Feasibility and benefits of a structured prehabilitation programme prior to autologous stem cell transplantation (ASCT) in patients with myeloma; a prospective feasibility study

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Expert article

Feasibility and benefits of a structured prehabilitation programme prior to autologous stem cell transplantation (ASCT) in patients with myeloma; a prospective feasibility study

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Abstract

Evidence supports the benefits of exercise-based rehabilitation in promoting recovery in myeloma patients following autologous stem-cell transplantation (ASCT). However, 'prehabilitation' has never been evaluated prior to ASCT, despite evidence of effectiveness in other cancers. Utilising a mixed method approach the authors investigated the feasibility of a mixed strength and cardiovascular exercise intervention pre-ASCT. Quantitative data were collected to determine feasibility targets; rates of recruitment, adherence and adverse events, including 6 minute walking distance (6MWD) test and patient reported outcome measures (PROMs). Qualitative interviews were undertaken with a purposive sample of patients to capture their experiences of the study and the intervention. The authors recruited 23 patients who attended a mean percentage of 75% scheduled exercise sessions. However, retention rates were limited, with only 14/23 (62%) completing the programme. In these patients, the 6MWD increased from a mean of 346 to 451 m (i.e. by 105 m, 95% CI 62 to 148 m) with no serious adverse events. Whist participants found the exercise programme acceptable and reported improvement in their physical fitness and overall mental health and wellbeing prior to ASCT, the study identified challenges in hospital attendance for the prehabilitation schedule whilst receiving induction or re-induction chemotherapy. Evaluation of digitally-enhanced directed but remote prehabilitation models for this patient group is warranted.

Trial registration number NCT03135925

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Contribution of paper

This feasibility study demonstrated that:

- A recruitment target of two patients per month is feasible in a definitive trial.
- Minimum average attendance at exercise session of was 66%.
- There was an 80% retention to 6-week follow up assessment.
- Patients found the intervention acceptable however, challenges were identified in consideration to hospital attendance.
- There were no serious adverse events.
- Assuming a target difference of 30 m in the change in 6MWD walked between the groups; a standard deviation of 80 m; equivalent to a standardised effect size of 0.38, 10% attrition, 90% power and 5% (two-sided) significance, a definitive trial would need to recruit and randomise 336 participants.
- Evaluation of digitally-enhanced directed but remote rehabilitation models of care for this patient group is warranted before embarking on a full trial.

Keywords: Prehabilitation; Exercise-based rehabilitation; Autologous stem-cell transplantation; PROMs

Background

Multiple myeloma is a cancer characterised not only by bone marrow infiltration of malignant plasma cells (causing anaemia and other cytopaenias), but also frequently widespread systemic features leading to variable degrees of bone disease (with pain, fractures and hypercalcaemia), immunodeficiency, infections, and renal failure. For the majority of patients, myeloma remains an incurable condition requiring sequential treatment of phases of disease activity. Fortunately, the number and types of available treatments have expanded over recent years and this has resulted in significant improvements in survival, particularly in younger age groups, to the extent that myeloma may be considered as a chronic relapsing-remitting disease in many patients [1]. Whilst many recently introduced therapies are 'novel' anti-myeloma agents, intensive consolidation with high-dose melphalan and autologous stem cell transplantation (ASCT) continues to provide a cornerstone of routine first line myeloma treatment. Second or salvage ASCT (sASCT) now also features in routine care of well-selected myeloma patients at first relapse in the modern era of treatment [2].

Despite improvements in survival, from the point of diagnosis and treatment the cumulative effects of myeloma combined with treatment-related toxicities have a significant impact on quality of life and at many levels of normal functioning [1,3–5]. Myeloma patients report more symptoms and limitations than those with other haematological malignancies post treatment [1,4,6]. Myeloma is also a disease of middle and older age, and there is a progressive impact of age-related co-morbidities and frailty.

Few myeloma patients engage in the recommended amounts of exercise during and following treatment and activity declines through treatment due to perceived barriers to exercise including pain, fear of injury and fatigue. Those who are sufficiently active before diagnosis of myeloma are more likely to be sufficiently active following treatment [7].

Rehabilitation following treatment in myeloma patients has been shown to improve physical performance; muscle strength and aerobic capacity; immunological function; psychological outcomes and reduce fatigue [8]. Exercise training for myeloma survivors has been shown to be safe and feasible during treatment with high attendance and adherence [9].

Studies demonstrate that patients pre-ASCT have reduced exercise capacity and increased co-morbidities compared with a normal population yet most rehabilitative interventions are focussed during and after treatment [10]. Cancer prehabilitation is defined as; *"a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments"* [12]. Prehabilitation is a potential solution to improve outcomes for this group of patients. A review of prehabilitation in pre surgical cancer patients [11] demonstrated the effective use of aerobic interventions in the management of patients undergoing thoracic surgery for lung cancer; identified the potential for its use in other oncology settings and called for further research to evaluate prehabilitation for wider groups of cancer patients [12].

