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Group psychological intervention for emotional distress in haematopoietic stem cell transplantation: A feasibility randomised clinical trial

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ABSTRACT

Purpose: Haematopoietic stem cell transplantation (HSCT) is an intensive procedure associated with elevated psychological distress, particularly during the initial stages. Based on self-regulatory theory, a prophylactic group intervention was developed to mitigate this distress by targeting perceptions of HSCT and coping. This study evaluated the feasibility of delivering the intervention and of conducting a randomised clinical trial to assess efficacy.

Methods: Adults from consecutive referrals at two transplant centres were randomised to the intervention or to treatment as usual at each site. Psychological distress (primary outcome), HSCT perceptions, and coping were assessed at baseline, on transplant day, and two and four weeks after transplantation.

Results: Of 99 eligible patients, 45 consented. Main barriers to consent were insufficient time prior to transplantation, competing priorities, being unwell, and travel distance. Of 21 participants randomised to the intervention, five attended. Main barriers to attendance included insufficient time prior to transplantation and having competing priorities. Groups could not be held sufficiently frequently to enable attendance prior to transplantation, as randomising participants to the control group limited accrual. Anxiety peaked two weeks following transplantation. Depression increased throughout the acute phase. Clinical levels of distress were observed in 42% of patients during HSCT. Intervention effects were small but sample sizes for a full trial appeared feasible.

Conclusions: Multimodal prehabilitation is required but there are specific barriers to delivering a group-based intervention and conducting a trial. Group prehabilitation requires customisation and better integration with routine care, such as patient screening, personalisation, and options for remote delivery.

1. Introduction

Haematopoietic stem cell transplantation (HSCT) is an intensive procedure aimed at a range of haematological and autoimmune illnesses with an initial, acute phase often lasting several weeks of exposure to high dose chemotherapy, isolation, complications, and debilitating side effects (e.g., fatigue and nausea; Amonoo et al., 2019; Prieto et al., 2005). Patients often report a psychologically overwhelming experience and clinical levels of anxiety and depression are common (Amonoo et al., 2019; Lee et al., 2005; Prieto et al., 2005; Tecchio et al., 2013). Such distress is thought to have negative effects on recovery with lower tolerance for physical symptoms, longer hospitalisation, and poorer immune response, treatment adherence, and survival (Amonoo et al., 2019; Pulgar et al., 2012).

Psychological prehabilitation has been found to alleviate psychological distress prior to other cancer treatments (Tsimopoulou et al., 2015) and therefore may be beneficial during acute HSCT. However, few such interventions have been developed in HSCT and those show limited benefits or do not address distress at its onset (Baliousis et al., 2016; Cioce et al., 2020). Furthermore, studies have methodological shortfalls such as limited control or high risk of bias (Baliousis et al., 2016; Bauer-Wu et al., 2008; Bevans et al., 2010; Cioce et al., 2020; Horton-Deutsch et al., 2007; Lounsberry et al., 2010).

Further, psychological intervention research in HSCT indicates that there may be feasibility issues, but these remain poorly understood. For example, psychological intervention uptake has been low in the period

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following transplantation, overall adherence to psychological interventions seems poor, and sample sizes decrease as interventions become more intensive and less self-directed (Baliousis et al., 2016; Braamse et al., 2016). Further, self-directed interventions in HSCT (and prehabilitation in cancer more generally) have limited benefits compared to those supported by a qualified healthcare professional (Baliousis et al., 2016; Grimmett et al., 2022). Understanding feasibility issues is necessary so that psychological prehabilitation in HSCT can target patients' needs effectively.

Another feature that has remained neglected in HSCT (Baliousis et al., 2016; Cioce et al., 2020) is the potential of group-based therapy. Group delivery can capitalise on the benefits of a shared social identity and social support for wellbeing, positive coping, and healthcare adherence in cancer and HSCT (Häusser et al., 2020; Luo et al., 2020; Moyer et al., 2009; Nørskov et al., 2021). However, group delivery is likely to have its own feasibility issues that require exploration.

From these considerations, the present study aimed to evaluate the feasibility of delivering a group-based preparatory psychological intervention targeted at reducing psychological distress during acute HSCT and of conducting a future full randomised clinical trial (RCT) to determine clinical efficacy. The objectives were to assess the: (1) feasibility of delivering the intervention and conducting the trial through examining accrual of referrals, the impact of participant eligibility criteria on accrual, study uptake, willingness to be randomised to and attend the intervention (patients), willingness to recruit participants and facilitate the group (staff), attrition, response rates, adherence to the protocol, and test the randomisation and data collection procedures; (2) reliability and validity of outcome measures in HSCT where physical symptoms may affect psychometric properties; (3) trajectory of distress over time to determine the optimal timepoint for analysis; (4) effect size estimates to help with sample size calculations for a full trial.

