PSYCHOLOGICAL INTERVENTION TO ALLEVIATE DISTRESS IN HAEMATOPOIETIC STEM CELL TRANSPLANTATION: A PHASE II STUDY

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Thesis submitted in part fulfilment of the requirements for the degree of Doctor of Clinical Psychology to the University of Nottingham

DECEMBER 2016

THESIS ABSTRACT

Background. Haematopoietic stem cell transplantation (HSCT) is an intensive procedure associated with psychological distress particularly during the first weeks (acute phase). Based on the self-regulatory model of adjustment to illness, a preparatory group intervention was developed aiming at alleviating distress by reducing negative perceptions of HSCT and fostering helpful coping.

Aims. The present study aimed to evaluate the feasibility of delivering the intervention and of conducting a trial to assess its efficacy. It also aimed to explore the applicability of the self-regulatory model in HSCT.

Methods. Participants were adults from consecutive referrals at two transplant centres. Half were randomised to the intervention and half to treatment as usual at each site. Psychological distress, HSCT perceptions, and coping were assessed at baseline (following consent), on transplant day, two weeks, and four weeks after transplantation.

Results. Of 99 eligible patients, 45 consented. Main barriers included inability to consent prior to transplantation, competing priorities, being unwell, and long travel distance. Of 21 participants randomised to intervention, five attended. Main barriers included being unable to attend 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 prevented sufficient accrual at each site. Anxiety peaked two weeks following transplantation but depression increased throughout the acute phase. Intervention effects were small but sample sizes for a full trial appeared feasible. Negative perceptions of HSCT and use of a range of coping styles (including styles considered helpful) predicted higher distress throughout the period.

Conclusions. The findings revealed considerable barriers to delivering a group-based intervention and conducting a trial to assess its effectiveness. This highlighted a need for better integration with routine care and alternative trial procedures. However, the findings illustrated complex psychological needs during the acute phase of HSCT and the role of negative HSCT perceptions and unhelpful coping in underpinning distress.

ACKNOWLEDGEMENTS

I am deeply grateful to my supervisors, Dr Mike Rennoldson, Prof Roshan das Nair, and Dr Dave Dawson for their generous feedback, guidance, and enthusiasm about the project. Special thanks go to Dr Mike Rennoldson for his enormous patience and determination with recruiting participants at one of the sites and the wisdom he imparted virtually at every step of the project. My sincere thanks go to Dr Jayne Mills, for sharing insights about the intervention, allowing its trial, discussing the procedure, and wholeheartedly supporting the implementation of the project. I am deeply grateful to Lynne Watson and Lisa Rachel also for permitting the evaluation of the intervention, for doing their utmost to support the project, and for persevering with recruiting participants in addition to their considerable clinical workload. Thanks also to the reception teams at both sites for retrieving clinical files and to Mr Aman Khanna for his support regarding the randomisation and allocation process to ensure I remained blind.

Most of all, I am indebted to all patients who agreed to participate, who did their utmost to contribute to the study in spite of going through extraordinary hardship.

I give special thanks to my father for his endless support and to my friends for their understanding and patience for the many times I disappeared and plans I postponed in order to focus on the project.

STATEMENT OF CONTRIBUTION

Systematic review. The trainee identified the topic, designed the method, undertook the analysis, and composed the discussion with feedback from the supervisor. The supervisor also screened the abstracts (in addition to the trainee) as a second rater.

Project design. The trainee collaborated with Dr Mike Rennoldson in designing the project with added guidance from Prof Roshan das Nair.

Ethics. The trainee completed most ethics applications and procedures except the costing paperwork at one of the two sites which was undertaken by Dr Mike Rennoldson.

Review of the literature. The trainee was responsible for the review of the literature (journal paper introduction and extended background section) with guidance by Dr Mike Rennoldson on relevant theories, amendments to the rationale, and additional papers.

Intervention. The intervention schedule was originally developed by Dr Jayne Mills and Ms Lynne Watson and was finalised for the project in collaboration with Dr Michael Rennoldson, the trainee, and Ms Lisa Rachael. The physiotherapy sections were developed by the physiotherapists. During the course of the study, the intervention was organised and facilitated by the staff teams at each site with no involvement by the trainee.

Recruitment. Dr Mike Rennoldson, Ms Lynne Watson, and Ms Lisa Rachael identified, approached, invited, and recruited participants. The trainee was not involved in recruitment. Mr Aman Khanna (medical professional at one of the NHS Trusts involved with the study) produced the randomisation codes according to the protocol, password-protected them, and emailed them to the interventionists.

Data collection. Data collection was undertaken primarily by the trainee except baseline questionnaires. Most patients completed these in their own time. Dr Mike Rennoldson, Ms Lynne Watson, and Ms Lisa Rachael supported participants with completing baseline questionnaires when needed. The trainee collected data for some baseline questionnaires.

Data scoring and analysis. Completed by the trainee with feedback on approach and alternatives to analysis by Dr Mike Rennoldson and Prof Roshan das Nair.

Write up. The thesis was drafted by the trainee with feedback and suggestions for amendments by Dr Mike Rennoldson, Dr Dave Dawson, and Prof Roshan das Nair, particularly on the journal paper prior to preparing it for submission to the journal.

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1 SYSTEMATIC REVIEW

PSYCHOLOGICAL INTERVENTIONS FOR DISTRESS IN ADULTS UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTATION: A SYSTEMATIC REVIEW [1]

Short title:
Systematic review of psychological interventions for distress in HSCT

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Research sponsored by Health Education East Midlands via the Trent Doctorate Programme in Clinical Psychology

Keywords:
cancer, oncology, stem cell, bone marrow, psychology, intervention

[1] Paper intended for the journal Psycho-Oncology. Author guidelines available at: http://onlinelibrary.wiley.com/journal/10.1002/%28ISSN%291099-1611/homepage/ForAuthors.html

Abstract

Objectives

To investigate the characteristics, methodology, quality, and efficacy of psychological interventions for distress in adult patients undergoing haematopoietic stem cell transplantation (HSCT).

Methods

A systematic review of relevant studies was conducted using six databases with supplementary hand searching. Included studies employed an experimental or quasi-experimental design, interventions included at least one psychological component, and outcomes involved psychological distress in affective terms. Data were abstracted and study quality was assessed using Cochrane Foundation criteria amended to include confounder and common factors control. Data were examined and synthesised using a narrative approach and meta-analysis.

Results

Eleven articles for nine interventions met the inclusion criteria out of 11070 abstracts. The studies varied in quality, general, intervention, and methodological characteristics while findings were mixed. Interventions tended to show better efficacy when incorporating a major psychological component involving cognitive behavioural or emotional processing methods with substantial interventionist input. However, this was also associated with methodological limitations and threats to internal validity such as poor confounder and common factors control. A meta-analysis yielded a small but significant pooled effect size estimate in favour of interventions with inconsequential heterogeneity. Risk of bias remained a concern.

Conclusions

Psychological interventions may provide some benefit in alleviating distress in HSCT but conclusions remain tentative in light of methodological limitations and risk of bias. Further research is needed to evidence the individual contribution of intervention components and mechanism of change together with improving intervention efficiency and methodological quality.

Background

Haematopoietic stem cell transplantation (HSCT) is a complex procedure aimed at a range of haematological and autoimmune illnesses and involves transfer of haematopoietic stem cells harvested either from the patient (autologous) or a matched donor (allogeneic) [1]. Over 45,000 individuals worldwide undergo the procedure annually often resulting in substantial benefits but the procedure remains very costly (up to £100,000 per transplant) and is very intensive [1]. The initial stages often involve administration of high doses of chemotherapy sometimes with radiation aiming at severe depletion of bone marrow cells including cancer cells and suppression of the immune system in preparation for engraftment [1]. This is followed by stem cell infusion to restore haematological and immune systems. The process can last several weeks involving very high levels of toxicity often in addition to previous chemotherapy, prolonged periods of isolation due to immunosuppression, and a range of debilitating side effects [1-3]. Physical side effects are often multiple with the greatest impact during the first 30 days and can include fatigue, disturbed sleep, weakness, nausea, pain, graft-versus-host disease (GVHD where donor immune cells attacks the patient's organs), and even death [1-3]. Long-term complications are also a concern such as elevated risk of mortality compared to the general population [4] and chronic health conditions with 20% of patients experiencing severe complications [5-7].

Psychological distress in HSCT and its sequelae

In light of the physical burden associated with the procedure, it is not surprising that patients undergoing HSCT experience considerable psychological distress. Patients report a consuming effort to prepare and an ongoing struggle with loss of agency, describing the procedure as "walk to hell and back" or "really, really hard" [8, p. 404]. Studies in adult HSCT have observed considerable loss of personal control and psychological distress, particularly during hospitalisation, with up to a quarter of patients meeting clinical criteria for anxiety and/or depression during the procedure [3, 9-13]. Following transplantation, psychological distress improves but can persist with studies reporting up to 40% of patients experiencing depression and up to 30% anxiety even one year later [14].

Apart from psychological well-being, the consequences of distress appear to affect physical well-being and recovery although research remains limited and correlational. Nevertheless, studies have observed a range of associations between psychological distress and worse treatment adherence, reduced pain and symptom tolerance, longer hospital stay,

and higher mortality [11, 12, 15]. In addition, stress, even in transient forms, has been associated with greater subsequent incidence of illness, harmful physiological changes, greater pain perception, suppression of the immune system, and higher risk of infections more generally [16]. In a procedure such as HSCT, which involves pain and substantial immune system recovery [1], distress may increase patients' vulnerability and impede the process.

The contribution of psychological intervention

The above research findings highlight the potential benefits of psychological intervention in alleviating distress in HSCT to enhance psychological well-being and supporting recovery. Research in the psychological needs of HSCT patients has indicated some potential areas for intervention. Findings suggest that pretransplant avoidance, lack of professional emotional and informational input, and a threatening perception of the illness and future together with loss of agency often present in HSCT patients can predict higher distress and physical symptoms [17-22]. Conversely, optimism and self-efficacy have predicted improved physical and emotional functioning following HSCT [23]. These findings are also in line with the wider theoretical literature of adjusting to health-related difficulties suggesting that illness appraisals and coping can play an important part in the process [24, 25].

In spite of evidence indicating the potential of psychological intervention in HSCT, relevant research remains limited compared to an extensive body of literature in related clinical areas and particularly cancer [26, 27]. For example, psychological therapies with educational, cognitive-behavioural, coping skills components, and so forth, have been shown to facilitate physical and emotional functioning, improve immune function, and enhance survival in cancer patients [26-28]. Such reviews of the literature have also been helpful in highlighting limitations of existing research such as poor methodology in participant selection, limited use of blinding, non-equivalent control interventions, and so forth. This is important to not only guide clinical judgment but also identify research needs towards better evidence base. However, while psychological interventions have begun to emerge in HSCT [e.g., 29, 30], such a resource does not exist at present. In light of marked discrepancies in outcomes and methods [e.g., 29, 30] this can be problematic as lack of clarity can misguide and hinder both clinical and research progress. To address this need, the present project aims to conduct a systematic review of the literature to answer the following questions:

1. What are the characteristics and efficacy of psychological interventions aiming at alleviating psychological distress in adult HSCT recipients?
2. What is the methodology and quality of the research evidence?
3. What participant, methodological, and intervention characteristics are common in studies demonstrating positive effects?

Methods

This review follows standardised guidelines of reporting systematic reviews and meta-analyses [31, 32].

Search strategy

A computerised search of major psychological, medical, and nursing literature and doctoral theses databases with a moderate degree of overlap was conducted [33, 34]: PsycINFO (1806 to June Week 1, 2014), MEDLINE (1946 to May Week 4, 2014), EMBASE (1980 to Week 4 May 2014), CINAHL (1982 to June 6, 2014), and ProQuest Theses (1862 to June 5, 2014). In addition, the first 300 results of Google Scholar (until June 20, 2014, listed by relevance) were screened for additional references together with hand searching tables of contents of the specialist journals Bone Marrow Transplantation, Psycho-oncology, and Journal of Psychosocial Oncology. Reference lists of all identified publications were also screened for additional publications. An attempt to trace unpublished research was made by contacting authors of research identified by these means (e.g., conference abstracts in journals) and the European Group for Blood and Marrow Transplantation.