In the 'intensive' pathway for younger myeloma patients, a window of opportunity exists to offer prehabilitation between diagnosis and the commencement of ASCT – usually a period of 4–6 weeks but this can be longer – during which time stem cell harvesting takes place prior to admission for high dose conditioning chemotherapy. Coleman *et al*. [13] studied 24 myeloma patients undergoing a home based exercise programme during chemotherapy and stem cell transplantation and identified that no patient injured themselves and that the intervention had positive effects on lean body weight, fatigue and sleep disturbance. They experienced high attrition rates, with 42% of patients leaving the study before completion. No evidence currently exists regarding the use of prehabilitation exercise interventions in myeloma patients who are due to receive ASCT. The primary aim of this study was to determine the feasibility of proceeding to a definitive trial

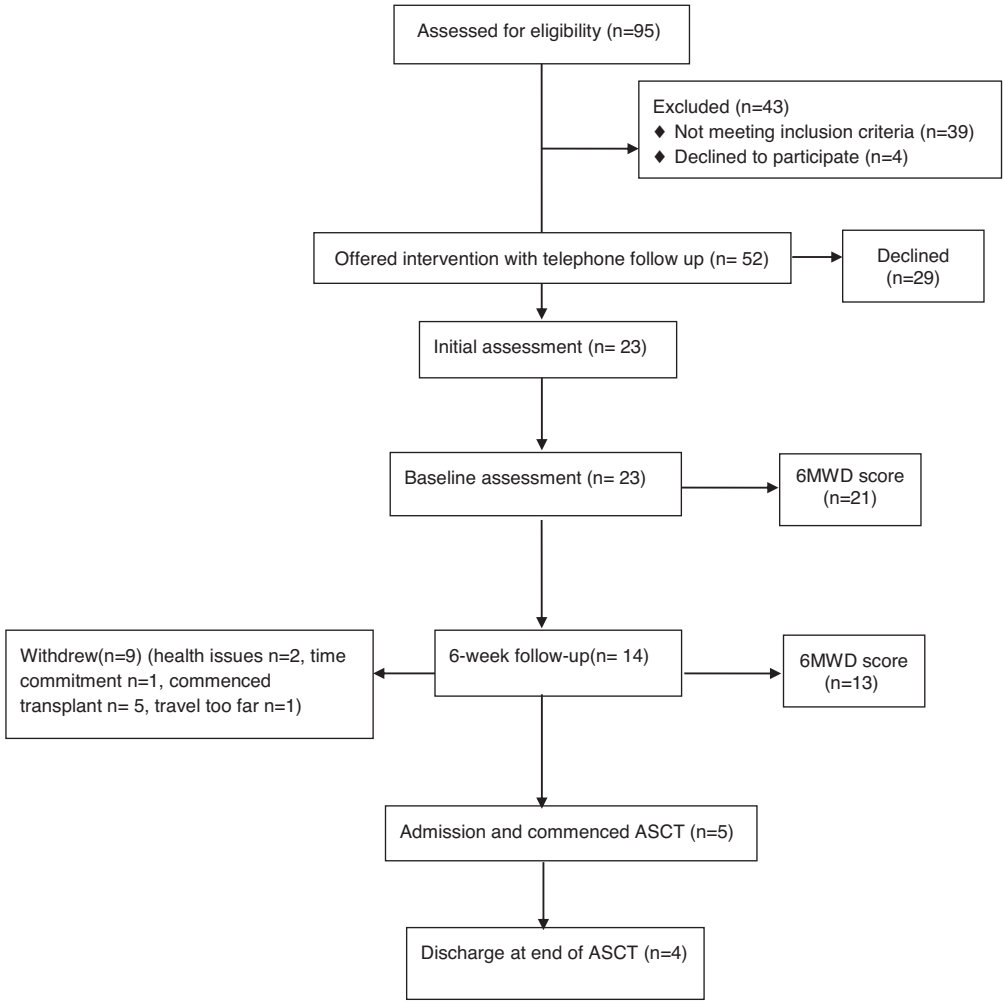

Fig. 1. Participant flow diagram.

of a mixed strength and cardiovascular exercise intervention before ASCT.

