Characterising the Effects of Exercise on Immune Cells in Blood Across the Myeloma Survivorship Continuum

Short title: Blood Immune Cell Changes in Response to Exercise in Myeloma

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TRIAL PROTOCOL: Version Five

SPONSOR: University of Bath

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Contents

List of abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse events
Allo-HSCT	Allogenic haematopoietic stem cell transplant
ANOVA	Analysis of variance
Auto-HSCT	Autologous haematopoietic stem cell transplant
BMI	Body mass index
BMPC	Bone marrow plasma cell
CI	Chief investigator
CRAB	Calcium, Renal insufficiency, Anaemia, Bone lesion (symptoms of multiple myeloma)
ECG	Electrocardiograph
EDTA	Ethylenediaminetetraacetic acid
HRA	Health Research Authority
HSCT	Haematopoietic stem cell transplant
IMWG	International Myeloma Working Group
IPAQ	International physical activity questionnaire
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple Myeloma
M-protein	Monoclonal protein
NK	Natural Killer
PAR-Q	Physical activity readiness questionnaire
PBMC	Peripheral blood mononuclear cells
PSQI	Pittsburgh sleep quality index
REC	Research ethics committee
RPE	Rating of perceived exertion
SAE	Serious adverse event
SF-36	36-item short survey
SMM	Smouldering Multiple Myeloma
VTD	Velcade® (bortezomib) Thalidomide Dexamethasone

WHO	World Health Organisation

Trial Summary

Trial Title	Characterising the Effects of Exercise on Immune Cells in Blood Across the Myeloma Survivorship Continuum	
Short title	Blood Immune Cell Changes in Response to Exercise in Myeloma	
Clinical Phase	I	
Trial Design	Pilot, single-centre, phase I trial	
Trial Participants	Three cohorts of patients will be invited to participate in the present study. These cohorts comprise three distinct stages of myeloma survivorship. Cohort 1 (pre-treatment) • Patients diagnosed with smouldering multiple myeloma (SMM) will be invited to participate Cohort 2 (first-line treatment) • Patients will be invited to participate during induction therapy for symptomatic multiple myeloma (MM) Cohort 3 (post-treatment) • Patients will be invited to participate who are in remission following a stem cell transplant treatment for MM	
Planned Sample Size	Cohort 1 (pre-treatment) n = 15 Cohort 2 (first-line treatment) n = 15 Cohort 3 (post-treatment) n = 15 Total sample size n = 45	
Study Duration	12 months	
	Objectives	**Outcome Measures**
Primary	1. Investigate whether an acute bout of exercise increases the frequency of NK cells, T cells and monocytes in peripheral blood. This response will be investigated at three distinct time points of myeloma survivorship: • Cohort 1 (pre-treatment) • Cohort 2 (first-line treatment) • Cohort 3 (post-treatment)	Frequency of NK cells, T cells and monocytes in peripheral blood collected at rest, immediately post exercise and 30-minutes post exercise. Measured via flow cytometry.
Secondary	1. Investigate whether an acute bout of exercise increases the frequency of polyclonal B cells and clonotypic B cells in peripheral blood. This response will be investigated at three distinct time points of myeloma survivorship:	Frequency of B cell subsets in peripheral blood at rest, immediately post exercise and 30-minutes post exercise. Measured via flow cytometry.

	• Cohort 1 (pre-treatment) • Cohort 2 (first-line treatment) • Cohort 3 (post-treatment)	
	2. Investigate whether an acute bout of exercise enhances the cytotoxicity of NK cells against a $CD38^+$ MM cell line. MM cell lysis will be measured using *ex vivo* assay models. This response will be investigated at three distinct time points of myeloma survivorship: • Cohort 1 (pre-treatment) • Cohort 2 (first-line treatment) • Cohort 3 (post-treatment)	A $CD38^+$ MM cell line will be labelled with a fluorescent dye that is released from within the tumour cell once the cell has died. The labelled MM cells will then be supplemented with peripheral blood collected at rest and immediately post-exercise using *ex vivo* assay models. The cytotoxicity of NK cells will be assessed by measuring the amount of fluorescence released, which is proportional to the amount of cell lysis.
	3. Investigate whether an acute bout of exercise enhances the efficacy of anti-MM therapies against a $CD38^+$ MM cell line. MM cell lysis will be measured using *ex vivo* assay models. This response will be investigated at three distinct time points of myeloma survivorship: • Cohort 1 (pre-treatment) • Cohort 2 (first-line treatment) • Cohort 3 (post-treatment)	A $CD38^+$ MM cell line will be labelled with a fluorescent dye that is released from within the tumour cell once the cell has died. The labelled MM cells will then be supplemented with anti-MM therapy and peripheral blood collected at rest, and immediately post-exercise using *ex vivo* assay models. The cytotoxicity of exercised blood in adjunct with anti-MM therapy will be assessed by measuring the amount of fluorescence released, which is proportional to the amount of cell lysis.
	4. Characterise the participants enrolled onto the study. This will be investigated at three distinct time points of myeloma survivorship: • Cohort 1 (pre-treatment) • Cohort 2 (first-line treatment) • Cohort 3 (post-treatment)	Participants will be characterised within each cohort by the following measures: • Body composition (height, body mass, hip/waist ratio, fat, and lean mass) • Well-being indices (stress, fatigue, sleep, QoL) • Physical activity • Resting blood pressure and heart rate • Resting immunological profile (phenotypic and functional analyses of PBMCs, differential blood count, viral infection history,

		immunoglobulins, complement proteins) • Inflammation (cytokines) • Resting metabolic factors and hormone levels (*e.g.* glucose, insulin, growth factors) •

Roles of trials sponsor

The sponsor takes formal responsibility for the initiation, management, and financing of the research.

Roles and responsibilities of the trial management group

A trial management group will monitor the progress and review the scientific rigour of the trial. The group will also monitor safety data, trial end points and recommend to the sponsor whether to continue, modify, or stop the trial. Meetings will be held quarterly.