2. Methods

2.1. Participants

Participating patients were from consecutive referrals (January to September 2015) at two haematology departments in different regions of England. Inclusion criteria were: (a) scheduled to receive HSCT for haematological malignancy; (b) over 18 years old; and (c) able to communicate in English to participate (including hearing ability for telephone data collection). The target sample size was 60 patients, sufficient to gather information on feasibility in line with guidance (Julious, 2005; Sim and Lewis, 2012). Participating staff were the clinical psychologists and physiotherapists (cofacilitating the intervention) and the bone marrow transplant coordinators (cofacilitating and intending to recruit participants).

2.2. The intervention

Our intervention "Preparation Group", described following the TIDieR guide (Hoffmann et al., 2014), was based on the *self-regulatory model* (Hagger and Orbell, 2021). The model has three components: (a) interpretation (e.g., appraisals about treatment consequences, timeline); (b) coping (e.g., distraction); and (c) appraisal of coping (e.g., effectiveness of distraction; Fig. 1). The model has been supported as useful in different populations and specifically HSCT and in physical recovery (Baliousis et al., 2017; Hagger and Orbell, 2021). Based on this model, our intervention aimed to alleviate distress by: (a) reducing negative perceptions of HSCT via the provision of information; (b) encouraging helpful coping within the context of the procedure; and (c) enhancing coping appraisals by demonstrating aspects of HSCT that can be managed.

The conversations around formalising the content of the intervention emerged after two years of one site developing and refining a group for allogeneic patients using patient feedback. The intervention was formalised and structured over a six-month period via peer supervision among facilitators and feedback from patient advisors who participated opportunistically in monthly formative discussions. The informational content of the intervention was based on The Seven Steps book (Kenyon, 2012). Our patient advisors were allogeneic patients, as a way of fast-tracking the process of formalising delivery and content, due to the increased likelihood of physical complications in this group. As the procedure is similar (though less severe in nature) for autologous patients, the content of the intervention applied to both patient groups. Patients provided feedback on what information was most relevant and the extent to which delivery could achieve the intervention's three psychological aims outlined above. To conduct the development process, we were guided broadly by a coproduction framework (Stilgoe et al., 2013) comprising of: (a) Anticipating effects of the intervention;

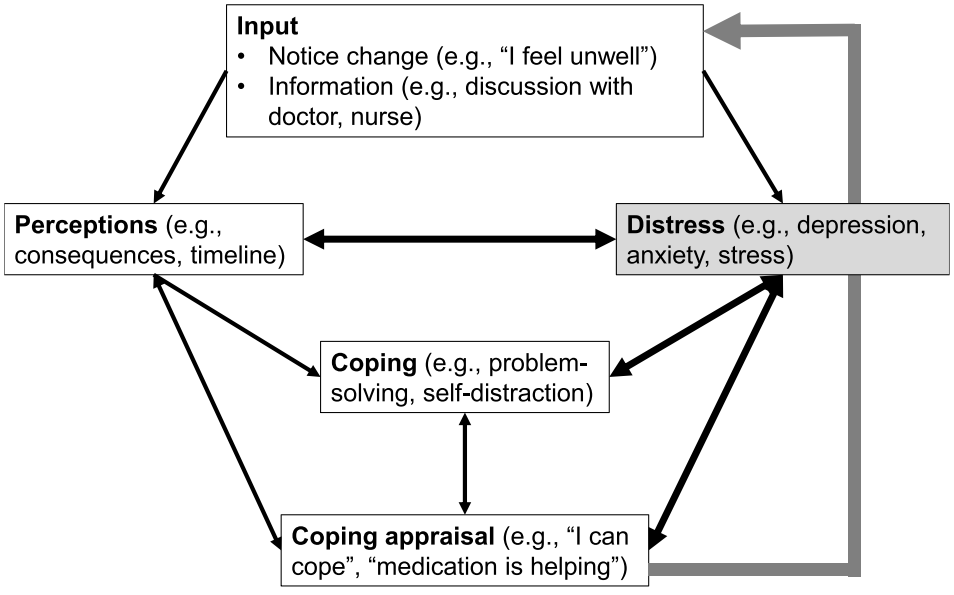

Fig. 1. The self-regulatory model suggests three interacting components in the process of psychological adjustment to illness: interpretation (or illness perception), coping, and appraisal of coping. Interpretation includes perceptions of the severity of the consequences of the illness, duration, identity (label and symptoms), concern, degree of understanding, and emotional impact. Coping involves strategies which the patient employs to mitigate their perceived psychological threat and related negative emotions. This is followed by appraisal of coping which evaluates the effectiveness of the coping efforts in a feedback loop (Hagger and Orbell, 2021).

(b) Reflexivity on how the intervention was experienced; (c) Inclusion of diverse patient feedback; and (d) Responsiveness by amending the content and process of the intervention accordingly.