Search terms were identified from a range of sources including systematic reviews of psychological interventions and distress in HSCT and analogous populations [14, 26-28] and terminology used in studies already identified during preliminary scoping of the literature [e.g., 29, 35, 36]. Additional related terms and relevant subject headings were further identified via the databases. Terms for the target population (e.g., stem cell$, bone marrow, etc.), intervention (intervention$, therap$, etc.), and outcomes (e.g., psycho$, distress, etc.) were grouped separately using OR and then combined using AND operators. Terms were added to the script sequentially from general to specific (where applicable) and were excluded for economy when they did not add any further publications. This process resulted in different but equivalent scripts for each database, presented in the online supplement[2].

Selection of studies

Consistent with the aims of the review, the following inclusion criteria were applied:

[2] The search strategy can be found as supplement at the end of the references, to evidence scope for the purposes of the RLS assessment though the same detail may not be required in a journal article.

- The target population included HSCT patients.
- Patients were adults (at least 18 years old).
- Psychological interventions were those that had explicitly included at least one component relevant to psychological theory, for example, coping, emotional processing, appraisals, and so forth. This excluded solely physical (including relaxation), art, occupational, medical interventions, or hypnosis.
- Outcomes were evaluated using at least a quasi-experimental design. Uncontrolled designs such as pre and postintervention comparisons were not included due to limited internal validity stemming from lack of control for concurrent effects [37] including that of undergoing HSCT.
- Interventions explicitly targeted and assessed psychological distress defined in affective terms (e.g., anxiety, depression, negative affect, etc.).

Data abstraction

To answer the research questions and aid the evaluation of study quality (see below), the following data were extracted by the first author:

1. ***Reference:*** author names, publication year.
2. ***Research design:*** Type (Randomised Controlled Trial [RCT], etc.), conditions, randomisation, allocation, blinding, confounder control.
3. ***Sampling:*** Site, selection, inclusion and exclusion criteria, accrual, attrition, sizes.
4. ***Disease information:*** Disease, transplant type, conditioning, side effects (particularly GVHD), functional impairment, admission days, time since transplant, number of readmissions, and differences between groups.
5. ***Demographic information:*** age, gender, ethnicity, marital status, socio-economic status (income, employment, or education), and differences between groups.
6. ***Intervention:*** components, timing, delivery (sessions, duration, and schedule), interventionist role, and adherence.
7. ***Outcome measures:*** Names, constructs, timing of administration, standardisation, reliability, and validity. Planned (e.g., as stated in published protocol) versus reported outcomes.
8. ***Analysis:*** Tests, intention to treat analysis, confounder control.

9. ***Key findings and data for meta-analysis:*** Significant effects, relevant comments, pre and postintervention or difference means and standard deviations per group, and sample sizes. Unpublished data were requested by authors.

Study quality

Use of composite scales with overall study quality ratings has not been empirically supported [38], therefore, a component quality assessment was employed consistent with Cochrane Foundation practice for clinical trial reviews [39]. It examined several sources of bias including:

- Selection (e.g., group equivalence): random assignment and allocation concealment
- Performance (e.g., group differences in treatment other than the intervention): blinding of participants and personnel
- Detection (group differences in outcome assessment): blinding of outcome assessors
- Attrition (e.g., groups differences in withdrawal): intention to treat analyses; however, high bias was assigned if attrition exceeded 60% due to potential unreliability of intention-to-treat analysis.
- Reporting (differences between reported and unreported findings): incomplete reporting of outcome data.

As blinding of the interventionists is generally not possible for psychological interventions, a decision was made to consider this criterion satisfactorily met where the comparison group was treatment as usual, the interventionist did not have major involvement with participants other than the intervention, and other care staff remained broadly unaware of the allocation.

Two further components were added: confounders and common factors. Because randomisation may not have been successful particularly in smaller studies, the former required either evidence that groups were comparable on confounding variables to demonstrate success or appropriate statistical control. Confounders included demographics (age, gender, ethnicity, marital status, socio-economic status), disease-related characteristics (disease, transplant type, side effects, hospital days, functional impairment, time since transplant, and readmission), and baseline outcomes. Having measured at least 70% of these

together with control for differences was considered low risk. These criteria followed relevant reviews, literature on predictors of distress in HSCT, and quality assessment practice [14, 26, 38, 40-42].

Common factors were incorporated because improvement in psychological therapies may reflect the therapeutic relationship, increased contact, common understanding of the problem, or other factors not specific to the intervention [43]. This component examined whether comparison groups involved some attentional equivalent to provide evidence that effects were more likely attributed to the intervention per se than common factors whilst recognising that constructs such as therapeutic relationship, common understanding, and so forth, may only be partially achieved with attentional control.

Quantitative data synthesis

To examine the efficacy of interventions, mean pre and postintervention change differences were calculated and standardised for each group. Signs were reversed so that a positive sign always reflected improvement. Where studies provided data for more than one relevant outcome, these were pooled to form a mean effect size per study. Data were then entered in a meta-analysis to estimate the overall weighted intervention effect of pre/post change difference between the two groups. Data were pooled using the generic inverse variance method with Hedges' *g* representing standardised mean differences (as described in [44]) selected to accommodate use of different outcome measures. This contains an adjustment for small samples [45], as expected in the present review. Where multiple postintervention data were available, data from the time point closest to the end of the intervention were entered first. Sensitivity analysis was then conducted using data from the final follow up instead.

Fixed effects models were used where heterogeneity was not significant otherwise random effects with the DerSimonian and Laird method were employed (as described in [44, 45]). Random effects generally produce wider confidence intervals and are considered more conservative as they adjust for considerable (and unexplained) heterogeneity [34, 44, 46]. However, this can be misleading if greater weight is assigned to smaller studies with higher risk of bias [44, 45] in which case fixed effects were preferred. Effect sizes were interpreted using Cohen's [47] guidelines with 0.2 considered small, 0.5 medium, and 0.8 large.

Heterogeneity was examined visually via the Forest plot and statistically using a Chi^2 test (Q statistic [44]). The I^2 statistic quantified heterogeneity with values up to 40%

representing relatively inconsequential, 30%-60% moderate, 50%-90% substantial, and 75%-100% considerable heterogeneity [44]. Publication bias, primarily due to underreported studies with null effects [34], was assessed via visual inspection of the funnel plot. Review Manager (Version 5.3) software [48] was employed with *alpha* level of significance set at 0.05 except for the *Q* statistic where an *alpha* level of 0.10 was adopted due to loss of power with smaller sample sizes and few studies [34].

Results

Included studies

Eleven studies met the inclusion criteria (Figure 1). The relatively large number of initial abstracts appeared due to the generic nature of search terms (e.g., distress also encompassing physical symptom distress, intervention often referring to HSCT itself). Of the included studies, nine were already published in peer-reviewed journals [29, 30, 49-55], two were in press [54] of which one was identified by its author via a conference abstract query [56], and another [57] was an unpublished doctoral thesis. Of these, one study was in Spanish [49] and translated by the author. Details of included studies are presented in Table 1 with overall effects in Figure 2. Hand searching and contact with the European Group of Blood and Marrow Transplantation did not reveal any additional studies.

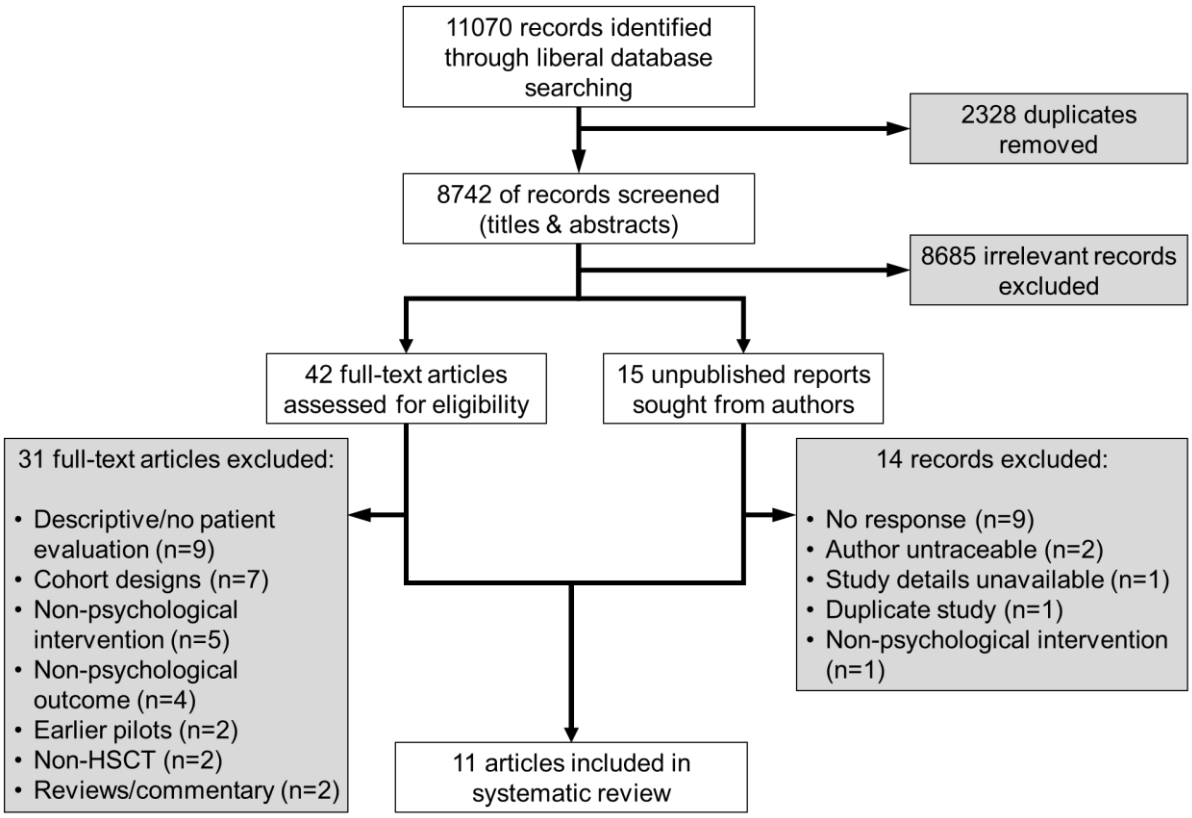


Figure 1. Flowchart of the selection of studies investigating psychological interventions in haematopoietic stem cell transplantation.

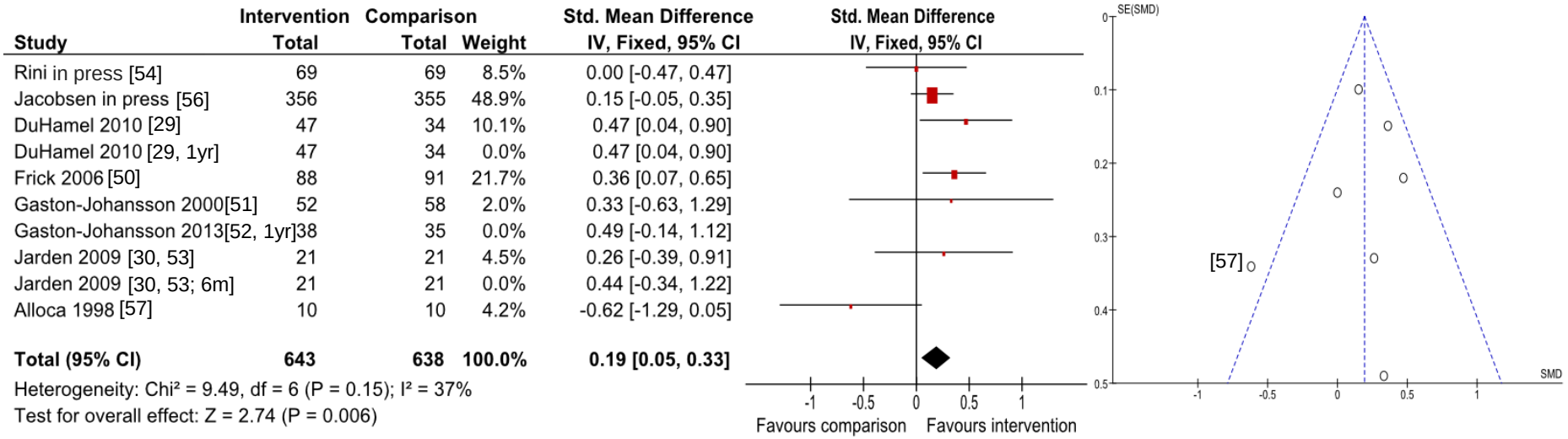


Figure 2. Forest plot of standardised pre/post change comparison between intervention and control groups with funnel plot for the evaluation of publication bias. Studies are listed in increasing risk of bias. Overall, there was a small pooled effect size estimate with non-significant heterogeneity. Follow up effects were calculated where available but not included in this estimate, as shown above, with sensitivity analysis yielding comparable results. Std.=standardised; IV=inverse variance; CI=confidence intervals; m=months; yr=year.