Methods

A mixed quantitative and qualitative data collection and analysis with a prospective feasibility study design was undertaken [14]. The full methodological details with sampling, inclusion and exclusion criteria and intervention have been published in the study protocol [15]. All patients with multiple myeloma who were awaiting ASCT (including first and second transplantation) were eligible to be invited to participate in this study. At the time of the study, this was approximately 70–80 patients per year. Assuming 70% of this population fulfil the inclusion criteria; this would give around 49–56 eligible patients per year; if 50% of eligible patients consent to take part in the study then the authors estimated to be able to recruit between 24 and 28 patients per year. Thus, in order for a definitive trial to be feasible the authors think the authors need to recruit eligible myeloma patients at a minimum recruitment rate of two per centre per month; i.e. 24 per year.

Ultimately, a total of 23 patients were recruited in 13 months however, nine withdrew (see Fig. 1) resulting in a small sample size of 13 for analysis.

Aims and objectives

The primary aim of this study was to determine the feasibility of proceeding to a definitive trial. The study objectives were to:

1. Assess the acceptability of the study to patients by measuring recruitment and retention to the study and through qualitative interview responses.
2. Explore reasons for non-consent to study participation.
3. Establish whether a target cohort of patients exists.
4. Determine the most appropriate recruitment points post diagnosis through, steering group feedback, the recruitment rate when compared with numbers invited to join the study and qualitative interview reports.

Table 1
Intervention description and replication check list (TiDieR).

	Item	Description
1	Brief name	Myeloma pre-habilitation exercise
2	Why	The interventions was based on mixed exercise programmes which have been shown to be safe and effective in myeloma survivors
3	What, materials and procedures	Materials: static exercise bike; treadmill; seated rowing machine; handheld weights; resistance equipment; heart rate monitor; gym ball; wall bars; wobble board Procedures: - cardiovascular exercises (treadmill, exercise bike, seated rowing machine) - upper and lower limbs strengthening exercises using body weight, handheld weight or resistance equipment - balance and core stability exercises
4	Who provided	Specialist physiotherapists with expertise in haematological conditions and exercise rehabilitation. Therapy assistants and non-specialist physiotherapists (under the supervision of specialist physiotherapist).
5	How	Face to face group exercise classes
6	Where	Physiotherapy gym within an acute hospital
7	When and how much	Up to six weekly sessions lasting 1 hour, including warm up and cool down. Each participant completed their individualised exercise program during the allotted time. Participants wore heart rate monitors and were advised to maintain their heart rate within a pre-calculated target range.
8	Tailoring	All participants were given an individualised exercise program to meet their needs and abilities. Programs were reviewed and modified as required based on observation and discussion with participants
9	Modifications	NA
10	How well	NA

5. Assess the suitability of inclusion and exclusion criteria by examining recruitment data.
6. Assess the acceptability of the intervention through qualitative interviews and retention rates during the study.
7. Determine duration of the intervention before transplantation commences by monitoring point of recruitment to the study and time to transplant.
8. Explore the appropriateness of outcome measures/completeness by qualitative interview responses, completion rates and time to complete.

Exercise intervention

The intervention consisted of an individualised, supervised exercise programme. Exercises were tailored to meet participants' ability, as identified by initial assessment by the physiotherapist. The exercise programme consisted of a combination of exercises completed in a circuit by participants:

- cardiovascular exercises (treadmill, exercise bike, seated rowing machine),
- upper and lower limbs strengthening exercises using body weight, handheld weights or resistance equipment,
- balance and core stability exercises.

Participants undertook a warmup and cool down at the start and end of each session. Participants wore heart rate monitors throughout the exercise programme and were advised to maintain heart rate within a calculated target range [16]. Throughout each exercise session participants recorded each activity on an exercise log sheet – this included number of repetitions, duration, any added resistance and the perceived effort. Exercise programmes were regularly reviewed and progressed or modified in line with participants' abilities.

The intervention was 6 weeks and occurred before patients underwent their ASCT. Participants may have subsequently undergone rehabilitation after their ASCT, but this was not captured in the study data (Table 1).

Feasibility outcomes

Feasibility outcomes were set as follows; 1) Recruitment target of two patients per month. 2) Minimum average attendance at exercise session of 66%. 3) 80% retention to 6-week follow up assessment. 4) Patient acceptability. 5) Adverse events.

Clinical outcomes

This was assessed with six-minute walk distance test (6MWD). The six minute walk test is a useful field test of functional capacity, is safe to administer and although has less correlation with peak oxygen capacity than the shuttle walk test, it is better tolerated by patients and is more reflective of activities of daily living as it is a submaximal exercise test [17] The six minute walk test has been found to be a valid and reliable test in patients with cancer [18].

Two sets of patient reported outcome measures (PROMs) were also assessed during the study; patients were allocated

Table 2
Two sets of PROMs assessed in the study.

