>
<th>Strongly agree</th>
<th>I don't know</th>
</tr>
</thead>
</table>

- Patients with blood cancer should be encouraged to be physically active
- Regular exercise can alleviate symptoms of fatigue for patients with blood cancer
- There is not enough evidence for health professionals to promote exercise to patients with blood cancer
- Regular exercise can improve quality of life for patients with blood cancer
- I do not feel confident making recommendations to blood cancer patients who ask about physical activity
- I know where or who to refer patients with blood cancer who require support to become more physically active
- Structured exercise should be part of the treatment pathway for blood cancer patients
### Physical Activity After Treatment

Please select the appropriate box that best represents your level of agreement or disagreement with the following statements.

19. Considering patients **AFTER COMPLETION OF TREATMENT** for blood cancer

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Neither disagree or agree</th>
<th>Agree</th>
<th>Strongly agree</th>
<th>I don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with blood cancer should be encouraged to be physically active</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular exercise can alleviate symptoms of fatigue for patients with blood cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is not enough evidence for health professionals to promote exercise to patients with blood cancer</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Regular exercise can improve quality of life for patients with blood cancer</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I do not feel confident making recommendations to blood cancer patients who ask about physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I know where or who to refer patients with blood cancer who require support to become more physically active</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured exercise should be part of survivorship/follow up care for blood cancer patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

20. **Discussing physical activity with blood cancer patients** is part of your role

- [ ] Strongly agree
- [ ] Agree
- [ ] Neutral
- [ ] Disagree
- [ ] Strongly disagree

21. **When you think a patient with blood cancer requires more support to become physically active**, who do you consider most suitable to refer them to?

- [ ] Clinical Nurse Specialist
- [ ] Physiotherapist
- [ ] Cancer Support and Information Advisor
- [ ] General Practitioner
- [ ] Community exercise provider
- [ ] Fitness instructor/personal trainer
- [ ] I don't know
- [ ] Other: [ ]

22. **Do you feel you have an appropriate professional in your current blood cancer service or multidisciplinary team to which you would refer patients who require support to become more physically active?**

- [ ] Yes
- [ ] No
- [ ] I don't know
Finally, we are interested in learning about Health Professionals' own levels of moderate to strenuous physical activity. This is the kind of activity that makes you feel at least a bit warm and out of breath and can include running, fast walking or other forms of physical activity.

25. On average, how many days per week did you engage in moderate to strenuous physical activity (like a brisk walk or run)?
   - Number of days

26. How long is your average session of moderate to strenuous physical activity in minutes? (i.e., a single running/walking/exercise session)?
   - Less than 10 minutes

27. Do you track your step count (with e.g., a phone app, smart watch, pedometer)?
   - Yes
   - No

28. What is your average step count per day? (choose one)
   - 0-4999 steps
   - 5000-6999 steps
   - 7000-9999 steps
   - 10000 or more steps
   - I don’t know
   - Prefer not to say
   - I do not track my step count
Further research

We would like to explore this research topic further by asking you more about your responses in a short telephone call. Would you be willing for us to contact you in the future about the possibility of taking part in the next phase of this study?

29. Would you be willing for us to contact you about taking part in a brief follow-up interview to this survey?
   - Yes
   - No

Further research

30. Please provide your contact details

   Name
   Email address
   Profession

In compliance with 2018 GDPR regulations, your email will be stored on a secure UCL server. We will only use your email to send an information sheet about the next study phase. If you decide not to take part in the second phase your email will be deleted from our database within 6 weeks of sending the second study information.

Please leave your best contact email address and our research team will send you an information sheet.

Thank You!

Thank for taking the time to complete this survey. If you have any questions about this survey, please contact the researchers using the details below.

Research Team:
- Orla McCourt
- Prof Kwee Yong
- Dr Abigail Fisher
- Dr Gita Ramdharry

Contact:
Orla McCourt at orla.mccourt.18@ucl.ac.uk

31. Click to submit your responses
Appendix M. University College London Ethics Committee approval for health professionals survey

20th March 2019

Professor Kwee Yong
UCL Cancer Institute

Dear Professor Yong,

Notification of Ethics Approval with Provisos
Project ID/Title: 14783/001: Exercise during and after treatment for blood cancers: perspectives of haematology healthcare professionals

Further to your satisfactory responses to my comments, I am pleased to confirm in my capacity as Joint Chair of the UCL Research Ethics Committee (REC) that I have ethically approved your study until 20th March 2021.

Ethical approval is subject to the following conditions:

Notification of Amendments to the Research
You must seek Chair’s approval for proposed amendments (to include extensions to the duration of the project) to the research for which this approval has been given. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing an ‘Amendment Approval Request Form’
http://ethics.prod.ucl.ac.uk/responsibilities.php

Adverse Event Reporting – Serious and Non-Serious
It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator (ethics@ucl.ac.uk) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Joint Chairs will decide whether the study should be terminated pending the opinion of an independent expert. For non-serious adverse events the Joint Chairs of the Ethics Committee should again be notified via the Ethics Committee Administrator within ten days of the incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Joint Chairs will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Final Report
At the end of the data collection element of your research we ask that you submit a very brief report (1-2 paragraphs will suffice) which includes in particular issues relating to the ethical implications of the research i.e. issues obtaining consent, participants withdrawing from the research, confidentiality, protection of participants from physical and mental harm etc.

Office of the Vice Provost Research, 2 Tavistock Street
University College London
Tel +44 (0)20 7679 6717
Email ethics@ucl.ac.uk
http://ethics.org/ucl.ac.uk
In addition, please:

- ensure that you follow all relevant guidance as laid out in UCL’s Code of Conduct for Research: http://www.ucl.ac.uk/ris/governance-and-committees/resgov/code-of-conduct-research
- note that you are required to adhere to all research data/records management and storage procedures agreed as part of your application. This will be expected even after completion of the study.

With best wishes for the research.

Yours sincerely

Dr Lynn Ang
Joint Chair, UCL Research Ethics Committee

Cc: Ms Oria McCourt, Dr Abigail Fisher & Dr Gita Ramdharry