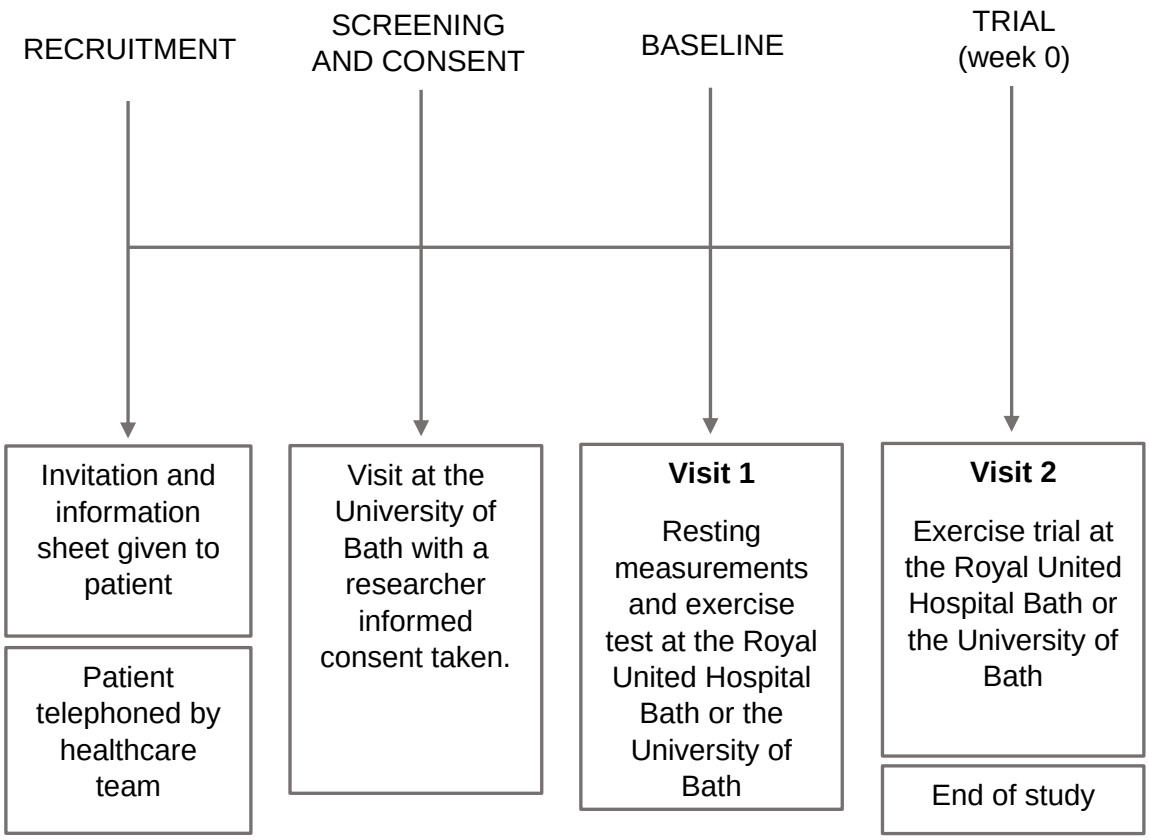
Protocol contributors

Contributor	**Expertise**
Dr John Campbell	Exercise oncology and immunology
Dr James Turner	Exercise oncology and immunology
Dr Sally Moore	Clinical management of patients with haematological disease
Dr Jim Murray	Clinical management of patients with haematological disease
Mr Harrison Collier-Bain	Exercise physiology

Key words

Multiple Myeloma; smouldering multiple myeloma; exercise; natural killer cells; T cells; B cells; health

Trial flow chart



Background and summary

Multiple Myeloma (MM) is an incurable, haematological malignancy of plasma cells that primarily reside in the bone marrow. MM is the second most common haematological cancer (Kazandjian, 2016) and accounts for 2% of all cancers and 2% of all cancer-related deaths in the UK (Cancer Research UK, 2017). The incidence of MM generally increases with age, with approximately two-thirds of patients diagnosed aged 65 years or more (Smith et al., 2015) and the highest incidence rates per 100,000 people between the ages of 85 and 89 years (Cancer Research UK, 2014).

Myeloma survivorship

Typically, MM develops from its pre-cursor, monoclonal gammopathy of undetermined significance (MGUS) with or without an intervening stage known as smouldering MM (SMM) (Kyle et al., 2002; O. Landgren et al., 2009). Both MGUS and SMM are diagnosed by the detection of serum monoclonal protein levels and bone marrow plasma cell (BMPC) infiltration with the absence of end organ damage (Rajkumar et al., 2014). SMM is considered a more severe disease, because the risk of progression to MM in the first 5 years is 10% per year (Kyle et al., 2007) compared to a 1% risk of progression to MM per year in MGUS (Kyle et al., 2002; 2018). Both MGUS and SMM are considered asymptomatic and therefore a ‘watch-and-wait’ disease management strategy is favoured. However, immunosuppression occurs in MGUS and SMM as a result of immune cell dysfunction (Talib Dosani et al., 2018; Pratt et al., 2007) and suppressed polyclonal immunoglobulins, known as, ‘immunoparesis’ (Gregersen et

al., 2009; Kyle et al., 2006; Pérez-Persona et al., 2007; Turesson et al., 2014). This immunosuppression may increase the risk of infections in people with MGUS and SMM compared to the general population (Kristinsson et al., 2009). There is debate surrounding when to treat SMM. This is because approximately 50% of people diagnosed with SMM will not progress to MM after 5-years and further, one-third of patients will not progress to MM at 10-years (Kyle et al., 2007). Additionally, treatments carry considerable short- and long-term risks due to their toxicity and there is a lack of clear data from randomised trials evidencing an overall survival or quality of life benefit with therapy (Rajkumar et al., 2015).

Symptomatic MM is characterised by the uncontrolled monoclonal growth of BMPC (Kyle et al., 2003) which usually secrete monoclonal immunoglobulin protein, known as 'M-protein' (Kumar et al., 2017), which are identical antibodies produced by a single plasma cell clone. In some patients (20%) myeloma cells only secrete monoclonal free light chains (part of the antibody) and in others (<3%), the myeloma cells secrete no M-protein (Kyle et al., 2003). Diagnosing MM requires the detection of serum M-protein concentrations ≥3g/dL, clonal BMPC ≥10%, with one or more myeloma defining events (MDE), such as, BMPC ≥60%, an involved to uninvolved serum free light-chain ratio ≥100, two or more focal lesions on an MRI, or the presence of end organ damage, defined by the International Multiple Myeloma Working Group (IMWG) as CRAB symptoms: hypercalcaemia (serum calcium >0.25 $mmol.L^{-1}$), renal insufficiency (serum creatinine >177 micromol/L), anaemia (Hb >2g/dL below the lower normal limit), bone lesions (one or more osteolytic lesions on skeletal radiography, computed tomography [CT] or positron emission tomography-CT) (Rajkumar et al., 2014). Consequently, there is a need to start treatment.

Treatment for multiple myeloma

Once diagnosed with MM, patients commence active treatment, which may consist of a range of drugs to control and manage the disease including: proteasome inhibitors (*e.g.* bortezomib), immunomodulatory drugs (*e.g.* thalidomide) and corticosteroids (*e.g.* dexamethasone) (Bertolotti et al., 2017). Subsequently, younger, fit (≤65 years of age) patients receive high-dose chemotherapy (*e.g.* melphalan) with a haematopoietic stem cell transplant (HSCT) (Kumar et al., 2017; Larsen et al., 2019). The HSCT may be autologous (Auto-HSCT) – uses stem cells harvested from the patient or allogenic (Allo-HSCT) – uses donor stem cells, with the former being the recommended therapy (Gonsalves et al., 2019). Despite the improved progression free survival of people treated with high-dose melphalan and auto-HSCT, patients are likely to suffer from relapse (Attal et al., 1996; Child et al., 2003) as a result of persistent tumour cells after therapy, known as, minimal residual disease (MRD) (Paiva et al., 2008), which represents the incurable nature of the disease.

In some cases, treatment regimens may include monoclonal antibody (mAb) immunotherapy, such as, daratumumab. For example, the National Institute for Health and Care Excellence (NICE) recommends the use of daratumumab as a monotherapy for relapsed/refractory MM in people who have received 3 prior therapies including a proteasome inhibitor and an immunomodulator (NICE, 2017). Additionally, daratumumab in combination with bortezomib and dexamethasone is recommended as an option for treating people with relapsed MM who have received one prior therapy

(NICE, 2019b). Daratumumab is a high affinity, first-in-class human immunoglobulin G1-k (IgG1-k) mAb against CD38, which is uniformly expressed on myeloma cells (Lonial et al., 2016; Van De Donk et al., 2018). Daratumumab induces cell lysis by complement dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC) (Syed, 2019), with ADCC primarily mediated by natural killer (NK) cells (Nijhof et al., 2015b). The recommendations for the use of daratumumab from NICE are based on the overall response rates (ORR) observed as a monotherapy in phase II studies (36%: Lokhorst et al., 2015; 29%: Lonial et al., 2016) and in combination with other drugs in phase III studies (92.9%: Dimopoulos et al., 2016; 82.9%: Palumbo et al., 2016) for people with relapsed/refractory MM. Although currently not part of the treatment plan as first line therapy in the UK, the favourable response rates and low toxicity of daratumumab has led to investigations of its use in the first line, with phase III studies showing positive ORR in people ineligible for transplant (90.9%: Mateos et al., 2018) and people eligible for transplant (92.6%: Moreau et al., 2019) when it is combined with other drugs (*e.g.* bortezomib, melphalan, prednisone and bortezomib, thalidomide, dexamethasone [VTD], respectively). Although the aforementioned clinical studies showed a slight increase in infections in groups treated with daratumumab, adverse events were clinically manageable with no overlap in overall toxicity.