PROMs 1		PROMs 2	
Category	Measure	Category	Measure
Physical activity/fitness	International Physical Activity Questionnaire	Physical activity/fitness	Godin Leisure Time
Mental wellbeing	Warwick – Edinburgh mental wellbeing scale	Mental wellbeing	Warwick - Edinburgh mental well-being scale
Quality of life	FACT– MM	Quality of life	EORTC QLQ C30 MY20
Self-efficacy with exercise	SCI self-efficacy for exercise scale	Self-efficacy with exercise	SCI self-efficacy for exercise scale

to complete one set of PROMs only (Table 2). Patients were allocated on an alternating basis to the two PROM groups based on the order in which they were recruited

The patient reported outcome measures used in the study were selected through PPI consultation. A focus group attended by three patients (1 pre-transplantation and 2 post-transplantation) was conducted in which study design was discussed, including a selection of proposed outcome measures. Representatives helped to identify the domains which they felt should be assessed, and the questionnaires which might be most effective.

Qualitative interviews

Patients who decline to take part in the exercise trial were asked if they would undertake a short telephone interview to ascertain their reasons for not taking part in the study. Participants who had been consented to take part in the trial and were undertaking the exercise programme were approached by a member of the clinical team and asked if they would be interested in taking part in a series of face-to-face or telephone interviews. Only two patients declined to take part in the qualitative interviews. The interviews were undertaken by an independent qualitative researcher.

Results and analysis

Demographics

The authors recruited 23 patients (mean and median age 65, range 53–78 years) over 13 months at a single centre (Sheffield Teaching Hospitals NHS Foundation Trust). The gender was similar between the two PROMs groups, (70% male, 30% female), but age was slightly higher in group 1 (mean 66.2, median 66 years) and lower in group 2 (mean 63.0, median 60 years).

Myeloma characteristics

Table 3 presents summary statistics on the length of time since the patient was diagnosed with myeloma.

Feasibility outcomes

Recruitment. Fig. 1 presents the participant flow diagram for the study. The study started with 95 potential participants, of which, 56 were eligible however, four declined to participate

Table 3
Myeloma diagnosis time (in years) summary statistics of the patients (N = 22).

Summary	Time since diagnosis (years)
Mean	2.2
SD	1.9
Median	1.3
IQR	(0.9, 2.8)
Min	0.5
Max	7.2

Table 4
Recruitment rate summary statistics.

Summary	Recruitment rate/month
Mean	1.8
95% confidence interval	(1.1, 2.5)
Median	2
IQR	(1.0, 3.0)
Min	0
Max	4

in the study and a further 29 declined when offered the intervention. The study recruited 23 patients (19 first ASCT, four sASCT) who attended baseline exercise sessions. Of these 23, 21 completed the 6-minute walking distance (the primary endpoint). At week 6, there were 14 patients remaining, of which 13 completed the 6MWD. The study aimed to collect data at the start and end of the transplant; data was collected from five patients at the start and four at the end.

The target recruitment was two patients a month for 12 months, therefore a total of 24 patients. The study recruited 23 patients over 13 months a rate of 1.8 patients per month (Table 4). The recruitment rate for the study was slightly under the target rate for most of the 12 month period.

Monthly recruitment rate

Exercise session attendance. The second feasibility criteria were to evaluate a minimum attendance rate of 66% for the exercise sessions. This was calculated using the number of sessions the patient was scheduled to attend. Occasional patients underwent ASCT sooner than the schedule could accommodate so were unable to complete the six sessions. Table 5 presents the summary statistics for the number and percentage of sessions attended. Mean and median number of sessions attended (4.5 and 5.0 respectively) exceeded the target of four sessions. The authors recruited 23 patients who attended a mean percentage of 75%, median 75% of their scheduled exercise sessions. The target percentage was 66%.

Table 5
Summary statistics for the number of sessions attended.

Summary	Number of sessions attended	Percentage of scheduled sessions attended
Mean	4.5	75%
SD	1.8	22%
95% confidence interval	(3.8, 5.2)	(66%, 84%)
Median	5	75%
IQR	(3.0, 6.0)	(58%, 100%)
Min	1	25%
Max	6	100%

Data showed that mean attendance was 4.5 weeks, with 11 participants attending for the full 6 weeks.

Retention and attrition rate. The study aimed to have a retention rate of at least 80%. This value was calculated using the patients who had a 6MWD at baseline and follow up as this is potentially the primary end point of the study. The retention rate in the study was 57% (13/23) which is lower than the target of 80%.

Adverse events (AE). Another feasibility criterion was the incidence of AE. There were 136 sessions in total (after the initial session) with one adverse event. Therefore, the mean number of adverse events was 0.01 with a 95% confidence interval of (0.00, 0.04).

Serious adverse events (SAE). The final feasibility criterion was the incidence of SAEs. There were no SAEs in the 136 sessions in total (after the initial session).