Details of components, content, aims, delivery, and psychological targets of the intervention are shown in Table 1. As the length of the intervention was relatively short, ensuring delivery was collaborative with the use of interventive questions (Padesky, 1993) aimed at placing emphasis being on what was most relevant to patients each time. The intervention was delivered in a single, 90-min, face-to-face, group session, at a pre-booked quiet room at the hospital. The sessions, provided in addition to treatment as usual (TAU, please see below), were to take place monthly and were facilitated by the Transplant Coordinator, Clinical Psychologist, and Physiotherapist. All professionals delivering the intervention were experienced senior clinicians in HSCT. No specialist training was required to deliver the intervention. The handout for the intervention is available as online Supplement.

Treatment as usual. TAU did not aim to address perceptions and coping though this may have occurred unsystematically as HSCT progressed. Patients participated in at least two discussions about the procedure with members of the clinical team. Patients were provided with written information packs about the procedure and the hospital stay, including The Seven Steps book (Kenyon, 2012). Specialist nursing staff provided support as required. Patients who experienced considerable distress received psychological input.

Psychological intervention fidelity. To establish fidelity between the two hospitals, the first group session was recorded and discussed in peer supervision between the facilitators across sites. Discrepancies from key elements listed in the intervention schedule were identified and delivery was amended accordingly.

2.3. Materials

We measured psychological distress with the Depression Anxiety Stress Scales (DASS-21) because it is brief (21 items) given the burden already placed on participants, and its ability to capture complex distress patterns (Antony et al., 1998; Henry and Crawford, 2005). DASS-21 provides subscale and total scores. Each subscale comprises seven items rated on a four-point Likert scale based on experience over the preceding week. Subscale scores range from 0 to 21, higher scores denote higher distress (Henry and Crawford, 2005). DASS-21 clinical cut-off scores are: Depression≥7, Anxiety≥5, Stress≥10 (Lovibond and Lovibond, 1995). The DASS-21 has shown good reliability (Cronbach's $\alpha = 0.82–0.94$) and validity in clinical samples (Antony et al., 1998; Henry and Crawford, 2005; Page et al., 2007).

2.4. Design

The study was prospective 2x4 mixed between-within-subjects parallel RCT (Wang and Bakhai, 2006). Considering documented distress patterns (Prieto et al., 2005; Tecchio et al., 2013), the within-subjects factor was time with four time points: prior to HSCT (baseline), on transplant day, and two and four weeks after transplant. The between-subjects factor was intervention plus TAU versus TAU alone (control). The dependent variables were overall distress (primary outcome) and depression, anxiety, and stress (secondary outcomes).

We used block randomisation with block size of four and 1:1 sequential allocation with separate randomisation codes for each site (Altman and Bland, 1999; Wang and Bakhai, 2006). Randomisation codes were computer-generated (Saghaei, 2004) and held by someone not involved in the study otherwise, keeping a log to ensure allocation was adhered to. The allocation was concealed from the outcome assessor only. The difficulties with participant blinding for interventions whose nature is not concealed (Wang and Bakhai, 2006), such as the present intervention means that it could not be an essential part of the design otherwise.

Table 1
Schedule of the intervention "preparation group" in the study.

Component	Description	Aim	Psychological Target
1. Introduction	*Introductions*, including role of staff. Describe *aims and plan* of the session		
2. Transplant coordinator	*Pretransplant tasks*: Arranging caregiver, childcare, financial & personal affairs, etc.	Challenge myths surrounding HSCT; promote clarity	Reduce negative and threat appraisals in connection with HSCT
	Information on practicalities of the process: Pretransplant investigations, donor work, transplant day onwards, medication, recovery		Facilitate concreteness of the HSCT experience
	Anticipating difficulties & dealing with difficult days/times: Isolation & implications, what to bring to hospital, what to expect (side effects and complications), going home		Introduce staff as a coping resource
	Importance of liaising with healthcare staff: Assistance with symptoms, emotional difficulties, concerns regarding going home, etc.		
3. Psychology: i. Foster adjustment	*Information on the emotional response* to life-threatening illness and subsequent intense treatment. (Elicited through Socratic dialogue)	Normalise & validate psychological response	Reframe coping self-appraisals influenced by the emotional response
ii. Coping skills	*Managing worry* (e.g., worry time, distraction)	Prepare patients for psychological challenge	Improve patient's effective use of approach & avoidance coping.
	Identifying previous coping strategies	Provide patients with ways of coping	Enhance coping appraisals (controllability)
	Managing emotion (e.g., self-soothing & relaxation, PMR, safe place)		
	Problem-solving & goal priorities		
	Communication skills with healthcare professionals to meet needs (Psychoeducation and eliciting from group using Socratic dialogue)		
4. Physio-therapy	*Importance of daily routine* (e.g., meals, personal hygiene)	Improve patients' understanding of the role of activity/exercise & their willingness to use it.	Improve effective use of approach & avoidant coping.
	Activity scheduling		Enhance coping appraisals (controllability)
	Breathing exercises		
	Importance of physical activity & examples		
	Introduction to rehabilitation group (postHSCT)		
	Dealing with physical symptoms (e.g., pain, fatigue) (Psychoeducation and eliciting from group using Socratic dialogue)		
5. Close	*Summarise discussion*		
	Reinforce take-home messages regarding misconceptions of threat, normalisation, active coping, and support from the healthcare team		

Note: HSCT, Haematopoietic stem-cell transplantation; PMR, Progressive muscular relaxation.