Physical activity and myeloma

Epidemiological evidence has found associations for a 20% reduced risk of myeloma in people who conduct higher vs lower leisure-time physical activity, with reduced risks also observed in 13 other cancers (*e.g.* breast, colon) (Moore et al., 2016). These associations suggest a protective effect of regular exercise on cancer, for example, the direct anti-tumour effects of lifespan engagement in exercise on the immune system (Ashcraft et al., 2016; Pedersen et al., 2015; Ruiz-Casado et al., 2017). Regular exercise may be an effective way to manage disease, and treatment-related symptom burden across myeloma survivorship and has been shown to be safe and feasible. For example, in a recently completed trial in our laboratory (ISRCTN: 65527208) the safety and feasibility of exercise was evidenced in people with MGUS and SMM. In active MM, the safety and feasibility of exercise has been evidenced in a review (Smith et al., 2015) and in a randomised controlled trial (RCT) during first-line anti-MM therapy (Larsen et al., 2019b). Considering the potential anti-tumour effects of exercise observed in epidemiological evidence, and the safety and feasibility of exercise, research is needed to understand the mechanisms underpinning the direct anti-tumour effects of exercise in myeloma.

Direct anti-tumour effects of exercise

Exercise is thought to have a direct anti-tumour effect throughout the lifespan (Ruiz-Casado et al., 2017), attributed to immune cell regulation, for example, transient increases in circulatory cells of the immune system such as lymphocytes (Campbell & Turner, 2018; Nielsen et al., 1996; Walsh et al., 2011). This response is driven by increased haemodynamic forces and catecholamine release causing a redistribution of cells from marginal pools in the blood vessels in addition to other lymphoid organs, such as the spleen, bone marrow and lymph nodes into peripheral blood (Shephard, 2003; Simpson et al., 2015). NK cells and T cells have shown preferential increases

of 10-fold and 2.4-fold, respectively, in response to acute exercise in healthy individuals (Campbell et al., 2009). With increases also reported to a lesser extent in B cells (2.2-fold) (Turner et al., 2016). The preferential mobilisation of these immune cells is primarily mediated by the cells expression of β_2-adrenergic receptors and their activation in response to increased adrenaline. This causes cell demargination from the endothelium and subsequent recirculation into the bloodstream (Graff et al., 2018; Simpson et al., 2015). Following acute exercise, these immune cells decrease below baseline values (Simpson et al., 2009; 2020), thought to represent the redistribution of cells from the bloodstream to tissues and organs, enhancing immune surveillance whereby immune cells identify and eradicate pathogens and malignant cells (Campbell & Turner, 2018).

The phenomenon of immune cell redistribution has been demonstrated in mice with flourescent cell tracking showing an increased accumulation of labelled T cells in the bone marrow, the lungs and the Peyer's patches in response to intense running exercise (Krüger et al., 2008). An additional mouse model observed that regular exercise increased the bone marrow infiltration of NK cells in non-tumour bearing mice, whilst, in tumour bearing mice a pronounced accumulation of NK cells was observed in the tumour (Pedersen et al., 2016). This accumulation of NK cells in the tumour was associated with reduced tumour incidence and growth, representing improved immune surveillance (Pedersen et al., 2016). In healthy humans, *in vitro* investigations have shown that an acute bout of exercise can increase NK cell frequency and the cytotoxicity per NK cell against haematological cancer cell targets (*e.g.* MM [RPMI-8226], Lymphoma [221 AEH]) (Bigley et al., 2014). Moreover, immune cell subsets that are the most responsive to exercise are highly cytotoxic, such as $CD56^{dim}CD16^{+}$ NK cells and effector-memory $CD8^{+}$ T cells and thus, may improve immune surveillance against malignant cells during exercise (Campbell et al., 2009). No study to date has investigated the effects of exercise on immune kinetics in myeloma and thus, further investigations into the role of exercise in asymptomatic and symptomatic blood cancers is warranted.

Considering that exercise has the potential to induce profound alterations to cellular compartments of the immune system, such as a redistribution of cells to and from the bone marrow, it may also be the case that exercise provokes kinetic changes to myeloma tumour cells. For example, exercise may move myeloma tumour cells from their bone marrow niche into peripheral blood. Myeloma is a malignancy of plasma cells, a terminally differentiated B-cell typically identified by high CD38 and CD138 expression (S. Kumar et al., 2010). Alike NK cells and T cells, B cells express β_2-adrenergic receptors (Kohm et al., 2002; Sanders, 2012) and are therefore, sensitive to mobilisation through exercise-induced catecholamines.

During exercise in healthy humans, B cells may be mobilised from the bone marrow into peripheral blood as mouse models have demonstrated a redirection of B cells from the bone marrow in response to acute stressors (Engler et al., 2004). In healthy individuals, high intensity exercise can evoke a transient, 100% increase in $CD3^{-}CD19^{+}$ B cells in peripheral blood (Campbell et al., 2009). The greatest magnitude of change has been observed for immature ($CD20^{+}CD27^{-}CD10^{+}$) B cells (125% increase) followed by memory ($CD20^{+}CD27^{+}CD38^{-}$) B cells (78% increase)

and naïve ($CD20^{+}CD27^{-}CD10^{-}$) B cells (63% increase) (Turner et al., 2016). Plasma cells in peripheral blood do not appear to increase in response to exercise in healthy humans (Turner et al., 2016), but it is not known how exercise affects plasma cells in people with myeloma, who have a greater plasma cell burden in the bone marrow. Exercise induced mobilisation of myeloma plasma cells into peripheral blood may facilitate the detection of MRD using next generation flow cytometry (Flores-Montero et al., 2017). In the absence of myeloma plasma cell mobilisation, it may still be the case that clonotypic myeloma precursor cells are mobilised by exercise. Indeed, hierarchical models of the multi-step process of MM development suggest a MM stem cell (Johnsen et al., 2016) exists that possesses the capacity to self-renew and proliferate (Agarwal & Matsui, 2012; Matsui et al., 2004). This clonotypic myeloma precursor resembles a memory B cell with a $CD138^{-}$ phenotype ($CD19^{+}CD20^{+}CD138^{-}CD38^{-}$) that is resistant to anti-MM drugs such as dexamethasone, lenalidomide and bortezomib (Matsui et al., 2008) and therefore may survive induction therapy regimens. Moreover, recent investigations using next generation flow cytometry (Flores-Montero et al., 2017) have shown the presence of myeloma tumour plasma cells ($CD19^{-}CD20^{+}CD38^{+}CD138^{+}$) circulating in peripheral blood in people with SMM and MM at diagnosis. These myeloma tumour plasma cells in peripheral blood have a similar phenotypic expression as their bone marrow counterparts however, with lower expressions of for example, CD38, CD138, CD81, CD56, CD27 and a tendency towards lower CD20 and CD19, representing a more immature phenotype (Sanoja-Flores et al., 2018). The continuous circulation of these cells may in part, represent the dissemination of myeloma cells and may be used to aid in the detection of MRD (Ghobrial, 2012; Sanoja-Flores et al., 2018).

As discussed earlier, B cells expressing CD19, CD20 and CD27 can be substantially mobilised during exercise which therefore suggests, that exercise has the potential to mobilise B cells with a phenotype that is similar to the clonotypic myeloma precursor. Although the effects of exercise on B cell mobilisation in people with myeloma remains largely unknown, the mobilisation of B cells representing a similar phenotype as myeloma precursors (*e.g.* memory B cells) in healthy individuals, accompanied by the potential for a redistribution of B cells from the bone marrow observed in mouse models (Engler et al., 2004), indicates that exercise may be an effective means to mobilise clonotypic myeloma cells in MM, which may in turn facilitate the detection of MRD.

Considering that exercise can evoke substantial increases in cytotoxic immune cells and that some anti-MM therapies such as daratumumab rely upon these cells to elicit myeloma cell death, exercise demonstrates the potential to be an adjunct to anti-MM therapy, providing indirect anti-tumour effects, described next.