General characteristics

The 11 studies described and evaluated nine interventions since 1998. Seven studies (six interventions) were from the United States of America [29, 51, 52, 54-57] and four (three interventions) were from European countries [30, 49, 50, 53]. All samples consisted primarily of white participants. Haematological malignancies (lymphoma, myeloma, and leukaemia) were the most frequently targeted disease with only two interventions for breast cancer patients. Two thirds of the interventions did not discriminate between allogeneic and autologous transplant patients.

Intervention characteristics

Interventions varied in timing, intensity, delivery, content, and the extent to which they targeted solely psychological distress or additional areas of functioning. Seven intended to alleviate distress following transplantation of which three also targeted distress during the procedure. Another two focused on distress during transplantation only. Regarding outcomes, only two interventions [29, 49] were aimed solely at psychological distress targeting either posttraumatic symptomatology or more generally anxiety and depression. The others had a broader scope also aiming at improving non-psychological functioning such as physical or social quality of life which were not in the focus of the present review.

Seven of nine interventions incorporated Cognitive Behaviour Therapy (CBT) methods (see [58] for an overview of such methods) with emphasis on cognitive components and two [50, 54] employed other approaches. CBT-based components included informational input or psychoeducation regarding various aspects of distress (e.g., stress) or cognitive processes (e.g., cognitive biases), cognitive restructuring, and coping skills training often with problem solving. One intervention [29] also included a behavioural component of graded exposure to traumatic memories. Relaxation and/or exercise featured in three of the interventions [29, 30, 51-53, 56] alongside psychological input and formed a major component in two interventions [30, 53, 56] which incorporated considerably less psychological input compared to others. The interventions using components other than CBT-based were less problem and more emotion-focused (active approach) aiming at fostering emotional processing via expressive means. Overall, five interventions involved a substantial psychotherapy component [29, 49-52, 57] with the remainder being less specialist (e.g., psychoeducation with relaxation, task instructions, etc.).

All interventions were delivered individually and for seven out of nine this was face to face during admission. One [51, 52] also had some remote input and the remaining two were delivered via telephone several months following HSCT [29, 54]. Interventions also involved varying degrees of guided and self-directed work with five out of nine incorporating both [29, 30, 51-54, 56] and only two consisting primarily of self-directed work [55, 56]. Self-directed components included relaxation, cognitive or coping skills practice, and expressive writing and were supplemented by printed material and/or verbal instruction. Four interventions involving substantial psychotherapy input [29, 49-52, 57] were delivered by healthcare professionals or specifically trained researchers. Less specialist interventions were facilitated by site staff or researchers. Generally, interventions with substantial psychotherapy input were delivered over four and up to fifteen sessions while delivery was more frequent for others and often over several weeks though this was mostly self-directed. Session length began at approximately 20 minutes and rarely exceeded an hour.

Methodological features

Most studies were RCTs comparing the intervention to a control group with only two using a quasi-experimental design (non-equivalent controls). All studies examined longitudinal change with all but one [49] including a baseline measurement prior to administering the intervention. Otherwise, methodology varied in sample size, type of control, outcomes, follow ups, data analysis, and confounder control.

Sample sizes per group ranged between those appropriate for pilot with approximately ten participants [49, 55, 57] to a large RCT with an excess of 300 participants while the remainder [29, 30, 50-54] were modest with 21 to 91 participants. Seven of eleven studies recruited consecutively prior to HSCT, two [49, 55] did not report sufficient information, one [29] screened participants for high distress (primarily trauma), and another [54] for at least mild survivorship difficulties (including distress). In five of eleven studies control groups were treatment as usual (TAU), in one [29] patients received no care, and in another [56] half of controls also engaged in regular exercise. In a further two studies [50, 54] comparison groups received input in addition to TAU including components of the intervention, attentional control, or a delayed intervention.

Regarding measurements and outcomes, seven of the nine interventions were evaluated near their completion. Follow ups (between three and twelve months) were reported for five interventions. Psychological distress was assessed with measures of anxiety,

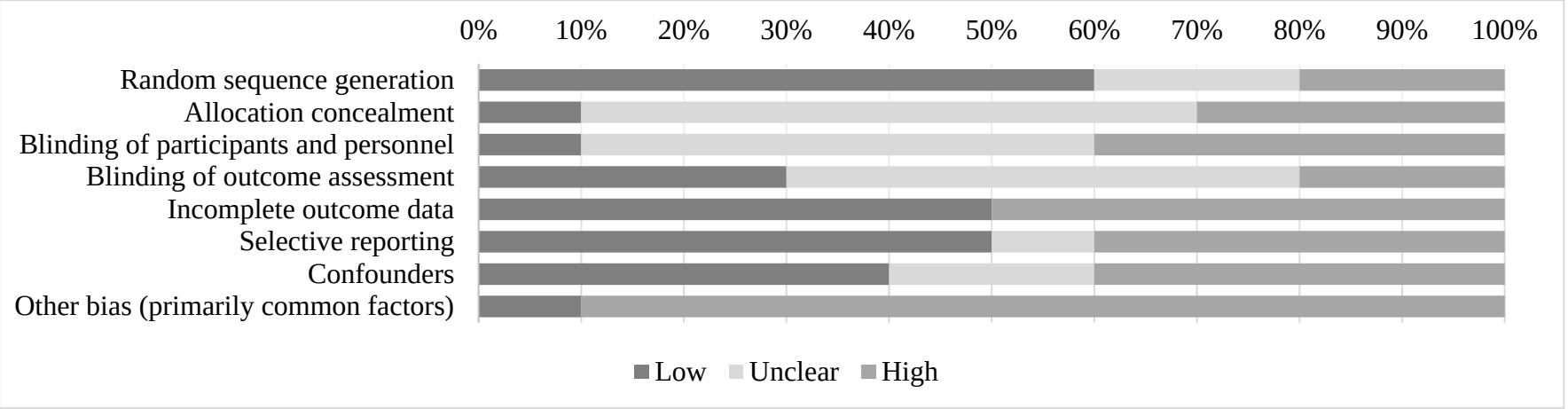
depression, posttraumatic stress, affective functioning, and general distress or psychological well-being. Five of nine interventions included more than one relevant outcome measure. Only one study also assessed process change (coping, [55]). All measures were standardised with acceptable validity and reliability as discussed in all studies and were self-reported with the exception of a clinician-administered trauma scale in one study [29].

Regarding analyses, multiple regression, analysis of variance, or equivalent non-parametric techniques were conducted as appropriate for the design except for four studies of which three [30, 49, 56] reported pairwise comparisons only and one [54] which reported an incomplete analysis. Where groups were found not to be equivalent in demographic, disease-related, or baseline information, most studies attempted statistical control except two [49, 55] which did not examine such confounding with one [49] also failing to measure baseline scores for controls. With the exception of three studies [51, 52, 56], sufficient information regarding adherence was also provided (attendance, logbooks, etc.). Only one study [55] demonstrated poor adherence (45%) but this was factored in the analysis.

Study quality

The quality of the included studies varied considerably. Figure 3 provides component ratings for each together with a graphic summary. Overall, the rating method appeared to differentiate between the types and degrees of bias across studies. Regarding selection bias, most studies were RCTs with low risk but this was limited by having neglected allocation concealment which all but one study did not comment on or address.

Performance, detection, and common factor bias were also poorly addressed. Regarding the first, four studies exhibited high risk of bias but this was less clear for five studies where the degree of interventionist involvement with TAU was uncertain, some control participants received other types of intervention, the success of participant blinding was uncertain, or there was insufficient information. Detection bias was high in two studies where the investigator was the outcome assessor but had been better addressed in three studies where the assessor was either blind or independent to the study. The remaining studies did not comment on assessor blinding. Common factor bias was only addressed by one study [54] via an active form of intervention. This type of bias was particularly problematic for another study [29] where controls received no therapeutic attention and results from the same project published elsewhere [59] observed a therapeutic relationship effect suggesting a common factors effect.



	Rini(in press) [54]	Jacobsen (in press) [56]	DuHamel 2010 [29]	Frick 2006 [50]	Gaston-Johansson 2000 [51]	Gaston-Johansson 2013 [52]	Jarden (2009) [30, 53]	Alloca 1998 [57]	Trask (2003) [55]	de Linares 2007 [49]
Random sequence generation	L	L	L	L	U	U	L	H	L	H
Allocation concealment	L	U	U	U	U	U	H	H	U	H
Blinding: participants & personnel	L	U	H	H	U	U	H	U	U	H
Blinding of outcome assessment	L	L	L	U	U	U	H	H	U	U
Incomplete outcome data	H	L	L	L	H	H	L	L	H	H
Selective reporting	U	L	L	L	H	H	L	L	H	H
Confounders	U	L	L	H	L	U	L	H	H	H
Other bias (primarily common factors)	L	H	H	H	H	H	H	H	H	H

Figure 3. Overall summary and details of component quality ratings for risk of bias for the studies included in the systematic review. Studies are ordered in increasing risk of bias from left to right. L=low risk of bias; U=unclear risk of bias; H=high risk of bias.

Attrition, reporting, and confounder biases were moderately addressed. Intention to treat analyses in approximately half of the studies indicated suitable attrition control but this was neglected in the remainder. Approximately half of the studies appeared to report outcomes as planned, outcomes were comparable to previous studies by the authors, or distress outcomes were a subset of the intervention targets thereby involving less risk of reporting bias. However, four studies failed to provide data for some of the administered outcome measures discussed in the method or measures used in preceding work, which questioned the validity of reporting. Finally, five of eleven studies demonstrated appropriate confounder control. This was unclear for two studies where control for baseline differences did not appear statistically valid (overfitting & incomplete analysis/Type II error). High risk of bias in the remaining studies included poor evidence of control for individual differences [49, 55, 57] or no baseline control [49, 50].

Key findings

Main results are summarised in Table 1 and overall effect sizes in Figure 2. Seven of the eleven studies (seven of nine interventions) reported some benefits including lower distress, improved emotional functioning, and less posttraumatic symptomatology. Of these, five were evaluated in the longer-term (three to twelve months) with benefits also present at the longest follow up. One of these [52] had not been effective during transplantation suggesting a possible delayed effect or lack of power though this discrepancy may be due to questionable baseline outcome control at follow up. In addition, three interventions appeared effective in HSCT patients that were more distressed due to close proximity to the time of transplantation [50] or relevant screening [29, 54]. However, the result reported as significant in one of these [54] did not reflect published statistical data which indicated a null effect (cf. Figure 2) with the significant outcome likely reflecting a statistical artefact; therefore, it was treated here as not significant.

Notwithstanding some intervention benefits, results appeared mixed both between and within studies. It was notable that none of the five interventions evaluated with more than one outcome measure resulted in benefits on all of them indicating potentially inflated Type I error. One study [57] also reported a (non-significant) effect in favour of the control group. The authors explained this as increased awareness and acceptance of distress in the intervention group but this had not been observed in any other study with a similar therapeutic approach and design and therefore did not appear plausible. This was also the

smallest study in the group and demonstrated poor controls in most quality domains. The resulting lack of precision suggests that the reported effect may have indeed been due to chance.