2.5. Procedure

The CONSORT diagram of the procedure is shown in Fig. 2. A member of the clinical team invited eligible patients following referral, undertook consent procedures, and assigned participants to interventions. Participants completed baseline measurements on site or returned them by post. Participants were invited to the group session via letter, and confirmed attendance via telephone. Participants completed the follow-ups over telephone with the outcome assessor. We asked participants for feedback on the procedure (calls, burden, etc.) and materials (ease of completion, etc.) at the final call with an open-ended question for each and further prompting if necessary. Relevant comments made at other times were also noted. Breaches of assessor blinding were noted. We also asked participants to indicate which physiological symptoms of the DASS-21 anxiety scale (items 2, 4, 7, and 19) may reflect HSCT side effects they experienced.

2.6. Ethical considerations

The National Research Ethics Service Committee East Midlands – Nottingham 1 in the UK approved the study on the 22nd August 2014 (Ref. 14/EM/1095). The study was registered with ClinicalTrials.gov (NCT02212236). We attended to ethical aspects specific to this study. As patients undergoing HSCT are under considerable strain we aimed to minimise any additional burden by participating in the study reflected in the brevity of the intervention and the use of short and targeted

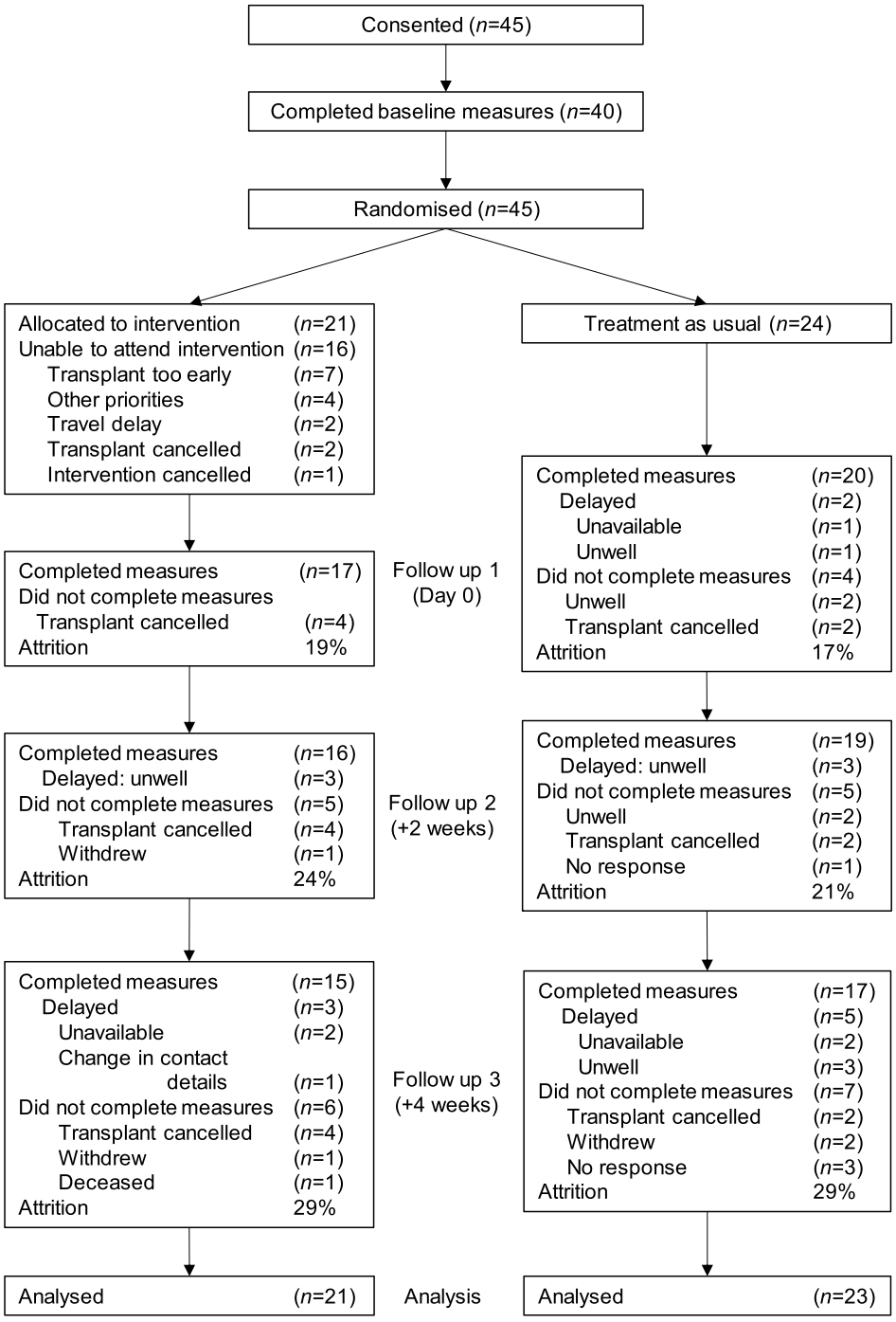

Fig. 2. CONSORT diagram of participant flow. The diagram indicates the number of patients who were allocated, attended, and not attended the intervention (with reasons for not attending). The diagram also shows the number of patients who completed and did not complete the measures at each timepoint (with reasons for not completing), and attrition at each follow up time point. Missing baseline measures were not returned following consent. Responses were delayed if they exceeded two days from their due time. Participants who missed a time point could still complete later ones without having to be excluded altogether. Participants who declined to be contacted for follow-ups were marked as withdrawn. Forty-four participants provided data for at least one time point for the analysis (144 data points in total). Day 0 = Day of transplantation.

measures. Participants were able to access support readily by nursing staff and the clinical psychologist on either site in the event that they experienced distress during the intervention or data collection.

2.7. Data analysis

Preliminary analyses involved descriptive statistics, input errors, outliers, assumptions, and missing data (Field, 2013; Snijders and Bosker, 2012). Descriptive statistics in relation to feasibility variables focused on accrual and uptake to the study and intervention, reasons for declining participation, attendance, reasons for non-attendance, response rates (attrition), and reasons for attrition. We used Cronbach's α coefficients to assess internal consistency (Field, 2013).

We assessed the success of randomisation through differences between participants randomised to intervention versus control on demographics, clinical characteristics, and baseline distress (Lewis and Warlow, 2004). We also examined differences between participants who attended the intervention versus those who did not to assess sampling bias. We used Chi-square tests (Fisher's exact test replicated $\chi 2$ for counts below five; Field, 2013), robust independent *t*-tests (with Bonferroni corrections, $\alpha = 0.01$, and bias-corrected bootstrapping with 1000 samples), and robust MANOVA for distress subscales (Field, 2013).