Indirect anti-tumour effects of exercise

The positive associations between exercise and immune cell frequency and function suggests that exercise has the potential to elicit indirect anti-tumour effects by augmenting anti-cancer therapies that utilise the immune system, such as mAb immunotherapy (*e.g.* daratumumab). For example, cytotoxic NK cells, which are highly sensitive to exercise induced mobilisation, are the primary mediator of daratumumab induced antibody dependent cellular cytotoxicity (ADCC) (Nijhof et al., 2015b). During

the ADCC response, the antigen-binding fragment of daratumumab interacts with CD38 on the target cell surface, which then binds to an Fc gamma receptor on an effector cell such as an NK cell or monocyte (Mellor et al., 2013; Van De Donk & Usmani, 2018). Upon binding, effector cells initiate a lytic attack ultimately resulting in cell death (Mellor et al., 2013). However, in a fraction of people with MM there is marked heterogeneity in the response to daratumumab (Nijhof et al., 2015a). *Ex vivo* models using bone marrow samples from MM patients incubated with daratumumab for 48-hours, showed that patients with a higher NK cell to myeloma cell and monocyte to myeloma cell ratio achieve greater target cell lysis via ADCC (Nijhof et al., 2015a), which may in part, explain the heterogeneity of the response to daratumumab in people with MM. This suggests, that methods employed to increase effector cell frequency, such as exercise, in adjunct with daratumumab may enhance the daratumumab mediated ADCC. However, the effects of exercise-induced increases in circulatory immune effector cells on the efficacy of daratumumab *ex vivo* has not been investigated and therefore remains unknown.

Given this, exercise may augment daratumumab induced ADCC through two mechanisms. Firstly, by an increase in the number of cytotoxic NK cells and non-classical monocytes in the peripheral blood, both of which have been shown to increase substantially in response to exercise (Campbell et al., 2009; Steppich et al., 2000) and express CD16 - an important receptor for ADCC (Chowdhury et al., 2014; Yeap et al., 2016) due to its ability to detect anti-body coated target cells (Vivier et al., 2008). Previous mouse models have demonstrated the potential for NK cells to migrate from the peripheral blood to the bone marrow after exercise (Krüger et al., 2008; Pedersen et al., 2016), where myeloma plasma cells primarily reside. This redistribution of NK cells may increase the pool of effector NK cells capable of ADCC in the bone marrow and thus, may improve the depth and efficacy of daratumumab. Secondly, it has been reported that there is a presence of immature, myeloma tumour plasma cells in the peripheral blood of SMM and MM patients (Sanoja-Flores et al., 2018). Despite the lower expression of CD38 on these myeloma tumour plasma cells, by increasing the pool of NK cells and monocytes capable of eliciting ADCC through exercise into the circulation where daratumumab is present, the ratio of effector NK cells and monocytes to myeloma cells will be increased. Thus, this process has the potential to improve the depth and efficacy of daratumumab and reduce the risk of MM dissemination.

Currently, there is limited research investigating the immunological responses to exercise in myeloma (Sitlinger et al., 2020) and therefore, it is unknown whether exercise can elicit direct and indirect anti-tumour effects in people with myeloma. Before investigating these anti-tumour effects, it is important to consider the dysregulation of the immune system across the myeloma survivorship continuum and how this may influence the effects of exercise.

Immune dysregulation across myeloma survivorship

Throughout myeloma survivorship, immune dysregulation occurs as a result of disease progression and/or its treatments and therefore, there is reason to doubt whether people with myeloma will benefit from the direct and indirect effects of

exercise. Considering this, it is important to examine the effects of exercise on immune cell kinetics and function at different stages of myeloma survivorship.

Smouldering multiple myeloma – pre treatment

Despite people with SMM considered to be asymptomatic, the disease is associated with immune dysregulation. For example, it has been shown that although people with high-risk SMM have normal absolute counts of CD56 NK cells and CD4 and CD8 T cells compared to age-matched controls, T cells have downregulated activation and proliferation markers with an increased frequency of regulatory T cells (Tregs) (Paiva et al., 2016), which are functionally immunosuppressive in MM development (T. Dosani et al., 2015). The increased frequency of Tregs in SMM may be due to their induced production by malignant plasma cells which may therefore, inhibit the cytotoxicity of NK cells against malignant plasma cells and thus, facilitate the development of MM (T. Dosani et al., 2015; Feyler et al., 2012). Moreover, people with SMM may present with B cell dysfunction as a result of suppressed polyclonal antibody production (immunoparesis) (Pérez-Persona et al., 2007). Therefore, it is important to examine the direct anti-tumour effects of exercise in people with SMM, who have not yet received anti-MM therapy but may still present with immunosuppression as any direct anti-tumour effects of exercise observed may provide a prognostic benefit to reduce the risk of progression to symptomatic MM. Furthermore, any beneficial effects of exercise observed in this population are likely to benefit people in a less progressed disease state, such as people with MGUS.

It is also important to examine the indirect anti-tumour effects of exercise in people with SMM. Firstly, studying this population enables investigations into the impact of exercise on the efficacy of daratumumab without the presence of confounding variables such as anti-MM therapies. Secondly, people with SMM may present with circulating myeloma tumour plasma cells in peripheral blood which express CD38 and therefore may be susceptible to lysis via daratumumab induced ADCC. Lastly, recently published data from the phase II CENTAURUS trial (C. O. Landgren et al., 2020) has shown single agent activity and an acceptable safety profile consistent to those observed in relapsed/refractory MM (Lokhorst et al., 2015; Lonial et al., 2016) when daratumumab is used as a monotherapy for people with intermediate-risk and high-risk SMM, supporting the initiation of a phase III study. This provides a further rationale for evaluating the effects of exercise on daratumumab induced ADCC *ex vivo* in people with SMM. Specifically, if exercise is observed to improve the ADCC response of daratumumab in this population *ex vivo*, this could have advantageous clinical applications for the prescription of exercise in adjunct with daratumumab.

Multiple myeloma – first line therapy

Throughout active MM, patients are likely to experience substantial immunoparesis which negatively effects survival and disease control (Heaney et al., 2018). Additionally, as the disease progresses, immune dysregulation occurs in the form of decreased NK cell frequency and functionality as well as quantitatively and functionally altered T cells (T. Dosani et al., 2015). Exercise presents as a potentially powerful mediator to elicit direct anti-tumour effects by an increase in the frequency and improved function of cytotoxic immune cells, such as NK cells in the peripheral blood, as well as indirect anti-tumour effects by an augmentation in daratumumab efficacy.

Therefore, it is important to investigate the effects of exercise during different stages of treatment in active MM. It is important to investigate the impact of exercise in people receiving induction anti-MM therapies. Induction therapies such as VTD may induce substantial toxicity in the form of myelosuppression, neutropenia, leukopenia and neuropathy (Bertolotti et al., 2017; Rosiñol et al., 2012; Wang et al., 2007), some of which may nullify the immunological changes induced by exercise. Moreover, the combined MM-related and treatment-related immunosuppression contributes to a substantially increased risk of mortality in the first 3-months after diagnosis (Augustson et al., 2005; Pratt et al., 2007). Accordingly, investigations of the effects of exercise on immune cell kinetics and function is warranted in people receiving anti-MM induction therapy. Moreover, although not currently used in induction therapy regimes in the UK, daratumumab has been approved by the Food and Drug Administration for use in untreated, transplant eligible patients in combination with VTD (D-VTD) in the US based on the results of the CASSIOPEIA trial (Moreau et al., 2019) and is currently under review in the UK (NICE, 2019a). Therefore, it is imporant to evaluate the effects of exercise on daratumumab induced ADCC in people receiving induction therapy.

Multiple myeloma – remission

Lastly, it is of importance to investigate the impact of exercise in people in MM remission, following completion of anti-MM treatment. This is because immune reconstitution may take months to years after a HSCT (Porrata et al., 2001a) and patients are likely to suffer from relapse (Usmani et al., 2013). Currently, the purpose of exercise prescribed after a HSCT is to improve the overall functioning of people treated (Persoon et al., 2017), however, the effects of exercise on immune kinetics and function following a HSCT in people with MM remains unknown. Therefore, it is important to investigate the direct anti-tumour effects of exercise in people in MM remission. This is because exercise has the potential to move clonotypic B cells into peripheral blood which may facilitate the detection of MRD following completion of anti-MM therapy. Additionally, any observations of increased frequency and function of immune cells in peripheral blood may improve immune surveillance and thus, may have a protective effect against MRD progression, reducing the risk of disease relapse.