Feasibility criteria summary

Table 6 shows the different feasibility targets and whether they were met, almost met, not met.

Clinical outcomes

Outcome scores all changed from baseline to the 6 week follow up (see Table 6). When assessing clinical outcomes it is important to understand what the is Minimally Clinically Important Difference (MCID) for each outcome used [19]. As a comparator, the only outcome to have a MCID is the 6MWD where a difference of 25–35 m (m) is considered clinically meaningful for patients with Chronic Obstructive Pulmonary Disease (COPD) [20].

Whilst this feasibility study did not set out to explore the MCID for each PROMs used the results suggest that a number of the scores changed over time with improvements in some scores (see Table 7). However, further analysis is underway to establish if these changes were meaningful to this patient group.

The primary outcome for the study was the 6MWD, which had an initial mean score of 346 m and a final mean score of 451 m, in the 13 participants who completed both assessments, a mean increase in distance of 105 m (95% t-distribution confidence interval 62 to 148 m). Table 6 also summarises the changes in a wide range of PROMs, which generally reflect improvement in function and quality of life with the exercise programme. Paired t-tests were conducted on all the clinical outcomes to determine the direction of any effects. It is important to note that the analysis is not powered to detect any significant differences as this is a feasibility study and no sample size calculations were performed prior to the study. Both parametric and non-parametric tests were performed and agreed.

Sample size for the main RCT

The primary outcome for the main RCT is the change in distance walked, on the 6MWD, from pre to post rehabilitation, that is from baseline to the 6 weeks follow up (see Fig. 1). This feasibility study saw a change (mean increase) of 105 m (95% CI 62 to 148) in the 6MWD test from baseline to the 6 week follow up post the rehabilitation intervention in the 13 participants who had pre and post 6MWD data. The minimum importance distance (MID) for the 6MWD is variable depending on the condition/population it is being used for, and varies between 14 and 40 m [20–22]. The standard deviation for the change in distance walked pre to post rehabilitation was observed to be 71 m (95% CI 51 to 118). The standard deviation of the post rehabilitation distance walked was 81 m (95% CI: 58 to 133).

The recruitment rate was estimated to be 1.8 patients per month. It has been suggested that recruitment rates within a hospital setting is likely to be 1.24; with this in mind the sample sizes have been calculated using conservative recruitment rate estimates of one and two patients per month.

If the authors assume a target difference of 30 m in the change in 6MWD walked between the groups; a standard deviation of 80 m; equivalent to a standardized effect size of 0.38, 10% attrition, 90% power and 5% (two-sided) significance, then the main trial would need to recruit and randomise 336 participants.

Table 8 shows that a target sample size of 336 participants with a recruitment rate of two patient/centre/month and 24 months of recruitment; the authors would need a seven centre trial.

The protocols for the qualitative data collection and analysis have been reported in the previously published study protocol [15]. The framework approach was used to analyse the qualitative data. This method is appropriate for identifying, analysing, and reporting themes and patterns within data. It is a flexible and useful research tool, which can potentially provide a rich and detailed, yet simple account of data. Early on in the analysis the transcripts were repeatedly read to develop an understanding of the breadth and depth of the data. During this process, data were labelled and coded in an iterative process whereby patterns and sequences of content over time were identified within and across all the participants. Emergent themes were further developed and refined

Table 6
Feasibility targets.

Target	Mean	95% confidence interval	Target met?
Recruitment target of two patients a month	1.8	(1.1, 2.5)	Almost met. The mean is below the target, however the target is within the confidence interval.
Minimum average attendance of 66%[a]	75%	(65.8, 84.1)	Met. The mean is above the target and the confidence interval contacts the target.
80% retention to 6 weeks	62%	(40.9, 79.2)	Not met. The mean is less than the target and the confidence interval is below the target.
Adverse events	*0.01*	(0.00, 0.04)	There was one adverse event out of 136 sessions. The adverse event was due to a long standing condition, which the exercise sessions aggravated. The remaining sessions were adjusted to suit the patient condition and they were able to continue.
Serious adverse events	*0*	(0.00, 0.03)	Met. There were no serious adverse events in the study.

[a] This percentage was calculated from the number of sessions the patient was scheduled to attend. The target of six sessions was difficult with some patients receiving the transplant early.

by analysing similarities and divergences between and within the participants, to form a coherent pattern.

Patient acceptability

Non-participants

Of the 33 patients that declined to take part in the exercise programme, all were approached and six agreed to undertake a short telephone interview to discuss the reasons for non-participation.