We assessed the optimum point of analysis (time points with highest distress) and obtained estimates of effect size and target sample sizes via Multilevel Modelling (MLM) with non-parametric bias-corrected bootstrapping (Rasbash et al., 2015b; Snijders and Bosker, 2012). Sample size estimations for a full trial (power = 0.80) used bootstrapped fixed and random parameter estimates of the overall effects during the acute phase of HSCT (Time points 2–4). Sample size estimation took account of the observed nonresponse rates and was adjusted for the multilevel data structure using the Design Effect formula (Browne et al., 2009; Twisk, 2006).

We used the mulrank(.) function (Field, 2013) on R Version 3.2.2 (R Core Team, 2015) for robust MANOVA, MLwiN Version 2.34 (Rasbash et al., 2015a) for MLM, MLPowSim Version 1.0 (Browne and Golalizadeh, 2009) for sample size estimations, and SPSS Version 22 (IBM Corp, 2013) for other analyses, with $\alpha = 0.05$. We analysed the open-ended feedback using basic content analysis (Weber, 1990).

3. Results

3.1. Feasibility

Bone marrow transplant coordinators were able to approach participants at one site but not the other where not enough time was factored in routine clinical care (participants were recruited by the clinical psychologist instead). In total, 99 of the 103 approached patients met eligibility criteria (43 of 44 and 57 of 59 per site). Of these, 45 patients (24 and 21 per site) consented to participate. Accrual was five participants per month (43% uptake). Of the 21 participants randomised to intervention, five attended (24%) of whom two did not eventually receive transplants. One of the scheduled intervention groups had to be cancelled due to insufficient accrual of participants able to attend. In most cases, attendance was not possible due to transplantation taking place before the scheduled intervention (Fig. 2). The need to divide the patients at each site between the two groups hindered accrual so that interventions could not be held frequently and timely enough. Attrition at each follow up was 17–19% at Follow up 1 and increased to 29% at Follow 3 (Fig. 2). Overall attrition (average probability of nonresponse) across all time points was 22%.

Randomisation remained concealed from the outcome assessor. One code was not used eventually because it was assigned to a patient after the individual provided verbal consent but was unable to provide written consent subsequently. This resulted in one of the randomisation blocks containing fewer intervention codes and an overall probability of being randomised to intervention of 0.48. The outcome assessor remained blind to randomisation in all but one case where a participant commented on having attended the group. The outcome assessor became aware that two participants had not attended a group, as limited accrual meant that it had not possible to schedule a group after these participants consented.

The process for establishing treatment fidelity across the sites indicated that all core elements of the intervention were included. Delivery was found to be more didactic at one site compared to the other. Delivery was adjusted accordingly to incorporate asking more exploratory questions and eliciting information from the group.