Differences in findings did not appear consistently related to many study characteristics. These included general characteristics, some intervention characteristics (use of CBT, & mode of delivery except for the interventionist), and some methodological features (screening for distress, design, outcome measure, and pairwise versus more appropriate statistical analyses). High risk of selection, detection, attrition, and reporting bias did not appear consistently related to effects either. Notably, the same was observed in relation to timing of the intervention to target distress during HSCT, following HSCT, or both.

Other study characteristics and risks of bias appeared related to results but were generally confounded. With one exception [57], interventions with more intensive psychotherapy components and substantial interventionist input [29, 49, 50, 52, 55] appeared to yield larger and more frequently significant effects compared to those where delivery was less psychotherapy-specific and more self-directed (e.g., instructions, workbook, physical methods as main component, etc.). This included both studies with psychological distress as sole target. Poorer adherence particularly in self-directed studies may have contributed to this, as evidenced in one study [55].

It was notable that the five interventions with substantial psychological input were among six [29, 49, 50, 52, 54, 55] of the seven studies reporting intervention benefits whose results exhibited considerable threats to internal validity. These were due to either poor confounder control (individual differences, baseline outcomes) or possible influence by common factors. Notably, the study demonstrating the largest effect and the only study involving relatively highly distressed patients was also the only one with no care as control [29]. This was in contrast with the only study including at least attentional control [54] which yielded a null average effect (in spite of some screening for higher distress). In addition, all studies with high risk of performance bias reported some significant intervention effects. Overall study quality appeared unrelated to effect size (Figure 2) but studies with lower risk of bias generally appeared to involve larger samples and yield smaller confidence intervals.

Meta-analysis

A meta-analysis using fixed effects models was conducted with data from nine of the eleven studies. The effect sizes of two studies [30, 53] were averaged as they referred to the same project. All data were published except for one study [56] for which data were obtained via the authors. Two studies were not included following no response to the data request [55] or due to untraceable contact details [49]. Available data from the more distressed subgroup were included for one study [54] as more representative of the patients that might be offered psychological input in practice. Only the attentional control group was considered from the same study, as it did not involve any of the components of the intervention. Results are presented in Figure 2.

There was a small but significant pooled effect size estimate 0.19, [0.05, 0.33] with relatively inconsequential and non-significant heterogeneity, Chi^2=9.49, df=6, P=0.15, I^2=37%. Sensitivity analysis with the longest follow up data yielded comparable results. All of the contribution to heterogeneity appeared due to the study by Allocca [57] with I^2 decreasing to 0% when this study was removed. This outlying effect may have been due to imprecision and poor methodology in this small study.

The loss of two studies due to data unavailability may have introduced bias in the meta-analysis. However, both were small with high risk of bias overall, therefore, their exclusion may have resulted in a more accurate and valid pooled estimate. The funnel plot (Figure 2) appeared approximately symmetrical (visual inspection) and even suggested a potential absence of small studies showing a positive intervention effect primarily due to the inclusion of Allocca's study [57]. However, this was the only unpublished report in the group thereby highlighting a potential risk of publication bias.

Conclusions

The present review examined the efficacy, characteristics, and quality of psychological interventions to alleviate distress in HSCT. An emerging body of literature was identified consisting of RCT (including pilots) and quasi-experimental designs. Eleven studies were identified for nine interventions and the evidence suggested some benefits that were maintained up to a year posttransplantation. Results varied and multiplicity of outcome measures indicated lack of clarity but a meta-analysis revealed limited overall benefits and a small pooled effect size estimate. A range of methodological limitations was also present suggesting a need to interpret evidence with caution.

Interventions were timed to target distress during HSCT and up to nine months postdischarge with diversity in terms of therapeutic modality, components, format, intensity, and delivery. Most interventions incorporated CBT-based components addressing appraisals, coping, problem solving, and so forth, or involved active emotional processing. All were supported by a professional in varying degrees and most involved some self-directed work. These were similar to interventions identified in other relevant clinical populations and more widely in health psychology [26, 60-66] though there was a notable absence of group delivery in HSCT.

Results appeared homogenous overall and the small number of studies limited conclusions but some patterns emerged. Interventions involving substantial psychological and interventionist input tended to be more efficacious compared to those with less psychological or more self-directed focus. However, this was confounded with methodological limitations and potentially adherence while the only unpublished study was contradictory [57]. In spite of an almost symmetrical funnel plot, this indicated possible publication bias although the study's limitations also suggested potential imprecision. Other characteristics did not appear consistently related to efficacy in light of small samples including whether interventions were timed and intended for distress during HSCT, following HSCT, or both.

The small pooled effect size estimate was comparable and often higher than similar contemporary interventions in other cancer populations when assessed with analogous measures of distress [60, 62]. However, they were generally lower than those reported in similar research in other illnesses such as diabetes [63] and coronary heart disease [65]. Possible floor effects may have contributed to attenuated efficacy, as studies did not generally

limit recruitment to patients with higher distress. This has been consistently observed in cancer literature more generally [67-69] though lack of screening at recruitment is also relatively common in other illnesses [e.g., 63, 64-66]. Such practice and its effects can prove misguiding when evaluating interventions and limit external validity thus highlighting a need for routine subgroup analyses and better screening where possible. The difference in effect size could also reflect the unique needs and many uncontrollable challenges faced by HSCT and other cancer patients [27] potentially indicating a need for more tailored interventions.

Mechanism of change

Support of the efficacy of interventions involving CBT-based or active emotion processing components is consistent with the HSCT literature highlighting avoidance coping, appraisal of HSCT as threat, or loss of self-efficacy as predictors of distress [17-21]. It is also supported by the wider theoretical literature of adjustment to health-related difficulties indicating that more benign appraisals about the situation and its sequelae, greater sense of control, and approach versus avoidance coping are considered important predictors of adaptation [24, 25]. The interventions aimed to address these in various ways, for example cognitive restructuring and psychoeducation for appraisals (e.g., [29, 49, 51]), problem-solving (e.g., [57]) and skills training (e.g., [51]) for coping, or emotional acceptance and processing (e.g., [50]). Relaxation, on the other hand, may reflect avoidance coping with stressors potentially contributing to smaller effects when used as a primary component (e.g., [56]).

These considerations are plausible but it was not possible to establish from the studies in this review whether the interventions operated via the above processes versus other mechanisms. There are three reasons for this. First, the majority of interventions incorporated more than one component but were assessed as a whole and without within-group control. Second, with one exception [55], no study employed a process measure to investigate the mechanism of change and even that study did not examine the relationship between process and outcome. Third, lack of control for common factors limited the present body of evidence almost in its entirety leaving open the possibility that reductions in distress may have reflected the influence of the therapeutic relationship, increased input, or other factors other than the intervention content per se.

In light of these considerations, several methodological improvements could enhance intervention studies in the field. These could include process change measurements,

experimental within-subjects control, and between-subjects control equivalent in interventionist attention. Multiple components with unclear benefits also pose an ethical issue in a population that is already burdened considerably which may contribute to poor outcomes. Therefore, it is important to improve intervention efficiency aiming at highest impact with fewest components. Delivery in a group format may also be helpful in reducing burden.

Quality of the evidence

The method of assessing quality appeared to capture the diversity of risk of bias together with some meaningful findings, for example, larger studies demonstrating lower risk of bias. However, lack of statistical analyses due to the small number of studies limited conclusions. In spite of the majority of studies classed as RCTs the quality assessment revealed several areas of weakness relating to allocation concealment, common factors, detection, and performance bias though the latter is inherent in delivering psychological interventions. While there was little variation in common factors ratings, the inclusion of this component was critical in evaluating the body of evidence and conclusions. Largely insufficient information on allocation and blinding highlighted a much neglected area in the literature and a need for better control and explicit reporting. Other areas of bias including randomisation, attrition, reporting, and confounder control were less problematic but could improve further. Overall, most information was from studies at unclear or high risk of bias which lowers confidence in the evidence.

Limitations

The review employed a comprehensive search strategy using six databases including theses and was supplemented by manual searches to maximise retrieval. However, the process was undertaken by one person and involved subjective judgement at different stages, for example, identifying publications, abstracting data, rating study quality, and analysis including visual inspections of distributions of effects and results. It follows that it is possible to have missed studies or data and alternative analyses by different individuals could yield different results.

A major limitation arose from a relative lack of studies, which restricted many analyses to visual inspections. Together with variability in interventions, methods, outcomes, methodological limitations, and risk of bias this made the results difficult to interpret and the

conclusions regarding efficacy and study characteristics associated with it tentative. Lack of power also indicated that the pooled effects might not be genuine while there was also a possibility of publication bias in spite of an effort to include unpublished studies. Finally, as studies were of western origin with primarily white participants, it is unclear whether findings would generalise to individuals from different backgrounds.

In conclusion, results suggested a potential albeit small benefit of psychological interventions for distress in HSCT particularly when involving a major psychological component such as CBT or emotional expression together with substantial interventionist input. Further research could examine individual components and process change together with developing interventions that are more efficient. Conclusions remain tentative in light of methodological limitations and threats to internal validity such as lack of control for common factors, high risk of bias, and possible publication bias. Future studies could address methodological limitations and improve reporting in order to increase confidence in the evidence and benefit clinical practice.

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Table 1. Summary of studies examining the efficacy of psychological interventions to alleviate distress in HSCT

Sources & design	Disease, transplant, & follow up	n_i/n_c	Intervention	Comparison	Relevant outcomes	
					Target	Key findings/comments
Interventions timed to target distress during HSCT only						
Allocca 1998 [57] Quasi-experiment	Breast cancer	10/10	<u>Components:</u> Problem and cognitive biases identification, cognitive techniques (restructuring, problem-solving, etc.), review and future planning <u>Delivery:</u> Individual (face to face) by CBT-trained nurse specialist <u>Timing & intensity:</u> Start within 48 hrs post-transplant 5x, approx. 35 mins, over 5-10 days.	TAU	Anxiety & Depression (HADS) Psychological well-being (QOLS)	Significant overall improvement in anxiety and psychological well-being but no significant differences between groups Non-significant increase in depression in intervention group
Jarden, Baadsgaard 2009 [30]; **Jarden, Nelausen 2009** [53] RCT	79% haem. malignancy Allogeneic <u>Follow up:</u> 6 months	21/21	<u>Components & delivery:</u> CBT-based psychoeducation, exercise, & relaxation training Individual exercise (face-to-face) by researcher & self-directed relaxation <u>Timing & intensity:</u> During admission 5x pw psychoeducation & exercise, 2x pw relaxation	TAU	Anxiety & Depression (HADS) Emotional functioning (QLQ-C30) **Affective functioning** (SCT-SAS)	No significant effects Significantly lower distress and less severity in intervention group

Interventions timed to target distress following HSCT only						
DuHamel 2010 [29] RCT	71% haem. malignancy Mixed <u>Follow up:</u> 3-12 months	47/34	<u>Components:</u> CBT for trauma – Education, self-monitoring & cognitive restructuring, graded exposure, communication skills training, relaxation training <u>Delivery:</u> Individual (telephone) by trained postdoctoral fellows & self-directed practice <u>Timing & intensity:</u> 10-16 wks post-HSCT 10x, approx. 1 hour	Assessed only	Trauma (PCL-C) **Distress** (BSI) **Trauma Diagnosis** (CAPS)	Total and intrusive thoughts scores improved similarly in both groups Faster improvement for intervention group Diagnosis less likely for intervention group at end of therapy Retained throughout follow up Possible common factors effect
Frick 2006 [50] RCT	92% haem. malignancy Autologous	88/91	<u>Components & delivery:</u> Daydream imagery for emotional processing Individual (face-to-face) by researcher (trained psychotherapist) <u>Timing & intensity:</u> 1-6 months postdischarge 15x, 15-30 mins	Delayed timing (6-12 months postdischarge)	**Emotional functioning** (QLQ-C30)	Significantly better improvement for early intervention group; potentially explained by increased disease severity Possible floor effects for late intervention group
Rini (in press) [54] RCT	87% haem. malignancy Mixed	69/ 59-69	<u>Components & delivery:</u> Expressive helping (expressive writing to help prospective patients) Instructions only (telephone) by study interviewer, otherwise self-directed <u>Timing & intensity:</u>	1. Expressive writing only 2. Writing to help peers only	**Distress** (BSI)	Lower in expressive helping group compared to peer helping and neutral writing in participants with high but not low survivorship difficulties.