The distance to get to the venue, and the location of the venue, was cited as one of the main reasons for non-participation in the study. The impact of feeling fatigued and not being able to manage other activities within the context of daily living and living with myeloma were also cited during the telephone interviews. Four of the six patients lived outside city boundaries and consequently travelling was an issue, as illustrated by the following quote:

'The main reason is I don't drive, I live in (place) and it would mean getting a train and then a bus' (TP1).

However, distance alone was not always the sole reason and four patients described how having to manage attendance at clinical appointments, alongside travel time, also contributed to their decision to not take part.

Participants

Of those taking part in the exercise programme, seven participants initially agreed to take part in the qualitative component of the study. Semi-structured interviews were conducted with a purposive sample of four participants who had completed the exercise programme prior to ASCT. Three participants were not contactable by telephone. The researcher met the participant at the penultimate exercise session. This enabled confirmation of consent to participate and the first interview date and time to be arranged.

It had been intended that interviews would be conducted at a number of time points: following completion of the exercise programme, prior to ASCT and post ASCT. This would capture the perspectives of the participants' over time, specifically in relation to the acceptability of the intervention. It became clear that for some participants that there was a short time frame between the exercise programme and the transplantation, therefore the decision was taken to complete two interviews, following the exercise programme and following ASCT. However, a number of factors influenced the ability of the participants to undertake two interviews, for example, the impact of the illness or the timing of ASCT post exercise programme.

Experience of the exercise programme

All the participants talked positively about their experience of the exercise programme. All of them felt well supported by the physiotherapists in that they were given exercises that were appropriate to their level of fitness and capability. Furthermore, the participants were given detailed instruction on how to undertake the exercises, and also how to improve their technique and fitness. This contributed to increasing the participants' ability to engage with the programme, as illustrated by the following quote:

'They were good at sorting technique. All of them were attentive and made sure you were okay' (P3).

One participant encountered challenges getting to the gym, especially when this meant travelling to the hospital for an extra day in the week. Also, the timing of the class meant that it was difficult to plan other activities in the day. This participant would have preferred an individually tailored programme of exercise that they could practice at home, with a reduced number of gym visits.

All of the participants described how the exercise programme had improved their level of fitness and stamina. Initially three participants struggled with the exercises as walking had been problematic due to bone pain and neuropathy. However over the six week programme their reported mobility had improved along with ability to manage the exercises more effectively.

All participants reported that the exercise programme had improved confidence, overall mental health and wellbeing, as summarised by the following quote:

Table 7
6MWD and PROMs baseline to 6 week follow up.

	N	Initial Mean (SD) Median (IQR)	Final Mean (SD) Median (IQR)	Mean change (SD)	95% CI	Median change	IQR
6 minute walking distance (m)	13	346.9 (100.9)	451.8 (80.7)	104.9 (71.4)	61.8, 148.1	98	53.0, 145.0
		380 (320,390)	443 (405, 495)				
IPAQ	6	2678 (2990)	3812(3842)	1134 (2223)	−1199, 3466	1622	−367, 2850
		1939 (586, 3170)	2638 (1408, 3995)				
Godin	7	19.9 (29.5)	34.0 (41.8)	14.1 (17.7)	−2.3, 30.5	9	0.0, 21.0
		3.0 (1.5, 26.5)	18.0 (6.0, 52.0)				
WEMWBS	12	47.5 (12.7)	50.8 (10.9)	3.4 (7.5)	−1.4, 8.2	3.5	−2.0, 7.0
		47.0 (38.0, 56.0)	51.5 (47.8, 56.8)				
ESES	13	28.7 (5.8)	30.2 (6.2)	1.5 (5.6)	−1.9, 4.9	2	−1.0, 4.0
		27.0 (25.0, 35.0)	30.0 (28.0, 36.0)				
FACT-MM-TOI	6	63.0 (25.3)	71.0 (14.5)	8.0 (28.3)	−21.7, 37.7	−2	−7.5, 8.8
		68.5 (55.3, 76.5)	73.0 (60.8, 80.8)				
FACT-G	6	68.3 (19.7)	65.5 (18.3)	−2.8 (12.3)	−15.7, 10.0	−0.5	−5.5, 6.0
		70.5 (67.3, 73.0)	69.0 (52.8, 74.0)				
FACT-MM	6	98.8 (34.2)	102.7 (19.5)	3.8 (31.9)	−29.6, 37.3	−1.5	−11.3, 9.0
		107.0 (94.8, 113.3)	98.5 (93.3, 111.3)				
EORTC QL2	5	62.5 (27.8)	69.4 (19.5)	6.7 (23.9)	−23.0, 36.3	8.3	−8.3, 25.0
		66.7(54.2, 72.9)	75.0 (56.3, 81.2)				
EORTC PF2	7	62.9 (27.2)	76.0 (20.5)	13.1 (8.6)	5.1, 21.1	13.3	9.2, 16.7
		66.7 (46.7, 80.0)	80.0 (60.0, 92.5)				
EORTC RF2	7	54.8 (45.9)	71.4 (36.9)	16.7 (19.2)	−1.1, 34.5	16.7	0.0, 25.0
		50.0 (16.7, 100.0)	100.0 (41.7, 100.0)				
EORTC EF	5	80.6 (20.2)	84.7 (12.3)	5.0 (12.6)	−10.7, 20.7	0.0	0.0, 8.3
		83.3 (83.3, 89.6)	87.5 (77.1, 91.7)				
EORTC CF	5	66.7 (33.3)	88.9 (8.6)	20.0 (29.8)	−17.0, 57.0	0.0	0.0, 33.3
		66.7 (50.0, 95.8)	83.3 (83.3, 95.8)				
EORTC SF	5	38.9(39.0) 33.3 (8.3, 58.3)	55.6 (39.0) 66.7 (29.2, 79.2)	10.0 (14.9)	−8.5, 28.5	0.0	0.0, 16.7