Overall, participants provided favourable feedback on the trial procedure. The majority (80%) commented that the procedure was not burdensome and found the questionnaires of sufficient length. Four participants (9%) reported that some questions did not apply to them and this made it difficult to follow what was asked. Two participants (4%) indicated that being asked questions about distress and their experience with the transplant made them reflect helpfully on their experience and feelings between time points. The majority (60%) also suggested that flexibility with telephone calls was helpful in allowing them to continue participating.

Randomisation appeared successful because participants randomised to intervention were comparable to those randomised to the control group on demographics, clinical and disease variables, and baseline distress (Table 2). Results were comparable for intervention attendees versus non-attendees, except that attendees were from the same site (patients at that site were initially ambulatory, i.e., attended day ward, prior to hospital admission). Of participants whose transplants were carried out, only three allogeneic patients (7%, of whom 1 was from the intervention group) received reduced intensity conditioning.

Table 2
Demographics, clinical characteristics, and baseline distress of participants in groups as randomised.

Characteristics	Intervention (n, %)	Control (n, %)	Test
Gender: male	12 (57%)	19 (79%)	$\chi^2(1) = 2.54$
Marital status			
Married/cohabiting	15 (71%)	19 (79%)	$\chi^2(1) = 0.47$
Single	3 (14%)	2 (8%)	
Other	3 (15%)	3 (13%)	
Education			
Mainstream only	11 (52%)	8 (33%)	$\chi^2(1) = 4.34$
Further	4 (19%)	8 (33%)	
Higher	2 (10%)	8 (33%)	
Not known	4 (19%)		
Diagnosis			
Multiple myeloma	11 (52%)	16 (67%)	$\chi^2(1) = 1.06$
NHL	7 (33%)	5 (21%)	
Other	3 (15%)	3 (12%)	
Transplant: Autologous	18 (86%)	22 (92%)	$\chi^2(1) = 0.40$
Age on transplant day (years)	*(Mean, SD)* 54.4 (14.7)	*(Mean, SD)* 63.4 (6.9)	$t(37) = 2.32$
Years since diagnosis	2.0 (3.4)	2.8 (3.6)	$t(43) = 0.72$
ECOG	0.47 (0.61)	0.71 (0.59)	$t(34) = 1.16$
Length of admission	Amb (5, 29%) 7.40 (4.28) Nonamb (12, 71%) 19.4 (3.5)	Amb (6, 27%) 9.50 (7.01) Nonamb (16, 73%) 22.3 (6.3)	$\chi^2(1) = 0.02$ *ts*(9–25)≤1.55
Distress	*Mean*(*SD*)	*Mean*(*SD*)	
Total distress	7.25(8.72)	6.79(4.84)	$t(26) = 0.01$
Depression	4.92(6.09)	2.86(2.39)	$F = 0.41$ (robust MANOVA)
Anxiety	2.05(3.39)	0.90(1.04)	
Stress	5.79(6.49)	3.43(2.60)	

Note: Amb, Ambulatory, autologous patients initially attending day ward; ECOG, Performance status on the Eastern Cooperative Oncology Group scale; NHL, Non-Hodgkin's lymphoma; SD, Standard deviation.

3.2. Reliability

We removed DASS-21 items 2 (dry mouth) and 7 (trembling) from the anxiety subscale as 56% of participants indicated that these items reflected side effects of HSCT rather than anxiety and were found to reduce reliability coefficients. Following this amendment, Cronbach's α coefficients across time points were 0.72–0.95 for total distress, depression, and stress, and 0.46–0.78 for anxiety (lower at later time points for anxiety).

3.3. Distress trajectories to determine measurement points

The mean levels of distress over time and parameter estimates were detailed in our study examining the theoretical underpinning of the intervention (Baliousis et al., 2017). The parameter estimates were comparable to those obtained when randomisation and its interaction with time were added to the model (Table 3). Regarding optimal measurements points for a full trial, overall distress and anxiety were highest at Week 2 following transplantation (Time point 3). Depression increased through to Week 4 (Time point 4), as did Stress but this increase did not reach statistical significance.

3.4. Sample size estimates

Power analysis was based on the parameter estimates from the acute phase only (Time points 2–4, Table 4). The probability of non-response during this period was 0.13. Results indicated that sample sizes of 105, 70, >1000, and 145 (for total distress, depression, anxiety, and stress, respectively) would be required to detect a significant main intervention effect.

4. Discussion

The findings indicated feasibility issues for the group intervention and trial. Several reasons curtailed uptake and attendance including insufficient time prior to transplantation, burden amidst other priorities (e.g., appointments), being unwell, and travel distance. Uptake was slower compared to studies in cancer and inpatient HSCT interventions (Bauer-Wu et al., 2008; Jarden et al., 2009; Moyer et al., 2009) though more in line with outpatient intervention studies, particularly RCTs (DuHamel et al., 2010; Goodwin et al., 2000; Lounsberry et al., 2010). This indicates procedural burdens and lack of integration with the clinical process (primarily due to the trial setup) as possible barriers. Lower distress prior to HSCT (with little awareness about what might follow) may have contributed to lower patient interest in the intervention (Moyer et al., 2009).