Studies have demonstrated that patients who achieve a negative MRD 100 days post-HSCT have improved progression free survival (Paiva et al., 2008; Rawstron et al., 2013). The development of next-generation flow for the detection of MRD has resulted in a robust post-treatment prognostic biomarker of tumour burden (Flores-Montero et al., 2017; Rawstron et al., 2013) as well as a method to non-invasively detect the level of circulating tumour plasma cells. Indeed, the quantification of circulating tumour plasma cells for MRD detection is not as sensitive as bone marrow MRD, however, it may provide insight into the regrowth and dissemination of tumour cells (Sanoja-Flores et al., 2018). Therefore, exercise may be utilised to facilitate the detection of MRD by mobilising clonotypic myeloma precursor cells from the bone marrow into the bloodstream, thus potentially accelerating the identification of disease progression in patients following anti-MM treatment. It is also important to investigate the indirect anti-tumour effects of exercise in people in MM remission. During recovery after an Auto-HSCT, absolute NK cell counts and NK cell function may recover as early as 14-days

post-HSCT (Porrata et al., 2001b), with $CD8^+$ T cells recovering at 1-month and $CD4^+$ T cells showing delayed recovery (Rueff et al., 2014). These NK cells are produced *de novo* from infused progenitor stem cells (Rueff et al., 2014) and are therefore not confounded by the impaired NK cell functionality induced by malignant plasma cells (T. Dosani et al., 2015). Thus, studying this population enables investigations into the impact of exercise on the efficacy of daratumumab without the presense of functionally altered NK cells in MM.

Summary

In summary, myeloma is a severe haematological cancer and despite considerable advances in treatment strategies in recent years, myeloma remains incurable as a result of persistent tumour cells resistant to anti-MM therapies. Therefore, new approaches to treat myeloma are warranted. As discussed herein, exercise presents as the most powerful non-drug modifier of immune function in healthy humans, but whether these positive adjustments in immunity occur in people with myeloma remains to be fully elucidated. Considering that myeloma causes immune dysregulation across survivorship, people with myeloma present as a fascinating population group to mechanistically examine the immunological direct and indirect effects of exercise in an attempt to reduce disease progression.

Aims and outcomes

The present study aims to characterise the effects of an acute bout of exercise on immune cell kinetics by identifying changes in immune cell frequency (*e.g.* NK cells, T cells, monocytes, B cells) in response to exercise, to assess the function of immune cells across myeloma survivorship and in response to acute exercise and to explore the proof of concept that exercise can improve the efficacy of anti-MM therapies using patient samples against a MM target cell line.

Primary objective

Investigate whether an acute bout of exercise increases the frequency of NK cells, T cells and monocytes in peripheral blood. This response will be investigated at three distinct time points of myeloma survivorship:

- Cohort 1 (pre-treatment)
- Cohort 2 (first-line treatment)
- Cohort 3 (post-treatment)

Outcome measure: Frequency of cytotoxic NK cells (*e.g.* $CD3^-CD56^{dim}$ and $CD3^-CD56^{dim}CD16^+$), cytotoxic T cells (*e.g.* effector-memory $CD3^+CD8^+$) and non-classical monocytes (*e.g.* $CD14^+CD16^+$) in peripheral blood collected at rest, immediately post exercise and 30-minutes post exercise. Measured via flow cytometry.

Secondary objectives

1. Investigate whether an acute bout of exercise increases the frequency of polyclonal B cells and clonotypic B cells in peripheral blood. This response will be investigated at three distinct time points of myeloma survivorship:

- Cohort 1 (pre-treatment)
- Cohort 2 (first-line treatment)
- Cohort 3 (post-treatment)

Outcome measure: Frequency of $CD3^{-}CD19^{+}$ B cell sub-sets including: immature B cells, naïve B cells, memory B cells, plasma blasts and plasma cells in the peripheral blood at rest, immediately post exercise and 30-minutes post exercise. Measured via flow cytometry.

2. Investigate whether an acute bout of exercise enhances the cytotoxicity of NK cells against a $CD38^{+}$ MM cell line. This response will be investigated at three distinct time points of myeloma survivorship:

- Cohort 1 (pre-treatment)
- Cohort 2 (first-line treatment)
- Cohort 3 (post-treatment)

Outcome measures: The percentage of $CD38^{+}$ cell lysis will be measured using *ex vivo* assay models.

3. Investigate whether an acute bout of exercise enhances the efficacy of anti-MM therapies against a $CD38^{+}$ MM cell line. MM cell lysis will be measured using ex vivo assay models. This response will be investigated at three distinct points of myeloma survivorship:

- Cohort 1 (pre-treatment)
- Cohort 2 (first-line treatment)
- Cohort 3 (post-treatment)

Outcome measures: The percentage of $CD38^{+}$ cell lysis will be measured using *ex vivo* assay models.

4. Characterise the participants enrolled onto the study by collecting the following measurements:

- Body composition (height, body mass, hip/waist ratio, fat, and lean mass)
- Well-being indices (stress, fatigue, sleep, QoL)

- Physical activity
- Resting blood pressure and heart rate
- Resting immunological profile (phenotypic and functional analyses of PBMCs, differential blood count, viral infection history, immunoglobulins, complement proteins)
- Inflammation (cytokines)
- Resting metabolic factors and hormone levels (*e.g.* glucose, insulin, growth factors)

Trial design

This study is a pilot, single-centre, phase I trial designed to characterise the effects of a single bout of exercise on the frequency and function of immune cells in the peripheral blood of people with SMM and MM.

Participant eligibility criteria

The following inclusion criteria define people who are eligible for the trial:

- A diagnosis of:

  SMM. Defined by IMWG criteria as the absence of MM defining events or amyloidosis, AND either: (i) serum monoclonal protein (IgG or IgA) >3g/dL OR urinary monoclonal protein >500mg per 24h, AND/OR (ii) clonal BMPC 10-60%.

  OR

  MM. Defined by IMWG criteria as signs of end organ damage including, hypercalcaemia (serum calcium >0.25 mmol.L^{-1} [>1 mg/dL] higher than the normal upper limit of >2/75 mmol/L [>11 mg/dL]), renal insufficiency (creatinine clearance <40mL/min or serum creatinine >177 micromol/L [>2mg/dL]), anaemia (Hb >2 g/dL below the lower normal limit, or a Hb <10g/dL), bone lytic lesions (one or more osteolytic lesions on skeletal radiography, computed tomography [CT], or positron emission tomography-CT [PET-CT]), known as CRAB symptoms (Rajkumar et al., 2014) who have either:

  - Completed their first cycle of induction therapy on one of the following regimes:
    - Bortezomib (Velcade®), thalidomide and dexamethasone (VTD)
    - Bortezomib (Velcade®), cyclophosphamide and dexamethasone (VCD)
    - Melphalan, prednisone and thalidomide (MPT)
    - Cyclophosphamide, thalidomide, and dexamethasone (CTD)
    - A different combination, *e.g.* monoclonal antibody (mAb) immunotherapy (*e.g.* daratumumab + VTD [D-VTD]) or,
  - Are in remission following a successful haematopoietic stem cell transplant

- Age ≥18 years

Sub-groups will be excluded due to safety risks:

- World Health Organisation (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status >1
- Pregnancy
- Deemed unsafe to exercise according to the Physical Activity Readiness Questionnaire (PARQ)
- Any comorbidity that is likely to progress or be exacerbated over the course of the trial period
- Cognitive impairment deemed a risk by the healthcare team for participation in the trial (*e.g.* diagnosis of neurodegenerative disease)
- Unable to understand explanations and/or provide informed consent
- Any condition and/or behaviour that would pose undue personal risk or introduce bias into the trial

Trial procedures

Recruitment

The Royal United Hospital Bath maintains an active database of people who are routinely monitored for SMM and MM, diagnosed by IWMG criteria. Patients who may be eligible to participate will be posted/given an invitation letter with a participant information sheet and will receive a follow up telephone call 14 days later from a member of the healthcare team to discuss the trial and gauge interest in participating. The study will be advertised to MM related charities and support groups, and suitable candidates will be invited to volunteer themselves indirectly to the researchers.

Persons who have expressed interest or volunteered in other studies of a similar nature (*e.g.* ISRCTN: 65527208) who meet the inclusion criteria will be posted/given an invitation letter with a participation information sheet and will receive a follow up telephone call 14 days later from a member of the healthcare team to discuss the trial and gauge interest in participating.

Those interested in participating will be asked preliminary screening questions with the aim of minimising the number of unnecessary visits for people who will be deemed ineligible at a later stage. Those who remain eligible will be invited to attend a screening visit at the University of Bath.