Table 7 (*Continued*)

	N	Initial Mean (SD) Median (IQR)	Final Mean (SD) Median (IQR)	Mean change (SD)	95% CI	Median change	IQR
EORTC FA	7	56.4 (32.5)	34.1(27.3)	−22.2 (29.9)	−49.9, 5.4	−11.1	−36.1, 0.0
		50.0 (44.4, 77.8)	33.3 (16.7, 44.4)				
EORTC NV	7	7.1 (13.1)	11.9(18.6)	4.8 (8.1)	−2.8, 12.3	0.0	0.0, 8.3
		0.0 (0.0, 8.3)	0.0 (0.0, 16.7)				
EORTC PA	7	42.9 (45.0)	42.9 (25.2)	0.0 (25.5)	−23.5, 23.5	0.0	−16.7, 16.7
		33.3 (0.0, 83.3)	33.3 (33.3, 66.7)				
EORTC DY	7	61.9 (40.5)	28.6 (40.5)	−33.3 (33.3)	−64.2, −2.5	−33.3	−33.3, −16.7
		66.7 (33.3, 100.0)	0.0 (0.0, 50.0)				
EORTC SL	7	23.8 (25.2)	38.1 (23.0)	14.3 (26.2)	−10.0, 38.5	33.3	0.0, 33.3
		33.3 (0.0, 33.3)	33.3 (33.3, 50.0)				
EORTC AP	7	19.1 (26.2)	33.3(33.3)	14.3 (32.5)	−15.8, 44.4	0.0	0.0, 33.3
		0.0 (0.0, 33.3)	33.3 (0.0, 66.7)				
EORTC CO	7	33.3 (38.5)	9.5 (16.3)	−23.8 (37.1)	−58.1, 10.5	0.0	−33.3, 0.0
		33.3 (0.0, 50.0)	0.0 (0.0, 16.7)				
EORTC DI	5	5.6 (13.6)	5.6 (13.6)	6.7 (14.9)	−11.8, 25.2	0.0	0.0, 0.0
		0.0 (0.0, 0.0)	0.0 (0.0, 0.0)				
EORTC FI	5	5.6 (13.6)	5.6 (13.6)	−6.7 (14.9)	−25.2, 11.8	0.0	0.0, 0.0
		0.0 (0.0, 0.0)	0.0 (0.0, 0.0)				
EORTC MYFP	4	62.2 (41.3)	61.1 (21.3)	−2.8 (26.3)	−44.6, 39.0	−11.1	−22.2, 8.3
		55.6 (55.6, 100.0)	66.7 (50.0, 77.8)				
EORTC MYBI	4	66.7 (47.1)	75.0 (31.9)	16.7 (19.3)	−14.0, 47.3	16.7	0.0, 33.3
		100.0 (33.3, 100.0)	83.3 (58.3, 100.0)				
EORTC MYDS	6	30.6 (22.4)	18.9 (16.8)	−11.3 (5.2)	−16.8, −5.8	−11.1	−15.3, −6.9
		30.6 (12.5, 44.4)	16.7 (5.6, 30.0)				
EORTC MYSE	6	18.8 (10.6)	12.9 (11.3)	−6.1 (4.5)	−10.8, −1.4	−3.3	−8.3, −3.3
		20.0 (12.5, 27.2)	13.3 (3.3, 21.7)				

Table 8
Sample size with target difference of 30 m in the mean difference in the change in distance walked with an SD of 80 m and 90% power and 5% two-sided significance level and 10% attrition and varying recruitment rates and recruitment durations.