Dividing the participants between two groups at each site appeared to pose a barrier to conducting the trial. Insufficient accrual for the intervention prior to the transplant was a main reason for not consenting to participate (due to the intervention being scheduled after the transplant) and not being able to attend the intervention following consent. These findings highlighted a feasibility issue posed by allocating 50% of participants to the intervention at each site. Such effects are not uncommon in psycho-oncology (Goodwin et al., 2000; Mills et al., 2006) but appear to be neglected in the limited HSCT feasibility studies (Bauer-Wu et al., 2008; Bevans et al., 2010; Horton-Deutsch et al., 2007; Lounsberry et al., 2010). The impact on accrual highlights dividing the participants at each site as a key barrier to conducting RCTs of group interventions in HSCT alongside already limited uptake in this population.

Another possible explanation for low uptake may have been relatively low baseline distress which may have affected how patients prioritised the intervention relative to other preparations (Braamse et al., 2016). As 42% of our participants experienced clinical levels of distress at some point during the acute phase (Baliousis et al., 2016), our findings indicate that a single preparation group may be insufficient to meet their psychological needs. This poses two challenges: first, how can patients at risk of developing distress be identified; and second, what would persuade patients to prioritise psychological prehabilitation.

Other aspects of the procedure, such as randomising participants, allocation concealment, assessor blinding, and collecting data over the telephone appeared feasible. Attrition was in line with HSCT studies using remote data collection but higher compared to data collection on site (DuHamel et al., 2010; Lee et al., 2005; Prieto et al., 2005). Reasons for attrition could not be noted (except in one case where the participant died) but may parallel some of the reasons leading to delays in data collection (e.g., feeling unwell, having other commitments). It is possible that support from a member of the clinical team could foster engagement and assist participants with completing the questionnaires at times most convenient to them.

4.1. Measures and outcomes

The intended primary outcome was total distress with the subscales of depression, anxiety, and stress. The patterns of distress we observed were reflective of the wider literature (Baliousis et al., 2017). Time-point 3 may be the optimal endpoint of analysis for total distress and anxiety in a full trial and Time point 4 for depression. As depression continued to increase through to Time point 4, a full trial should include longer-term follow up. The estimated required sample size of up to 145 participants

Table 4
Parameter estimates used in power analysis.

Parameter	Total distress	Depression	Anxiety	Stress
β	−2.66	−1.65	0.19	−1.14
σ^2_{0j}	30.3	6.50	1.33	8.81
σ^2_{0ij}	38.9	10.3	2.48	9.41

Table 3
Fixed Parameter Estimates and Standard Errors after Adding Randomisation and its Interaction with Time.

Measure	$\Delta\chi^2$	R^2_1	β(*SE*)						
			Time Point 2	Time Point 3	Time Point 4	Randomisation	Randomisation x Time		
							T2	T3	T4
Total distress	3.48	nil	0.02 (0.37)	3.72[a] (1.50)	2.72 (1.53)	2.15 (2.18)			
	8.21	nil	2.19 (2.11)	4.35[a] (1.94)	5.00[a] (2.11)	4.65 (3.17)	−4.60 (2.82)	−1.39 (2.80)	−4.77 (2.95)
Depression	0.43	<0	−0.85 (0.71)	1.58[b] (0.51)	**3.51[b] (0.84)**	0.92 (1.22)			
	9.14	3%	0.39 (0.73)	1.63[a] (0.78)	**3.11[b] (1.06)**	1.61 (1.28)	−2.72[a] (1.18)	−0.13 (2.14)	−2.00 (1.61)
Anxiety	3.10	1%	0.45 (0.30)	**1.52[c] (0.38)**	0.15 (0.29)	1.13 (0.65)			
	4.82	5%	0.41 (0.30)	**1.56[b] (0.49)**	0.14 (0.26)	1.12 (0.63)	0.10 (0.62)	−0.15 (0.50)	0.001 (0.004)
Stress	−0.61	<0	**−0.03 (0.33)**	0.63 (0.63)	0.69 (0.68)	−0.11 (1.24)			
	2.63	2%	**1.15 (1.04)**	0.94 (0.85)	1.54 (1.00)	1.97 (1.65)	−2.55 (1.47)	−0.68 (1.31)	−1.83 (1.43)

Note: $\Delta\chi^2 = -2\log$ Likelihood change compared to baseline, $\Delta df = 1$ for Randomisation and 4 when the interaction was included. Parameter estimates in bold indicate where the model showed better fit with predictors set random at Level 2.
[a]$P < .05$; [b]$P < .01$; [c]$P < .001$.

to detect an intervention effect for distress, depression, and stress may be feasible. The required sample size for an effect on anxiety exceeded 1000 participants and seems infeasible. However, these estimations are not absolute and should be viewed in the context of limited attendance to the intervention.