	Follow up: 3 months		9 months to 3 years post-HSCT 4x weekly, 20 mins	3. Neutral writing		Incomplete analysis & possible Type II error. Expressive helping group appeared to have lower baseline distress also but control for this was questionable while published data indicated null effect.
Trask 2003 [55] RCT	n/k	26 in total	Components & delivery: Workbook psychoeducation – coping, problem-solving, CBT principles Instructions only (face to face) by author, otherwise self-directed Timing & intensity: Discharge onwards, self-directed	TAU	Distress (BSI) **Anxiety** (STAI) Coping (WOC)	No significant effects 2 & 6 months postdischarge 45% of intervention participants had not utilised workbook 1 month postdischarge. Anxiety was significantly lower in those who did 2 & 6 months postdischarge compared to those who did not Unclear influence of individual differences on adherence
Interventions timed to target distress during & following HSCT						
de Linares 2007 [49] Quasi-experiment	Haem. malignancy Follow up: 100 days	10/6	Components: Informational, practical coping skills, stress management (psychoeducation & cognitive restructuring), communication with family Delivery: Individual (face to face) Timing & intensity: 4x since and during admission	TAU	**Anxiety & Depression** (HADS)	Fewer clinical criteria for anxiety and depression in intervention group on transplant day and 100 days later No baseline measurement for controls
Gaston-Johansson 2000; **2013** [51, 52]	Breast cancer Autologous	52/58	Components: Coping – psychoeducation, cognitive restructuring education & coping, coping	TAU	Anxiety (STAI) Depression (BDI)	No significant effects

RCT	Follow up: 1 year	38/35	skills training, relaxation with guided imagery training Delivery: Individual (1st session face-to-face then computer/telephone) by social worker, nurse, researchers, & self-directed practice Timing & intensity: 2 wks prior to then during admission & top-up 3 months later 5x (3x during admission) 1st 1.5 hours, then 20 mins		**Psychological functioning** (QOLI-CV)	Higher in relation to intervention Possible overfitting: limited baseline outcome control
Jacobsen (in press) [56] RCT	89% haem. malignancy Mixed	356/ 355	Components & delivery: Stress management with relaxation, imagery, and coping elements (50% also engaged in exercise) Individual (face-to-face) by trained site personnel & self-directed Timing & intensity: Since admission, ongoing 3x instruction (introduction & reinforcement 30 & 60 days post-HSCT) otherwise self-directed.	TAU (50% also engaged in exercise)	Psychological functioning (SF-36)	No significant effects 100 days and 6 months posttransplantation Intervention adherence was unclear

Note. Sources are listed by name of first author with studies and outcomes supporting intervention benefits in bold lettering. Follow up period mentioned where available. n_i/n_c=intervention and comparison group sample sizes respectively; RCT=randomised clinical trial; HSCT=haematopoietic stem cell transplantation; haem=haematological; CBT=Cognitive-Behavioural Therapy; #x = number of sessions (e.g., 2x=2 sessions); pw=per week; TAU=treatment as usual; HADS=Hospital Anxiety and Depression Scale; QLQ-C30= The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SCT-SAS= Stem Cell Transplantation Symptom Assessment Scale; wks=weeks; PCL-C=Posttraumatic Stress Disorder Checklist-Civilian Version; BSI=Brief Symptom Inventory (global scale only);

CAPS=Clinician-Administered Posttraumatic Stress Disorder Scale for Diagnostic and Statistical Manual for Mental Disorders, 4th edition; mins=minutes; n/k=not known; QOLS=Quality of Life in Bone Marrow Transplant Survivors, City of Hope National Medical Centre Questionnaire; WOC=Ways of Coping; STAI=State-Trait Anxiety Inventory; BDI=Beck Depression Inventory; QOLI-CV=Quality of Life Index-Cancer Version; SF-36=Medical Outcomes Short-Form 36 (version 2.0).

Supplemental material: search terms

Population

- **MEDLINE**

  (Hematopoietic Stem Cell Transplantation/ OR Bone Marrow Transplantation/) OR ((Stem cell$ OR bone marrow) AND (transplant$))

- **PsycINFO**

  (Stem cell$ OR bone marrow) AND (transplant$)

- **EMBASE**

  (exp hematopoietic stem cell transplantation/ OR exp bone marrow transplantation/) OR ((Stem cell$ OR bone marrow) AND (transplant$))

- **CINAHL**

  ("Stem cell*" OR "bone marrow") AND ("transplant*")

- **ProQuest**

  AB,TI(((Stem-cell*) OR bone-marrow) AND (transplant*))

- **Google Scholar**

  (("Stem cell" OR "bone marrow") AND (transplant OR transplantation))

Intervention

- **MEDLINE**

  (exp Psychotherapy/ OR exp Counseling/ OR Patient education as topic/) OR (intervention$ OR therap$ OR counsel$ OR self-help group$ OR support group$)

- **PsycINFO**

  (exp Prevention/ OR exp Treatment/ OR exp Counseling/ OR exp Psychotherapy/ OR Support groups/) OR (intervention$ OR therap$ OR counsel$ OR self-help group$ OR support group$)

- **EMBASE**

  (exp “psychological and psychiatric procedures”/ OR exp counselling OR exp self help/ OR exp support group/) OR (intervention$ OR therap$ OR counsel$ OR self-help group$ OR support group$)

- **CINAHL**

  (MH “Clinical Trials+”) OR ((“intervention*” OR “therap*” OR “counsel*” OR “self-help group*” OR “support group*”))

- **ProQuest**

  AB,TI(intervention* OR therap* OR counsel* OR (self-help-group*) OR (support-group*))

- **Google Scholar**

  (intervention OR therapy OR therapies OR counselling OR ((“self-help” OR “self help”) AND group) OR (support AND group))

Outcomes

- **MEDLINE**

  (exp emotions/ OR exp affective symptoms/ OR exp affect/ OR adaptation, psychological/ OR interpersonal relations/ OR Exp mental disorders/) OR (psycho$ OR social OR distress OR anxi$ OR depress$ OR stress OR quality of life OR mental health OR psychiatr$ OR mental disorder$)

- **PsycINFO**

  (exp Adjustment/ OR exp Emotions/ OR exp Satisfaction/ OR exp Life experiences/ OR exp Mental Disorders/ OR exp Psychiatric Symptoms/) OR (psycho$ OR social OR Distress OR anxi$ OR depress$ OR stress OR quality of life OR mental health OR psychiatr$ OR mental disorder$)

- **EMBASE**

  (exp emotion/ OR mental disease/) OR (psycho$ OR social OR Distress OR anxi$ OR depress$ OR stress OR mental health OR psychiatr$ OR mental disorder$) [C]

- **CINAHL**

  (MH "Psychological Processes and Principles+") OR ("psycho*" OR "social" OR "distress" OR "anxi*" OR "depress*" OR "stress" OR "quality of life" OR "mental health" OR "psychiatr*" OR "mental disorder*")

- **ProQuest**

  AB,TI(Psycho* OR social OR Distress OR anxi* OR depress* OR stress OR (quality-of- life) OR (mental-health) OR psychiatr* OR (mental-disorder*))

- **Google Scholar**

  ((psychological OR psychology OR psychologic OR psychosocial OR "psycho social" OR "psycho-social") OR social OR distress OR distressed OR anxiety OR anxious OR depression OR depressed OR stress OR stressed OR ("quality of life") OR ("mental health") OR (psychiatry OR psychiatric) OR (mental AND (disorder OR disorders)))

[C] Quality of life added 2127 irrelevant papers mostly in relation to quality of life of HSCT as intervention. Consequently, quality of life terms were excluded from the final EMBASE script to reduce the probability of human error whilst screening the pooled database list of abstracts.

2 JOURNAL PAPER

Perceptions of haematopoietic stem cell transplantation and coping predict emotional distress during the acute phase[D]

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Research sponsored by Health Education East Midlands via the Trent Doctorate Programme in Clinical Psychology. The authors report no conflicts of interest.

[D] This paper focuses on the theoretical findings of the study whose wider aim was to examine the feasibility of a psychological intervention for distress during acute HSCT as well as its theoretical underpinnings. It is formatted for submission to the journal Bone Marrow Transplantation. Guidelines for authors can be found at http://www.nature.com/bmt/for_authors.html

Abstract

This study tests whether a widely used psychological model of adjustment to illness, the *self-regulatory model*, predicts the patterns of distress observed in the acute phase of hematopoietic stem cell transplantation (HSCT). We argue that efforts to develop effective psychological interventions for this population will benefit from being grounded in an already well developed psychological approach. Consecutively referred adults (n=45) from two transplant centres were assessed at baseline on transplant day, and two and four weeks after transplantation for psychological distress, perceptions of HSCT, and coping. Anxiety peaked two weeks following transplantation but depression increased throughout the acute phase with 42% reporting clinical levels of distress at any time. As predicted by the self-regulatory model, higher distress was reliably associated throughout the period with negative perceptions of HSCT, controlling for the effects of confounding variables. More mixed support was found for the model's predictions about the impact of coping styles upon distress. The findings provided initial evidence for the impact of HSCT perceptions and coping on distress during acute HSCT. They also suggest the basis for psychological intervention, though replication and further investigation for the use and impact of coping strategies remains necessary.

Introduction[E]

Haematopoietic stem cell transplantation (HSCT) is a complex and intensive procedure whose acute phase can last several weeks, involves high toxicity, prolonged isolation, and a range of debilitating side effects (e.g., fatigue and nausea).[1-3] Patients report an overwhelming experience and loss of agency, describing the procedure as “walk to hell and back” and “really, really hard”.[4] Surveys of psychiatric morbidity in HSCT patients have found that approximately half of patients meet clinical criteria for anxiety or depression during the first weeks with anxiety often highest around admission and depression increasing thereafter.[3, 5-7] The impact of such distress on recovery from HSCT has been documented and may include reduced pain and symptom tolerance, longer hospital stay, and poorer treatment adherence, immune recovery, and survival rates.[8-13] [F]

Clinical and demographic predictors of psychiatric morbidity during HSCT have been extensively investigated.[3, 5, 10, 14-16] However, the literature on psychological predictors of distress is less well developed. From this work, disparate factors such as personal control and meaning-making,[5] sense of coherence,[17] acceptance of distress,[18] and diversion of attention from pain[10] appear to be important. However, we argue the absence of a unifying and well-developed psychological theory from this research has hampered the development of timely and effective psychological interventions for HSCT patients. This may partly explain the sparse and limited effectiveness of such interventions in HSCT and lack of clarity regarding what contributes to outcome.[19] [G]

The most widely applied model of psychological adjustment to illness is the *self-regulatory model*.[20-23] It conceptualises the process of psychological adjustment to illness as comprising three interacting components: interpretation, coping, and appraisal of coping. A person’s interpretation, or illness perception, includes their view of the severity of its consequences, duration, identity (its

[E] The extended background of the thesis (Section 4) discusses the literature presented herein in further detail within the broader framework of the intervention examined in the project but not included in the present paper.
[F] See Section 4.1 in the thesis for further information on HSCT and its sequelae.
[G] See Section 4.2 in the thesis and the systematic review (Baliousis et al., 2015) for further details on the HSCT psychological intervention literature.

label and symptoms for the person), concern, level of understanding, and emotional impact. Coping describes the process of implementing strategies to reduce the psychological threat perceived by the person, and any resultant negative emotions. Appraisal of coping forms a feedback loop, evaluating the effectiveness of the person's coping efforts.[22]