As part of routine care, people with SMM and MM are regularly contacted by the healthcare team via telephone and post (*e.g.* to update on clinic appointments, to discuss results from regular disease monitoring tests and to make contact about relevant patient events such as Myeloma UK meetings). Therefore, this recruitment method is deemed suitable by the healthcare team as it is familiar to the patient and reflects usual communication practice. Consent to use personal data (*e.g.* address / telephone number / medical history / age) is not being collected prior to screening as only members of the healthcare team will access this information and at this stage this information is being used solely to identify people who are potentially eligible to participate and to advertise the trial.

Screening

Telephone screening questions were developed by the researcher and haematologist with the aim of reducing the number of unnecessary face-to-face screening visits. The criteria checked during telephone screening are simple self-report questions:

- World Health Organisation (WHO) / Eastern Cooperative Oncology Group (ECOG) performance status
- Pregnancy
- Physical Activity Readiness Questionnaire (PARQ) (a brief questionnaire that is standard to complete in exercise settings, *e.g.* when joining a gym. It covers aspects of medical status that are used to determine a person's safety to exercise. People who give positive responses (answering 'yes') will require clearance to participate from the haematologist during face-to-face screening).

Exclusion criteria that require the clinical judgement of the haematologist will be discussed between the researcher and haematologist prior to face-to-face screening visits:

- Any comorbidity that is likely to progress or be exacerbated over the course of the trial period
- Cognitive impairment deemed a risk by the healthcare team for participation in the trial (*e.g.* diagnosis of neurodegenerative disease)
- Unable to understand explanations and/or provide informed consent
- Any condition and/or behaviour that would pose undue personal risk or introduce bias into the trial.
- Recent blood counts at levels that are deemed to pose undue risk by the healthcare team.

Disease activity history, comorbidities and concomitant medications will be accessed from medical records by the researcher for reporting of eligibility after informed consent has been obtained.

A 12-lead electrocardiogram (ECG) will be recorded at screening to assess any cardiac abnormalities which may be exacerbated by exercise. The ECG trace will be anonymised and shared via NHS mail with a cardiologist at the Royal United Hospital for review.

Consent

Written informed consent will be taken during the screening visit once patient eligibility has been confirmed and any questions about the trial have been answered.

People who elect not to participate during the initial telephone call, 14 days after receiving the recruitment material, will be asked during their next routine clinic appointment if they are willing to provide written informed consent to share their demographic data. This will be reported cross-sectionally at one time point to characterise people that decide not to take part for the primary trial outcomes and will inform future design (*e.g.* recruitment strategies) of a larger RCT in this patient group.

Trial assessments

The trial comprises two measurement visits: one baseline visit, and one trial visit.

Participants in Cohort 1 (pre-treatment), Cohort 2 (first-line treatment), and Cohort 3 (post-treatment) will attend the Royal United Hospital Bath or the University of Bath for Visit 1.

Participants in Cohort 1 (pre-treatment), Cohort 2 (first-line treatment), and Cohort 3 (post-treatment) will attend the Royal United Hospital Bath or the University of Bath for Visit 2.

Visit 1 (Baseline)

Participants in Cohort 1 (pre-treatment), Cohort 2 (first-line treatment), and Cohort 3 (post-treatment) will attend the Royal United Hospital, Bath or the University of Bath for a baseline visit lasting approximately 55-minutes. A table showing the duration and structure of visit 1, is shown in table 1.

To measure the ventilatory threshold of participants and to prescribe the exercise intensity for visit 2 the following tests will be carried out in all 3 cohorts.

After screening, participants in all cohorts will undergo visit 1. Participants will undergo a sub-maximal, ventilatory threshold fitness test on an ergonomic exercise bike to assess ventilatory kinetics and inform visit 2.

Table 1: Measurement protocol and timing for visit 1 to be completed at the Royal United Hospital, Bath.

Time period	Procedure	Description	Duration
0 – 5 min	Meet / greet	Research team meets the patient, explains the study procedures.	5 min
5 – 15 min	Rest in a seated position	Resting blood pressure measurements collected	10 min
15 – 30 min	Body composition	Body mass and composition via bio-electrical impedance, height.	15 min
30 – 50 min	Ventilatory threshold test	Cohort 1 (pre-treatment): Sub-maximal exercise test Cohort 2 (first-line treatment): Sub-maximal exercise test Cohort 3 (post-treatment): Sub-maximal exercise test	20 min
50 – 55 min	Debrief	Second appointment is scheduled	5 min

Resting measurements

Blood pressure: Blood pressure measured with an automated sphygmomanometer applied to the left arm during rest will take place before acute exercise to determine safety to exercise. Blood pressure measurements will be repeated in a lying position and standing position for evidence of postural hypotension. (unsafe if: blood pressure ≥200/120mmHg (ATS & ACCP, 2003) or participant reports new symptoms).

Anthropometrics and body composition: Body mass and body composition will be measured using digital Tanita scales and height using a stadiometer. Body mass index (BMI) will be calculated by dividing body mass (kg) by height (m) squared. Waist circumference (cm) will be measured at the narrowest point between the lowest rib

and iliac crest, and hip circumference (cm) will be measured at the widest point of the gluteal using a tape measure.

Ventilatory threshold test

Ventilatory threshold will be determined using a sub-maximal cycling test to a rating of perceived exertion (RPE) ≤17 or 80% of predicted heart rate maximum (HR_{MAX} [220 – age]) on a Lode cycle ergometer. The test will consist of 3-minutes of rest followed by 3-minutes of unloaded (0 watts) cycling followed by an incremental phase of exercise with an increase in workload (watts) of between 5 and 25 watts every minute (ATS & ACCP, 2003). The increment will be adjusted based on age, physical activity level and gender, to achieve the desired RPE or HR within 5-10 stages. ECG, blood pressure and blood oxygen saturation will be monitored continuously. RPE and HR will be recorded at the end of each stage. The test will be terminated if the participant fails to conform to the exercise test protocol, experiences adverse signs or symptoms, or requests to stop.

Health and safety: Participants unable to comply with the exercise test, for example due to a health problem raised during the exercise test (*e.g.* abnormal ECG or blood pressure response) or serious discomfort exercising, will discontinue involvement in the study on safety grounds. Abnormal test results will be referred to a cardiologist who will provide follow-up care and advise on the participants continued involvement in the study. The decision on whether to repeat baseline measures will be discussed with the trial management group; *e.g.* if follow-up care results in a considerable delay, there may be a need to repeat baseline measures prior to commencing further trial activities.

Free living measures

Participants will be given a physical activity monitor at the screening visit after informed consent has been obtained. This allows measures to be completed prior to Visit 1 which will be scheduled a minimum of 10-days after screening.

Physical activity: Participants will be given a BodyMedia Sensewear armband to wear for 10-days prior to visit 1 for the measurement of free-living physical activity. The monitor is worn on the upper arm and records acceleration and skin temperature continuously. No identifiable data is collected by the BodyMedia Sensewear. Participants will be provided with instructions on how to use the monitor which emphasises the importance of wearing the monitor continuously aside from during waterborne activities *e.g.* showering/swimming. Data from complete days (>80% wear time) will be reported to characterise the physical activity levels between cohorts. The BodyMedia Sensewear will be loaned to the participant for the duration of the measurement only. The devices are covered by the University of Bath insurance policy.

Visit 2 (Exercise trial)

Participants in Cohort 1 (pre-treatment), Cohort 2 (first-line treatment), and Cohort 3 (post-treatment) will attend the Royal United Hospital Bath, or the University of Bath, for approximately 1-hour and 45-minutes for a measurement visit scheduled between

06:00 and 11:00 on a weekday. The duration and structure of visit 2 to be completed at the Royal United Hospital Bath or the University of Bath is shown in table 2.

Participants will be asked to arrive well hydrated, having avoided food and caffeine since 22:00 the night before and having avoided strenuous exercise and alcohol for 24-hours. Participants will be given £5 to contribute towards travel costs to the Royal United Hospital Bath, or the University of Bath at the end of the trial. A sugary snack will be available for participants to consume following the visit.