Findings were generally supportive regarding the appropriateness of the DASS-21. The measure appeared applicable to HSCT overall but two items of the anxiety subscale appeared confounded by physical symptoms and reliability coefficients for this subscale decreased over time as physical symptoms increase (Prieto et al., 2005). Other anxiety scales (e.g., Hospital Anxiety and Depression Scale) have shown better reliability in HSCT (Jarden et al., 2009; Lee et al., 2005; Prieto et al., 2005; Tecchio et al., 2013; Trask et al., 2003) but they have also shown considerably stronger positive correlations and more overlap with the DASS stress rather than the anxiety subscale (Antony et al., 1998; Crawford and Henry, 2003). Together with the required sample size to detect an effect, the anxiety subscale may be excluded in a full trial in favour of the stress subscale.

4.2. Limitations and strengths

The findings need to be viewed considering limitations, some of which will transfer to a full trial. Findings may not generalise to other healthcare settings or patients of different demographic backgrounds and conditions that were underrepresented in this study. As attrition was associated with poorer physical functioning or higher stress, results may also not generalise to those patients. Some DASS-21 scores were below clinical cut-offs with resulting loss of sensitivity having made intervention effects difficult to detect.

The barriers to consenting to the study and attending the intervention may have overshadowed subsequent feasibility issues. For example, studies show limited intervention adherence by patients across cancer care including HSCT (Baliousis et al., 2016; Moyer et al., 2009; Newell et al., 2002). Had more participants attended the intervention, such factors may have emerged here also.

Strengths included multisite involvement, a prospective design, examining feasibility in relation to key RCT features to inform further research and development of interventions, and attempts to control for sampling bias via recruitment from consecutive referrals with attention to attrition. The analysis (MLM, bootstrapping, and robust tests) aimed to minimise bias for optimal estimations for a definitive trial.

4.3. Implications

The findings have implications for the design and procedure to improve feasibility. Regarding the RCT design, a cluster randomised design (Wang and Bakhai, 2006) could help address some barriers to conducting the trial posed by randomised control and the recruitment procedure at separate sites. Reversal of control and intervention sites about halfway in recruitment could help control for site effects. Two further areas may address sampling and attrition bias: (a) examining differences between patients who declined to participate versus those who consented; and (b) facilitating direct rather than telephone contact with the outcome assessor. Cancer patients often experience difficulty with participating in research due to the many complications (Moyer et al., 2009) and this may be more prominent during acute HSCT. Identifying characteristics of patients who decline to participate may help assess the representativeness and accuracy of findings as well as identify adjustments to improve access to the intervention and research. Direct contact may support rapport with participants and the completion of questionnaires to reduce attrition (at the expense of outcome assessor blinding). These considerations together with the recruitment difficulties in one of the sites indicate the importance of integrating the trial and intervention more with routine clinical care. Refining the research procedure in consultation with key stakeholders and allowing for some variation to tailor the procedure to each site appear important prior to progression to the definitive trial.

The significant clinical levels of distress we observed during HSCT indicate the importance of multi-modal psychological preparation. There are two major implications for the design of the intervention considering the limited attendance we observed and its probable relationship with low distress pre-transplantation (Braamse et al., 2016). One implication is the possibility of redesigning the intervention so that it is stratified, for example, whereby patients are screened into a universal (e.g., light information only), low intensity (e.g., guided self-help), or high intensity (psychologist) intervention. The second is the possibility of personalising intervention to the concerns, needs, and risk factors of patients, including how people perceive and access preparation. This may or may not permit group delivery, depending on the extent of common ground, and attention should be paid to close integration of prehabilitation with the rest of the clinical process. Further, remote delivery has opened access to interventions with promising findings (Wang et al., 2017), may prove a worthy alternative to addressing the patients' barriers to participating, and would enable pooling participants from different sites. Addressing these uncertainties will require codesigning revisions to the intervention with patients.

5. Conclusions

The impact of feasibility issues with delivering and evaluating interventions in HSCT has been neglected but it is important towards building more robust evidence base and interventions which patients can access. Our results provide insights into feasibility issues with integrating the trial and intervention with routine care prior to HSCT and targeting patients who need it the most and in a way that fits with where patients are at. A redesigned intervention and trial are warranted. Our findings offer some clear suggestions for what researchers and clinicians need to pay attention to and how they can proceed to a definitive clinical trial to evaluate the effectiveness of preparatory psychological intervention to alleviate distress during HSCT with attention to personalisation and close integration with routine care.

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CRediT authorship contribution statement

Michael Baliousis: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Michael Rennoldson:** Conceptualization, Methodology, Investigation, Resources, Supervision, Writing – review & editing. **David L. Dawson:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Roshan das Nair:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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