All three elements of the model have been investigated extensively and largely validated in other health populations. For example, more negative illness perceptions have been found to predict a range of health-related outcomes including emotional and physical well-being.[22, 24-32] Distinctive coping patterns appear to yield different results. Avoidant coping may be unhelpful, whilst engaging with the challenges of the illness and accessing social resources to support coping may be more helpful.[32-34] Positive appraisals of coping have also been found to predict emotional well-being.[22, 32] Crucially, all three elements of the model have also been associated with physical recovery, predicting complications, treatment adherence, return to work, and general physical functioning.[22, 26, 29, 35, 36] Should such findings be replicated in an HSCT population, the model, which has supported the development of effective interventions in other health populations,[25, 26] may be a promising guide to effective interventions in HSCT. [H]

Of the self-regulatory model's components only coping has been studied in HSCT. However, these studies have focussed on the recovery period several months after HSCT,[37-39] therefore, the impact of coping during the acute phase remains unclear since coping styles can have different effects depending on circumstances.[34] The self-regulatory model refers to illness and the extent to which it might apply to HSCT, where it is treatment-related toxicity that poses the greatest challenge in the acute phase, requires corroboration. Therefore, the present study examined the applicability of the self-regulatory model[20-22] to acute HSCT. We hypothesised that: (a) more negative perceptions of HSCT will be associated with higher levels of distress; (b) avoidance-based coping styles (e.g., disengaging, denial, self-distraction, etc.) will be associated with higher

[H] See Section 4.3 in the thesis for further details on the self-regulatory model and the evidence on the role of perceptions and coping strategies in adjustment and well-being.

levels of distress; and (c) approach-based coping styles (e.g., active coping, planning, seeking support) will be associated with lower distress. [I]

Method[J]

Participants[K]

Participants were recruited from consecutive referrals between January and September 2015 at two haematology departments in different regions of England. Inclusion criteria were: (a) HSCT for haematological malignancy; (b) 18 years or older; and (c) sufficient command of the English language to participate in the study. Where appropriate, ambulatory care was offered and accepted by some patients, although in practice an admission took place for all participants during the study.

Materials[L]

We used brief, well established self-report measures. We followed standard practice by assessing the elements of the self-regulatory model via the Brief Illness Perceptions Questionnaire (Brief IPQ)[40] and Brief Coping with Problems Experienced (Brief COPE) questionnaire.[22, 41]

In light of the complex distress patterns in HSCT (anxiety, depression, traumatic stress, etc.)[3, 5, 6, 9], we measured the dependent variable of distress using the Depression Anxiety Stress Scales (DASS-21) due to its coverage of three constructs and clinical validity in this respect.[42, 43] DASS-21 measures depression, anxiety, and stress, and provides a total distress score.[42, 43] Each subscale comprises seven items rated on a 4-point Likert scale with total scores between 0-21 for each (higher scores denote higher distress).[43] Moderate level cut-offs are representative of clinical populations.[44, 45] The instrument has good to excellent internal consistency (Cronbach's α = 0.82-0.94), good criterion validity, acceptable discriminant validity, moderate sensitivity to clinical change,

[I] See Section 5 of the thesis for further information on aims and objectives including those of the broader feasibility study regarding the intervention.
[J] Section 6 of the thesis also contains information on the intervention and treatment as usual.
[K] See Section 6.1 in the thesis for further information on sampling.
[L] See Section 6.4 in the thesis for further details on measures, the pro-forma for collecting demographic and clinical information, and rationale for their selection.

and acceptable to good temporal stability (r = 0.71-0.81) in clinical samples.[42, 43, 46-48]

The Brief COPE has been widely used and is relatively short yet comprehensive[41, 49, 50] consistent with the study's aims. It measures several theoretically-derived coping styles. Self-distraction, denial, disengagement, venting, and self-blame are generally considered avoidance-based whilst active coping, support, positive reframing, planning, humour, and acceptance (vs. denial) are considered approach-based but groupings can vary across contexts[33, 34, 49] and have not been established in HSCT. Each style comprises two items rated on a 4-point Likert scale with total scores from 0-6 (higher scores denoting more frequent use).[41] The instrument has good construct, concurrent, and predictive validity in relation to emotional well-being and adjustment in different clinical populations including HSCT.[33, 38, 51-55] Some limitations to reliability similar to other coping measures have been reported with Cronbach's α between 0.50-0.90 and test-retest reliability coefficients between 0.42-0.89 (6-8 weeks).[33, 41, 49, 50]

The Brief IPQ is based on the self-regulatory model and assesses illness and coping appraisals (consequences, timeline, identity, concern, understanding, emotional impact, personal, and treatment control). It contains eight items rated on an 11-point Likert scale with higher scores reflecting higher endorsement.[40] A higher summary score (0-80) reflects more negative perceptions (items 3, 4, and 7 are reverse-scored).[55, 56] The measure has been validated in several clinical populations.[22, 55-58] It has acceptable internal consistency (Cronbach's α = 0.58-0.82) and stability (r = 0.42-0.88 up to six weeks),[40, 56] and good concurrent, predictive, and discriminant validity.[40, 55, 56, 58] We adapted it for HSCT (see online supplement) as the original measure refers to illness.

Design and procedure[M]

We used a longitudinal design with four time points (Figure 4) to examine the relationships between emotional distress and psychological processes over time. A member of the clinical team invited eligible patients to take part following

[M] See Sections 6.5, 6.6, 6.8, and .9 in the thesis for further details on design, procedure, ethics, and service user involvement respectively.

referral to the service. Interested patients provided consent after reviewing the study materials and were given the opportunity to ask questions. At time point 1, participants completed baseline questionnaires on site or returned them via the post. Participants completed the same questionnaires over the telephone at three further time points: on transplant day, and two and four weeks after the transplant. In light of HSCT's physical side effects (mucositis, etc.)[2], we also asked participants to attribute physiological symptoms of DASS-21 anxiety (items 2, 4, 7, and 19, referring to dry mouth, breathing difficulty, etc.) to clarify whether they reflected HSCT side effects rather than anxiety, and remove them in the case of the former. We recorded participant characteristics and nonconcordant events (intensive care, patient leaving isolation, psychological input) from clinical records. A National Research Ethics Service Committee in the UK approved the study. A patient panel helped develop the study procedure.

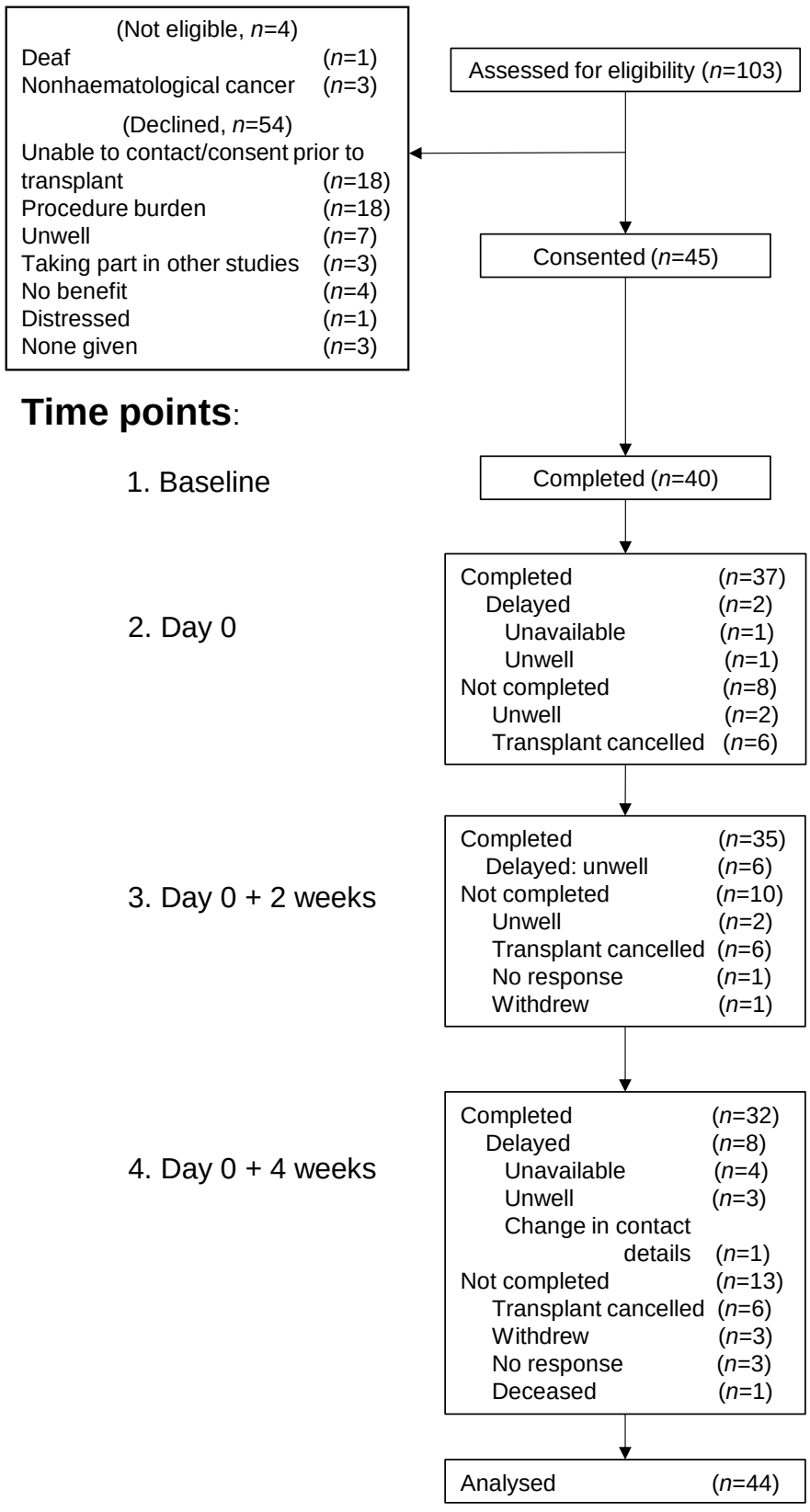

Figure 4. Diagram of procedure and participant flow. Responses were delayed if they exceeded two days from their due time. All available data were included in analyses. Day 0 = Day of transplantation.

Data analysis[N]

Preliminary analyses examined descriptives, input errors, outliers, assumptions, and missing data.[59, 60] We used Cronbach's α coefficients to assess internal consistency[59] and removed DASS-21 items that could not be differentiated from HSCT's side effects. In light of missing data and assumption violations, we used Multilevel Modelling (MLM) with nonparametric bias-corrected bootstrapping to include all available information and improve accuracy.[60, 61] We examined the effect of time (categorical predictor) and participant characteristics (covariates, including site) on distress and the effect of time on HSCT perceptions and coping styles. For the main analyses, we used MLM to examine the change of HSCT perceptions and coping style over time and their relationship with distress across all time points whilst controlling for previously significant covariates. We assessed model improvements ($\Delta\chi^2$) and explained variance (R_1^2) at each step of model development.[60] We also examined improvements by taking account of variance across participants (random effects) for significant predictors.[60] The level of significance was $\alpha=0.05$.

Results

Preliminary analyses[O]

[N] See Section 6.7 in the thesis for further details on computations, initial analyses, assumption violation checks, analyses relating to the feasibility component of the project, analyses regarding the theoretical component featuring in this paper, and software.

[O] See Sections 7.1 in the thesis for further details on participant characteristics, results relating to the intervention feasibility component, Cronbach's α coefficients, and assumption checks.

Table 2 presents characteristics of the 45 participants recruited. We removed DASS-21 items 2 (dry mouth) and 7 (trembling) as these reduced reliability coefficients, and 56% of participants indicated that these items reflected side effects of HSCT rather than anxiety. Cronbach's α coefficients determining internal consistency across time were 0.72-0.95 for total distress, depression, and stress, and 0.46-0.78 for anxiety (lower at later time points). For HSCT perceptions, coefficients were 0.63-0.68. Two items (both coping appraisals) appeared to reduce coefficients from over 0.70. Acceptance, positive reframing, behavioural disengagement, denial, self-blame, self-distraction, and venting showed at least one coefficient below 0.50 (common in coping research)[50] suggesting limitations to reliability. Other coefficients were up to 0.94.