Rate recruitment patient/centre/month	Significance level	Power	SD	Mean difference	Standardised effect size	Total sample size dropout 10%	Recruitment duration/months	No. of centres
1	5%	90%	80	30	0.38	336	12	28
1	5%	90%	80	30	0.38	336	18	19
1	5%	90%	80	30	0.38	336	24	14
1	5%	90%	80	30	0.38	336	30	12
1.5	5%	90%	80	30	0.38	336	12	19
1.5	5%	90%	80	30	0.38	336	18	13
1.5	5%	90%	80	30	0.38	336	24	10
1.5	5%	90%	80	30	0.38	336	30	8
1.8	5%	90%	80	30	0.38	336	12	16
1.8	5%	90%	80	30	0.38	336	18	11
1.8	5%	90%	80	30	0.38	336	24	8
1.8	5%	90%	80	30	0.38	336	30	7
2	5%	90%	80	30	0.38	336	12	14
2	5%	90%	80	30	0.38	336	18	10
2	5%	90%	80	30	0.38	336	24	7
2	5%	90%	80	30	0.38	336	30	6

'It proved that I was capable of doing things, it made me more positive that in the future I may get some of my health back, maybe I will be able to play badminton again. Suddenly all your social life goes out of the window especially if it has been sports based, you don't do it anymore and it leaves big gaps' (P2).

Completing exercise logs

All of the participants logged their exercise activity during their gym sessions, although initially some had needed assistance. Although three participants highlighted that the forms demonstrated some improvement in their performance/fitness, they felt the forms did not totally capture the improvement. As participant two described:

'Sometimes the form didn't reflect that I was getting better. I would set off and do 5 minutes on the exercise bike, I found that easy so they upped it to 10 minutes. I'd still say breathlessness 12 or whatever, but that's because I was doing twice as long on the machine so you would have to read the form a little more carefully to see I was actually upping the duration of what I was doing. So maybe that needs building into the form in some way'. (P2)

To address this issue, three participants mentioned that it would be useful to have space on the form to note where exercise levels had increased, such as time on an activity, or increased level of difficulty. One participant stated how they had written on the form where they spent longer on an activity so that the improvement in stamina could be seen.

Discussion

This study has assessed all the feasibility criteria outlined in the original protocol, demonstrating that recruitment is feasible, with 74.9% of participants attending scheduled exercise sessions. However, the retention rate was below the required rate of 80% with only a 57% retention rate. Whilst the authors have been able to calculate a sample size and sampling period with seven recruiting centres the qualitative data highlighted a number of issues with the model of rehabilitation being provided in this feasibility study. Participants found the exercise programmes acceptable and four participants interviewed felt the programme had improved their physical fitness and enhanced their overall mental health and wellbeing.

Whilst there were improvements in a wide range of PROMs, which generally reflected improvement in function and quality of life the observed improvement in the 6MWD by a mean of 105 m (95% confidence interval 62 to 148 m) is encouraging, with no serious adverse events. As the MCID for the 6MWD is between 14 and 40 m, this observed improvement is certainly clinically meaning-

ful [21–23]. However, despite the potential benefits, it is very clear that some participants encountered challenges in attending the hospital for the prehabilitation programme during their induction/re-induction chemotherapy in the run up to ASCT (mean attendance was 4.5 weeks). The sample size for the qualitative interviews was small and data saturation was not achieved, this being a limitation of the study.

A recent UK policy document relevant globally for rehabilitation models [24] recommends the need for public health service providers to support more flexible rehabilitation pathways that allows patients to move from 'acute complex specified rehabilitation' to different phases of specialist rehabilitation within their region or local community.

As some of our participants found it difficult to attend for acute complex specialist rehabilitation, there is a need to explore the potential benefits of local rehabilitation, which would alleviate the problems identified in traveling to acute hospital services during induction/re-induction chemotherapy, improving the retention within a prehabilitation programme thereby extending its potential benefits in the run up to ASCT. However, local rehabilitation would not be able to offer specialist services for this complex patient group, and may therefore require support from specialist services.

It is now highly relevant to test whether digitally enhanced information and communication technologies can promote a more self-care or directed care model [25,26], thereby providing the means for on-going real time direction or delegation and review from medical and rehabilitation specialists.

Conclusion

This feasibility study has demonstrated that it would be possible to undertake a fully powered multi centred RCT to investigate a prehabilitation intervention for patients with myeloma due to undergo ASCT. There were both objective and subjective benefits, from both physical and a psychological perspectives, which could potentially benefit myeloma patients during a phase in their treatment associated with the start of 'deconditioning'. However, evaluation of digitally-enhanced directed but remote rehabilitation models of care for this patient group is warranted before embarking on a full trial.

Ethical approval:Ref. No. 16/YH/0304BradfordRC Yorkshire & The Humber – Bradford Leeds Research Ethics Committee.

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Appendix A. Supplementary data

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