Table 1: Measurement protocol and timing for visit 1 to be completed at the Royal United Hospital Bath, or the University of Bath.

Time period	Procedure	Description	Duration
0 – 5 min	Meet / greet	Research team meets the patient, explains the study procedures.	5 min
5 – 30 min	Controlled seated rest and questionnaire completion	Resting blood pressure measured following 25 minutes of rest and questionnaire completion. See below details of questionnaires.	25 min
30 – 35 min	Resting blood sample	Resting blood sample collected from an antecubital vein via venepuncture	5 min
35 – 65 min	Acute bout of exercise	Cohort 1 (pre-treatment): 30 minutes at an intensity 10-15% above ventilatory threshold Cohort 2 (first-line treatment): 30 minutes at an intensity 10-15% above ventilatory threshold Cohort 3 (post-treatment): 30 minutes at an intensity 10-15% above ventilatory threshold	30 min
65 – 68 min	Blood sample immediately after exercise	Post exercise blood sample collected from an antecubital vein via venepuncture within 3 minutes of exercise cessation	3 min
68 – 98 min	Rest in a seated position	Participants will rest in a seated position for 30 minutes	30 min
98 – 103 min	Blood sample 30 minutes after exercise	30 minutes post exercise blood sample collected from an antecubital vein via venepuncture	5 min
103 – 105 min	Debrief	Patient is thanked for participation	2 min

Questionnaires

General health status: Incidence of recent infections, smoking status, alcohol intake (AUDIT-C), menopausal status (females only), stress (perceived stress scale), anxiety and depression (Hospital Anxiety and Depression Scale) and demographic information will be self-reported by the participant.

Quality of Life: Health related quality of life (QoL) will be assessed using the 36-item short survey (SF-36) which includes eight domains: physical functioning; bodily pain; role limitations due to physical health problems; role limitations due to personal or emotional problems; emotional wellbeing; social functioning; energy/fatigue; general health perceptions and is validated for use with older adults. Overall QoL will be assessed using the Satisfaction with Life Scale: a 5-item questionnaire scored using a 7-point Likert scale that is validated for use in older adults.

Frailty: The International Myeloma Working Group (IMWG) frailty score is a validated questionnaire assessing aspects of frailty including comorbidities, basic activities of daily living (ADL) and instrumental ADL. The score is interpreted as fit (score = 0), intermediate-fitness (score = 1) or frail (score ≥ 2). Increased frailty is associated with mortality and treatment toxicity in people with MM (Palumbo et al., 2015).

Sleep quality: The Pittsburgh sleep quality index (PSQI) is validated to assess sleep quality and pattern in older adults. It is a 19-item questionnaire scored using a 0-3 Likert scale, with a total score >5 indicating poor sleep quality.

Fatigue: The functional assessment of chronic illness therapy (FACIT) fatigue scale is validated to assess fatigue in older adults. It is a 13-item scale scored using a 0-4 Likert scale, with a total score <30 indicating severe fatigue.

Physical activity: The international physical activity questionnaire (IPAQ) short form is validated to assess moderate and vigorous intensity physical activity and sedentary time.

Resting measurements

Blood pressure: Blood pressure measured with an automated sphygmomanometer applied to the left arm during rest will take place before acute exercise to determine safety to exercise. Blood pressure measurements will be repeated in a lying position and standing position for evidence of postural hypotension. (unsafe if: blood pressure ≥200/120mmHg (ATS & ACCP, 2003) or participant reports new symptoms).

Resting blood sample: A venous blood sample will be drawn from an antecubital vein via venepuncture for all cohorts by a trained phlebotomist after resting for 25-minutes.

- **Cohort 1 (pre-treatment):** A total of 34mL will be drawn from an antecubital vein for later analysis; 24mL in sodium heparin tubes (3 x 8mL), 5mL into an EDTA tube (1 x 5mL) and 5mL into a serum tube (1 x 5mL).
- **Cohort 2 (first-line treatment):** A total of 34mL will be drawn from an antecubital vein for later analysis; 24mL in sodium heparin tubes (3 x 8mL), 5mL into an EDTA tube (1 x 5mL) and 5mL into a serum tube (1 x 5mL).
- **Cohort 3 (post-treatment):** A total of 34mL will be drawn from an antecubital vein for later analysis; 24mL in sodium heparin tubes (3 x 8mL), 5mL into an EDTA tube (1 x 5mL) and 5mL into a serum tube (1 x 5mL).

Acute bout of exercise

Participants will perform a warm-up on a stationary cycle ergometer (an ergonomic Lode bike) for a minimum of 5-minutes. A supervised acute bout of exercise will then commence for 30-minutes. Target power output (watts) will be prescribed and monitored using power output and ventilatory data measured during the submaximal test in visit 1, along with RPE.

In all cohorts, participants will be given a wattage and HR zone that corresponds to the target percentage of 10-15% above their individual ventilatory threshold. The ventilatory threshold is the point during exercise where ventilation begins to increase at a faster rate that oxygen uptake.

The duration and intensity of exercise has been prescribed based on previous literature showing substantial increases in the mobilisation of NK cells in the peripheral blood in response to acute bouts of cycling exercise (Bigley et al., 2014). An RPE guide (Borg 7-20) will be used to confirm exercise intensity and used for people who may present with a blunted HR response due to for example, beta blockers.

Immediately post-exercise blood sample: Within 3-minutes of exercise cessation a second blood sample will be drawn from an antecubital vein via venepuncture for all cohorts.

30-minute post-exercise blood sample: Following 30 minutes of rest a third blood sample will be drawn from an antecubital vein for all cohorts.

In all Cohorts, a total of 34mL of blood will be drawn immediately after exercise, and 30-minutes after exercise for later analysis; 24mL in sodium heparin tubes, 5mL into an EDTA tube and 5mL into a serum tube.

Safety of exercise

Evidence has shown that exercise is safe throughout all stages of the myeloma survivorship continuum. Nonetheless, to remain vigilant, the safety of the trial will be monitored by the incidence and severity of adverse events (SAEs). Recording and reporting of SAEs will follow University of Bath policy – The chief investigator (CI) will report any SAEs to the sponsor within 24-hours. A written SAE report (health research authority [HRA] form) will be made by the lead researcher and sent to the CI who will assess the seriousness, causality, and expectedness. Where the SAE is related and unexpected, the CI will notify the research ethics committee (REC) within 15-days of receiving the report. AEs will be discussed by the trial management group, see table 2.

Table 2: Definitions of adverse events

Definitions of adverse events	
Term	**Definition**
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that product.
Serious Adverse Event (SAE)	A serious adverse event in the context of this trial is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity

	Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Withdrawal criteria

Participants may be withdrawn from the trial if there is a change in their eligibility *e.g.* disease progression or treatment failure. Contraindications and limitations to exercise may be identified during screening which will result in participants being withdrawn on safety grounds. All withdrawals will be discussed with the haematologist and reported in primary outcomes.

Storage of clinical samples

Samples will be collected at each time point and processed in a laboratory at the University of Bath:

In all Cohorts, a total of 34mL of blood will be drawn for later analysis; 24mL in sodium heparin tubes (3 x 8mL), 5mL into an EDTA tube (1 x 5mL) and 5mL into a serum tube (1 x 5mL).

Pre-, post- and 30-min post- exercise:

- 5mL into serum tubes, from which serum will be extracted and stored in multiple aliquots at −80°C for later analysis (*e.g.* disease activity, immune competence, inflammation, hormones, and metabolic factors).
- 5mL into EDTA tubes, from which a small fraction (50 µL) will be used to assess the leukocyte differential/whole blood cell count. This 50 µL of whole blood is destroyed and rendered acellular during measurement. This process will be repeated twice, and the average values reported. From the remaining 4.5mL plasma will be extracted and stored in multiple aliquots at −80°C for later analysis (*e.g.* disease activity, immune competence, inflammation, hormones, and metabolic factors).
- 8mL into sodium heparin tube, from which whole blood will be analysed by flow cytometry or stored at −140 to −150°C for later analysis (*e.g.* phenotypic and functional measures of immune competence, sequencing, and molecular biomarkers).
- 8mL into sodium heparin tube, from which whole blood will be used in a functional assay or stored at −140 to −150°C (*e.g.* phenotypic and functional measures of immune competence, sequencing, and molecular biomarkers).
- 8mL into sodium heparin tube, from which peripheral blood mononuclear cells (PBMCs) will be isolated by density gradient centrifugation and analysed by flow cytometry or stored at −140 to −150°C (*e.g.* phenotypic and functional measures of immune competence, sequencing, and molecular biomarkers).