Table 2. Participant characteristics (n=45)

Characteristics	**Overall (*n*, %)**
Gender: male	31 (69%)
Marital status	
Married/cohabiting	34 (76%)
Single	5 (11%)
Other	6 (13%)
Education	
Mainstream only	19 (42%)
Further	12 (27%)
Higher	10 (22%)
Not known	4 (9%)
Diagnosis	
Multiple myeloma	27 (60%)
NHL	12 (27%)
Other	6 (13%)
Transplant: Autologous	40 (89%)
Age on transplant day (years)	*(Mean, SD)*
	59.5 (11.7)
Years since diagnosis	2.40 (3.47)
Performance status (ECOG)	0.58 (0.60)
Length of admission	Ambulatory (*n*=11, 28%)
	9.40 (5.27)
	Nonambulatory (*n*=28, 72%)
	21.1 (5.5)

Note. SD = Standard deviation; NHL = Non-Hodgkin's lymphoma; ECOG = Eastern Cooperative Oncology Group scale; Ambulatory = Patients initially attending day ward.

Of the 184 possible data points (45 participants completing questionnaires up to four times) 144 were completed (Figure 4). Of these, 15% were delayed (more than two days overdue). Regarding missing data, Little's test was significant, $\chi^2(127)=163.99$, $P=0.015$, and missing data were related to poorer baseline performance status (physical functioning) at time points 2 and 3, ts(3.6-7)≥3.4, Ps≤0.03, and higher baseline and time 2 stress at time point 3, $t(8.9\text{-}34)\geq 2.5$, $P\leq 0.04$. Missing data could, therefore, be considered mostly random for MLM.[60] Of noncondordant events, one participant received psychological input (time point 3), which may have affected distress.

Effects of time and participant characteristics[P]

We observed a significant main effect of time for all distress scales except stress (Table 3). This was also reflected in the proportion of patients reporting at least moderate distress (Table 3), reaching 42% at any time during the acute phase (time points 2-4). Compared to baseline, total distress was significantly higher at time point 3, depression was higher at time points 3 and 4, and anxiety was higher at time point 3. As covariates, younger participants reported less depression, males reported less distress overall, and those with better baseline performance status reported less anxiety and stress across time points, $\Delta\chi^2(\Delta df=1)\geq 4.58$, $Ps\leq 0.03$. No other covariates reached statistical significance, $\Delta\chi^2(\Delta df\leq 2)\leq 5.51$, $Ps\geq 0.06$ (see online supplement for fixed parameter estimates). Estimation terminated (converged) when random effects were added for performance status (total distress), ambulatory treatment (depression), and length of admission (total distress) only (models did not improve significantly).

[P] See Section 7.1.5 in the thesis for further details on effects of time, participant characteristics on distress, and parameter estimates. Section 7.2. contains details on the analysis regarding intervention effects.

Table 3. Mean distress over time (with percentage of patients reporting at least moderate levels) using multilevel modelling

Measure	***M*(*SD*)**						**Effect of time**		
	T1	T2	T3	T4	$\Delta\chi^2$	R_1^2	β(*SE*)		
							T2	T3	T4
Total distress	9.84(10.93)	9.89(6.87)	15.0(10.5)	13.6(10.2)	10.6*	nil	0.08(1.60)	3.74* (1.48)	2.74(1.47)
Depression	3.84(4.60) (13%)	2.47(2.64) (9%)	4.90(3.94) (18%)	5.39(5.13) (24%)	31.1***	15%	-0.83(0.57)	1.56** (0.56)	2.17** (0.78)
Anxiety	1.45(2.49) (7%)	1.38(1.78) (11%)	2.42(2.32) (27%)	1.00(1.24) (4%)	28.2*** (Δ*df*=4)	<0	0.46(0.27)	1.53*** (0.38)	0.16(0.32)
Stress	4.55(4.94) (11%)	4.58(3.41) (4%)	4.64(5.09) (9%)	4.80(4.34) (9%)	18.2**	<0	-0.05(0.76)	0.63(0.60)	0.66(0.67)

Note. *M* = Mean; *SD* = Standard deviation; T1-4 = Time points 1-4; $\Delta\chi^2$ = -2log Likelihood change compared to baseline, Δ*df* = 3 for fixed effects models and 5 for random effects models unless specified otherwise; R_1^2 = Explained variance compared to intercepts-only model; β = Fixed parameter estimate (compared to baseline); *SE* = Standard error; Shading = Predictor set random at Level 2.
***P<0.001; **P<0.01; *P<0.05.

Psychological processes[Q]

Overall, negative HSCT perceptions were higher at time points 3 and 4 compared to baseline, $\Delta\chi^2(\Delta df=3)=31.4$, $P<0.001$, but the difference did not reach significance for subscales, $\Delta\chi^2(\Delta df=3)\leq 6.61$, $Ps\geq 0.09$. More negative perceptions of HSCT and the majority of subscales measured were significantly associated with higher distress across the study period (with identity and understanding showing no relationship with stress [Table 4]).

Of the coping styles, use of self-distraction, active coping, emotional and instrumental support, humour, and positive reframing was higher compared to baseline across time points 2 to 4 (time point 2 only for humour and time points 2 and 3 for reframing), $\Delta\chi^2(\Delta df=3)\geq 8.42$, $Ps\leq 0.04$, but not use of other styles, $\Delta\chi^2(\Delta df=3)\leq 7.48$, $Ps\geq 0.06$. As shown in Table 4, more frequent use of avoidance-based (unhelpful) styles was significantly associated with higher distress. However, more frequent use of approach-based or coping styles considered helpful was also associated with higher distress. The effects of HSCT perceptions and coping remained unchanged after controlling for age, gender, and performance status.

[Q] See Section 7.3 in the thesis for further details on the analyses concerning HSCT perceptions and coping including change over time, random parameters (variance across participants), and resilience in relation to distress.

Table 4. Summary of multilevel models for distress with negative HSCT perceptions and coping styles as predictors

Scale	Total distress			Depression			Anxiety			Stress		
	$\Delta\chi^2$	R_1^2	β(*SE*)	$\Delta\chi^2$	R_1^2	β(*SE*)	$\Delta\chi^2$	R_1^2	β(*SE*)	$\Delta\chi^2$	R_1^2	β(*SE*)
Negative HSCT perceptions	60.5***	34%	0.37*** (0.07)	53.8***	28%	0.17*** (0.04)	42.2***	38%	0.07*** (0.20)	36.9***	28%	0.13** (0.04)
Consequences	24.8***	<0	0.85*** (0.22)	18.8***	6%	0.45*** (0.11)	6.23*	3%	0.15* (0.06)	47.5***	<0	0.29** (0.12)
Timeline	40.1***	<0	1.18** (0.41)	33.1***	<0	0.42* (0.19)	41.4***	<0	0.26* (0.11)	33.7***	<0	0.45*
Identity	42.0***	<0	0.75** (0.26)	25.3***	4%	0.49*** (0.10)	23.9***	<0	0.19** (0.06)	28.6***	<0	0.14(0.14)
Concern	16.4***	<0	1.30*** (0.28)	34.9***	<0	0.50*** (0.13)	31.1***	<0	0.21** (0.07)	35.5***	<0	0.56*** (0.15)
Understanding	25.6***	<0	-1.15* (0.50)	11.4***	7%	-0.53** (0.19)	32.1***	<0	-0.26* (0.12)	1.72	5%	-0.37(0.20)
Emotional impact	71.7***	<0	1.72*** (0.24)	41.0***	35%	0.79*** (0.11)	42.9***	<0	0.30*** (0.08)	38.0***	37%	0.79***

Personal control	-0.35	nil	0.02(0.20)	0.02	nil	-0.02(0.13)	16.2**	<0	0.08(0.12)	0.15	nil	0.05(0.13)
Treatment control	2.13	nil	0.11(0.36)	0.32	1%	-0.10(0.18)	0.79	nil	0.08(0.09)	0.54	nil	0.13(0.18)
Coping												
Self-distraction	2.38	5%	0.66(0.42)	0.48	1%	0.15(0.20)	1.83	1%	0.14(0.10)	4.52*	10%	0.45* (0.21)
Denial	28.0***	35%	3.53** (1.04)	23.3***	28%	1.98*** (0.36)	27.9***	33%	0.46(0.28)	6.58*	16%	1.16** (0.42)
Behavioural disengagement	29.6*** (Δ*df*=2)	33%	4.28** (1.47)	35.0*** (Δ*df*=2)	34%	2.64*** (0.69)	24.4***	32%	0.38(0.44)	11.6***	10%	1.51** (0.46)
Venting	28.8***	28%	2.54** (0.73)	14.1**	nil	0.70* (0.33)	19.5***	18%	0.56*** (0.14)	28.0*** (Δ*df*=2)	33%	1.32*** (0.32)
Self-blame	44.0***	47%	3.44** (1.05)	19.6***	28%	1.20* (0.46)	47.1***	44%	0.58* (0.25)	28.4***	34%	1.51*** (0.34)
Active coping	2.71	5%	0.66(0.40)	2.09	3%	0.28(0.19)	1.54	1%	0.12(0.10)	2.23	9%	0.30(0.19)
Emotional support	9.69**	6%	1.02* (0.40)	3.5	5%	0.44* (0.21)	3.15	2%	0.16(0.11)	6.01*	6%	0.50* (0.20)

Instrumental support	12.0***	15%	1.34*** (0.37)	8.18**	10%	0.54** (0.19)	7.36**	4%	1.76** (0.29)	9.06**	16%	0.63** (0.20)
Positive reframing	1.13	2%	0.42(0.39)	0.01	nil	-0.02(0.19)	2.83	2%	0.16(0.10)	2.62	4%	0.31(0.19)
Planning	10.4**	13%	1.24** (0.39)	3.77	5%	0.37* (0.18)	2.50	5%	0.15(0.09)	29.0***	42%	0.76** (0.25)
Humour	0.25	nil	0.20(0.40)	1.08	nil	-0.20(0.19)	20.7***	29%	0.25(0.13)	0.88	nil	0.18(0.19)
Acceptance	0.01	nil	0.04(0.44)	0.001	nil	0.01(0.22)	0.001	nil	0.003(0.110)	nil	nil	0.002(0.213)

Note. HSCT = Haematopoietic stem cell transplantation; $\Delta\chi^2$ = -2log Likelihood change compared to the baseline model, Δdf = 1 for fixed effects models and 3 for random effects models unless specified otherwise; R_1^2 = Explained variance compared to intercepts-only model; β = Fixed parameter estimate; *SE* = Standard error; Shading = Predictor set random at Level 2; Random effects models did not converge for consequences (depression and anxiety), personal control (depression), treatment control (anxiety), understanding (stress), emotional impact (depression, stress) and instrumental support (total distress and depression).

***P<0.001; **P<0.01; *P<0.05.

Discussion[R]

We examined whether HSCT perceptions and coping predict distress during the acute phase of HSCT in line with the self-regulatory model.[20-22] The results supported the model given that negative HSCT perceptions and coping styles predicted distress during acute HSCT. This extends the literature during this period of HSCT, which has previously focused predominantly on clinical and demographic variables.[3, 5, 10, 14-16]

Perceptions of HSCT and coping[S]

The results support the hypothesised role of negative interpretations about HSCT in maintaining distress, including how physical symptoms are perceived. This is consistent with qualitative research findings highlighting loss of meaning and interpretations of threat in HSCT[4], and with the wider literature on cognitions in depression, anxiety, and stress, suggesting the relevance of negative outlook, perceptions of threat, and challenge respectively.[62, 63] The effect of perceived emotional impact of the procedure was particularly high, indicating that patients experiencing distress generally attributed this to HSCT and, in conjunction with other perceptions of HSCT (e.g., lengthy course), may compound distress. However, the large association between distress scales and this Brief IPQ item also suggests the measures may overlap conceptually.