Benefits of participating

Participants will be provided with bespoke feedback on their results within two months of their last visit. This will include blood pressure, body composition and physical capacity during acute exercise, with reference to the population normatives and recommended guidelines. Feedback to patients or clinicians will not be provided on data collected from blood samples because most of the measurements are preliminary research parameters and are not diagnostic.

Participants will be provided with £5 to cover costs of parking and public transport to the Royal United Hospital, Bath.

Risks of participating

The trial has been designed to reduce risks and burdens as much as possible, with the further aim of reducing potential risks and burdens further by strict adherence to best practice.

The exercise components of the trial (acute exercise session) carry a risk of injury and acute complications.

- The acute risks of exercise will be minimised by performing thorough screening at trial entry via medical note review by the haematologist. Physical activity readiness questionnaire (PAR-Q), blood pressure checks and resting ECG.
- Risks will also be assessed before the exercise session by measuring blood pressure and asking participants if they have had any symptoms of health change since their last session.

Taking a blood sample brings risks including pain, bleeding, bruising, embolism, and infection. These risks are controlled by adherence to best practice. People with SMM and MM will be familiar with the sensations associated with venous blood sampling as blood samples are collected as part of routine care.

Wearing activity monitors for prolonged periods may, in some cases, result in some minor skin irritation, but this will be minimal and good practice minimises this risk. Participants will be provided with verbal and written information on how to use the activity monitors to minimise this risk.

The questionnaires employed in this study will also ask patients about their mental health, anxiety, and well-being. These questionnaires could make the patient realise that they may need to seek help for their mental health. Therefore, the research team have ensured that a clinical psychologist is available by referral, should their direct health care team deem it necessary.

Statistics and data analysis

Sample size

This is a pilot study and the first to investigate the effects of exercise on the number of immune cells in the blood of people with myeloma and therefore, there is limited information available to enable a formal sample size calculation. This pilot trial will

provide preliminary data to determine that a future RCT has promise and is not futile and to perform a sample size calculation.

Studies in healthy humans that have recruited 7 to 13 participants have shown that a single session of exercise can significantly increase the number of NK cells, T cells (Bigley et al., 2014; Campbell et al., 2009), B cells (Turner et al., 2016), and monocytes (Steppich et al., 2000) in the blood. A more variable response is expected in this participant population, due to the different stages of MM survivorship and thus different treatment regimens in different participants. Therefore, up to a maximum of 15 participants will be recruited in each of the cohorts. This number of participants accounts for participant dropout that is expected to be at least 20% due to treatment progression, desire to withdrawal, and death. With three separate cohorts of 15 participants, this study aims to recruit a total number of 45 participants. We estimate that the target can be reached within a suitable time frame so that the findings can be submitted for a PhD thesis (12 months).

Statistical analysis plan

The mobilisation of immune cells in response to exercise will be tested for normality (*e.g.* Shapiro-Wilk) and log-transformed if required. Repeated Measures Analysis of Variance (ANOVA) will be performed to assess changes over time (pre and post), with between group factors used to assess differences between the cohorts. Post-hoc pairwise comparisons between time-points will be performed where necessary. Descriptive statistics will be presented for each cohort.

Monitoring, audit, and inspection

The University of Bath, as Sponsor, will monitor and conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the Department of Health Research Governance Framework for Health and Social care (April, 2005), and in accordance with the Sponsor's monitoring and audit policies and procedures.

Patient safety will be monitored on an ongoing basis by the research and healthcare team. A formal data monitoring committee will not be convened as this is a small single-centre pilot study, the lead researcher (PhD student, Harrison Collier-Bain) will present an update on safety at quarterly trial management group meetings, together with the haematologist(s) (Dr Moore and/or DR Murray and/or Dr Crowe), the CI and primary supervisor (Dr Campbell), secondary PhD supervisor (Dr Turner) and patient representative(s).

Ethical and regulatory considerations

Research Ethics Committee (REC) review

Before the start of the trial, approval will be sought from an NHS REC for the trial protocol, informed consent forms, participant information sheet and recruitment letter. Substantial amendments will require review by the NHS REC and will not be implemented until the NHS REC grant favourable opinion.

Public and patient involvement

People diagnosed with SMM and MM were invited to contact the research team to discuss the proposed trial design. Discussions were held on the following topics, with feedback on each point incorporated into the trial protocol and other trial documents.

- Proposed recruitment strategies, including invitation letters and follow-up invitation phone calls from the haematology department.
- Wording of trial documents, including the participant information sheet and consent forms.
- Practicalities of participant involvement in the trial, including: total time commitment, time of day preferences for people who are retired and people who are in full-time work, travel to the Royal United Hospital.
- All research measurements being taken in this trial, including blood sampling, and the exercise trial.
- Timing of the measurement visit, in particular during treatment.
- Use of activity trackers (*i.e.* BodyMedia Sensewear) to monitor participant physical activity levels in the 10-days preceding the exercise trial, which included a discussion about patient desire to wear such technology as this is a motivating factor for them to lead a healthier lifestyle.
- Any reservations of attending the Royal United Hospital and the protocols used (*e.g.* exercise testing and blood sampling) in light of the COVID-19 pandemic.

People with SMM and MM will also be involved in the analysis of results via trial management group and dissemination of findings through Myeloma UK – for which Dr Moore (haematologist) chairs meetings of the Myeloma UK South West Group.

Regulatory compliance

Participant samples will be stored in accordance with the Human Tissue Act 2004.

Protocol Compliance

Prospective, planned deviations to the protocol are not allowed under the UK regulations on research trials. Accidental deviations can happen at any time and should be documented and reported to the CI. Frequently recurring deviations can be classified as a serious breach. Deviations are not anticipated as the research team is relatively small and each member has been closely involved in the writing of this protocol.

Competing interests

There are no competing interests that will influence design, conduct or reporting of this trial.

Indemnity

The Sponsor (University of Bath) insurance will cover the legal liability for harm to participants arising from the design, management and conducting of this research.

Amendments

Substantial amendment to the document submitted in the original REC application will be submitted using a valid notice of amendment to REC and to the trial sponsor. Non-

substantial amendments will be made throughout the trial as needed. The CI will be responsible for determining whether and amendment Is substantial. Substantial amendments will be highlighted in a new version of the document.

Data management and confidentiality

The University of Bath will act as the Data Controller for data generated by this trial.

Identifying data (name, partial date of birth, contact details and next of kin details) will be kept by the Royal United Hospitals Bath NHS Foundation Trust. This data will be stored in a password-protected Excel spreadsheet on a secured NHS network drive. This data will be deleted following the final study contact. Signed consent forms will be stored in a locked cupboard and kept for a minimum of10-years to evidence the consent process.

Deidentified study data, coded with a unique study ID assigned to each participant, will be kept by the University of Bath. This data will be stored on a University of Bath secured research data storage drive which is backed up daily by the Universities IT department. The study-specific folder can only be accessed by the research team. Hard copies of trial data will be scanned and stored digitally on the Universities secured network drive and will be stored in a locked filing cabinet at the University of Bath and shredded after study completion. Study data will be kept for a minimum of 10-years in line with the University of Bath research data policy (see: https://library.bath.ac.uk/research-data/data-management-plans/home).

Post-trial care

Participants will be given bespoke feedback on their results after completing the trial period. This will include blood pressure, body comparison and physical capacity from the exercise trial, with reference to population normatives and recommended guidelines.

Access to the final trial dataset

All protocol contributors named in this document will have access to the final trial dataset. Requests for access by other researchers within the Department for Health at the University of Bath will be approved by the trial management group.

Dissemination policy

The data arising from this trial will be submitted for publication and presented at conferences and meetings. It will also be reported as part of a PhD thesis. People will be notified of outcomes of the trial via Myeloma UK South West.

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