The lack of association between coping appraisals (personal and treatment control) and distress was contrary to expectations. However, these items did not appear internally consistent within the Brief IPQ. This has also been observed in other studies[64] and the items have shown variable ability to predict distress,[22] which might suggest a limitation to the contribution of coping appraisals (and the self-regulatory model) in some populations, including HSCT. However, the complexity of HSCT, heterogeneity of care[2], and social desirability when rating helpfulness of treatment (treatment control) may have introduced complexity in these appraisals that was not possible to capture in the project. The null results may also reflect the findings in relation to coping.

The findings indicated that several coping styles were ineffective. Whilst this was expected for avoidance-based styles, it was not for those that are

[R] See Section 8 in the thesis for further discussion of the findings.
[S] See Section 8.2 in the thesis for further discussion of the findings on HSCT perceptions and coping.

considered helpful in the wider literature such as planning and seeking support.[34, 49] Studies examining the post-acute period of HSCT have not observed reliable effects of these latter styles[38, 39] but it is possible that the circumstances of acute HSCT may render many coping strategies ineffective or counterproductive. For example, an adverse effect of planning has been noted in acute cancer care but not subsequent periods.[65] Furthermore, social support is believed to provide a resource for coping[34] but the acute phase of HSCT, with isolation and disabling side effects,[2] may render attempts to use this resource inert.[10] These observations may also explain the lack of reliable associations between distress and perceptions of personal and care control.

Distress patterns

Results replicated the pattern of high but declining anxiety and increasing depression that has been found in HSCT studies, including the acute phase.[3, 5-7] The pattern of anxiety may reflect perceptions of uncertainty and threat at the beginning of the procedure, the increase in depression may reflect perceptions of a lengthening timeline, severe consequences, and ineffective coping, whilst stable stress may suggest a sustained level of challenge. However, anxiety peaked after transplantation in the present sample rather than closer to the transplant day reported previously.[3, 5, 7, 10, 14] This could be due to using the DASS-21 which separates stress from anxiety, possible confounding in the latter by physical symptoms after transplantation, and ambulatory care resulting in later admission which may be unexpected. Patients also wait to see whether the transplant is engrafting well or not during the period following HSCT, which may contribute to anxiety. Lower distress in younger individuals, men, and those with better performance status supports findings from previous studies.[3, 10, 14] Overall, our findings highlighted considerable complexity in patients' psychological needs.

Limitations and strengths[T]

The findings need to be viewed in light of some limitations. The correlational evidence was unable to establish causation. HSCT perceptions and coping may also interact with physical functioning in predicting distress but such effects were not examined. Social desirability may have resulted in more

[T] See Section 8.4 in the thesis for further discussion of strengths and limitations.

favourable reports, for example of coping style use. Results may not generalise to individuals with poorer physical functioning or higher stress, in light of the attrition. They may also not generalise to other settings, minority groups, younger individuals, allogeneic patients, or patients with rarer diagnoses than the present sample. The novel Brief IPQ adaptation requires further validation whilst the Brief COPE is not exhaustive so that the observed effects regarding coping may not apply to other styles. Statistically, lack of convergence in some random effects models, limited internal consistency of some scales, and the small sample may have introduced bias. Finally, the number of tests may have inflated Type I error, particularly for coping styles where overall analysis was not conducted. However, the findings are strengthened by a longitudinal design showing reliable and enduring effects, and a new and promising scale for HSCT perceptions. Consecutive referrals with reasons for nonparticipation, two sites, and the heterogeneity of the sample enhanced external validity. Finally, MLM with bootstrapping maximised the dataset, accounted for variability across participants, and improved statistical validity.

Overall, the findings highlighted complex emotional needs during HSCT and a potential role for perceptions of HSCT and coping in underpinning distress. Addressing the diverse negative HSCT perceptions via well-established approaches such as psychoeducation,[66, 67] self-regulatory interventions,[25, 26], targeted provision of information to patients during routine care, and cognitive restructuring[68, 69] may be beneficial. Promoting helpful coping may require a shift from problem-engagement alone featuring heavily in HSCT interventions and cancer generally[19, 70, 71] towards experience-engagement (e.g., via mindfulness[18, 72]) and extending support resources (e.g., peer network).[73] This may also promote physical and immune recovery in light of relevant findings.[8-10, 22] However, replication with larger samples and other clinical subgroups and settings remains necessary. Future studies into the role of physical functioning, perceptions, coping, and distress, and establishing causality (e.g., via psychological intervention) appear necessary. [U]

[U] See Sections 8.5-8.7 in the thesis for further discussion of clinical and research implications and overall conclusion.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank our patients who kindly participated in this study and the staff teams for supporting the project, particularly Lynne Watson and Lisa Rachel for their diligence with identifying participants. The study was supported via training funds by Health Education East Midlands, UK.

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3 EXTENDED PAPER

3.1 EXTENDED BACKGROUND

3.1.1 Haematopoietic stem cell transplantation and its sequelae

Haematopoietic stem cell transplantation (HSCT) is a complex procedure to treat a range of haematological and autoimmune illnesses and malignancies that are primarily life-threatening such as myeloma, lymphoma, leukaemia, anaemia and immunosuppressive diseases (Copelan, 2006). It involves transfer of haematopoietic stem cells harvested either from the patient (autologous) or a matched donor (allogeneic; Copelan, 2006). At a cost of up to £100,000 per transplant, over 3,000 individuals undergo the procedure every year in the UK which often results in substantial benefits including cure for some patients (Copelan, 2006; National Health Service [NHS] Commissioning Board, 2013).

The acute phase of HSCT is very intensive. At first, the patient's bone marrow and cancerous cells are ablated (killed off) with chemotherapy and/or radiotherapy exposing the person to very high levels of toxicity often in addition to previous chemotherapy (Copelan, 2006). This is followed by infusion (transplantation) of the new stem cells and a period of recovery lasting several weeks and requiring prolonged isolation to allow the marrow, blood, and immune systems to return to healthy levels of functioning (Copelan, 2006). At this stage, the side effects are diverse and often very aggressive including mucositis (pain and inflammation of the body's mucous membrane causing ulcers, etc.), Graft versus Host Disease (GVHD, when transplanted immune cells attack the patient's organs), pain, fatigue, weakness, nausea, sleep disruption, gastroenteritis, infections, and so forth (Anderson et al., 2007; Copelan, 2006; Larsen, Nordstrom, Ljungman, & Gardulf, 2004; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005). These often subside beyond the first 30 days of the procedure but sometimes can burden patients for several years and more than the illness which HSCT was originally intended to alleviate (Copelan, 2006; Mosher, Redd, Rini, Burkhalter, & DuHamel, 2009). Consequently, HSCT is often the last course of treatment after previous treatment failure or relapse of cancer (Copelan, 2006).

In light of the intensity, toxicity, and side effects of the procedure, it is not surprising that patients undergoing HSCT experience considerable loss of personal control and psychological distress. Studies describe the distress as multi-faceted including stress, anxiety, depression, anger, uncertainty, and so forth, with levels being highest during the acute phase and decreasing only after several weeks (Dakanalis, Assunta Zanetti, & Clerici, 2013; Fife et al., 2000; F. Keogh, O'Riordan, McNamara, Duggan, & McCann, 1998; Lee et al., 2005; McQuellon et al., 1998; Molassiotis, van den Akker, Milligan, Goldman, & Boughton, 1996; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Prieto et al., 2002; Tecchio et al., 2013). Notably, pretransplant distress is reported to be highly predictive of distress following the transplant (Lee et al., 2005), indicating an early onset and poor outlook.

The impact of such distress on recovery has been documented. The literature on HSCT highlights negative outcomes of distress such as worse treatment adherence, reduced pain and symptom tolerance, longer hospital stay, and higher mortality (Akaho et al., 2003; Hoodin & Weber, 2003; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, Espinal, et al., 2005; Prieto et al., 2002; Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002; Syrjala & Chapko, 1995). In other health populations, distress (even transient) has been associated with greater incidence of illness, harmful physiological changes, greater pain perception, suppression of the immune system, and higher risk of infections (Glaser & Kiecolt-Glaser, 2005; Godbout & Glaser, 2006; Ogden, 2012). As HSCT involves substantial immune system suppression and then recovery prior to discharge (Copelan, 2006), the presence of distress can prolong the process and increase patients' mortality. The consequences of distress on emotional and physical wellbeing during HSCT highlight a need for robust psychological intervention.

3.1.2 Psychological interventions in HSCT

The literature on psychological interventions in HSCT is very limited (Baliousis, Rennoldson, & Snowden, in press). Interventions involving psychological components (e.g., cognitive behavioural input, emotional processing, coping skills training) supported by trained staff tend to show more

effectiveness (Baliousis et al., in press). However, the literature is sparse and shows small effects, lack of or poor controls, high risk of bias, and lack of clarity regarding psychological mechanism (Baliousis et al., in press; Bauer-Wu et al., 2008; Bevans et al., 2010; Horton-Deutsch, O'Haver Day, Haight, & Babin-Nelson, 2007; Lounsberry, Macrae, Angen, Hoeber, & Carlson, 2010). Furthermore, few interventions seek to address distress during the acute phase of the procedure when the need appears highest and those that do show very limited benefits and fail to address distress at its onset prior to transplantation (Baliousis et al., in press; Dakanalis et al., 2013; Fife et al., 2000; F. Keogh et al., 1998; Lee et al., 2005; McQuellon et al., 1998; Molassiotis et al., 1996; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Prieto et al., 2002; Tecchio et al., 2013).

A plausible reason for the lack of effective intervention during acute HSCT may be the barriers to accessing and delivering interventions posed by the logistics, intensity, and clinical burden of the procedure, such as many medical treatments, complications, and so forth (Antin & Raley, 2013; Copelan, 2006). Studies have identified such barriers in other cancer populations (Moyer, Knapp-Oliver, Sohl, Schnieder, & Floyd, 2009) but the empirical evidence from HSCT is indirect such as poor overall adherence to interventions and smaller samples in studies examining more intensive interventions during the acute phase relative to self-directed ones (Allocca, 1998; Baliousis et al., in press; Bauer-Wu et al., 2008; de Linares et al., 2007; Horton-Deutsch et al., 2007). However, the limited benefits associated with self-directed interventions (Baliousis et al., in press) highlight a need to develop a better balance between intensity of input and burden so that interventions remain effective as well as accessible to patients. For this to occur, a better understanding of feasibility issues with delivering interventions during acute HSCT appears essential. The present study included a feasibility component to address this need.

Another possible reason for the scarcity and limited effectiveness of interventions is lack of application of a coherent theoretical model. Evidence from psychotherapy suggests that a coherent theoretical framework appears essential for the success of interventions (Wampold, 2001) but the intervention literature on HSCT shows little theoretical grounding (Baliousis et al., in press). As argued in the journal paper, this limitation appears to reflect the focus on

disparate factors that characterises the wider research on psychological underpinnings of distress during HSCT (Bauer-Wu et al., 2008; Fife et al., 2000; Pillay et al., 2015; Schulz-Kindermann et al., 2002). It follows, that establishing firm theoretical grounding is likely to be important in developing effective interventions in this population and is in line with the Medical Research Council's (MRC's) guidance for developing interventions (Craig et al., 2008). The *self-regulatory model* provided this basis in the present study, as the most widely applied model of psychological adjustment to illness (Hagger & Orbell, 2003; Leventhal et al., 1997; Ogden, 2012; Sharpe & Curran, 2006). The model has received extensive support in other health populations but has not been applied to HSCT. The theoretical component of the present study sought to explore the model's applicability as a basis for intervention in HSCT.

3.1.3 The self-regulatory model

Illnesses such as haematological malignancies involving disrupting procedures like HSCT can impact adversely on many domains in an individual's life (Ogden, 2012). Adjustment often reflects a process of adaptation towards more positive views of self and the world and more helpful coping strategies to improve psychological, social, and physical wellbeing (Ogden, 2012; Sharpe & Curran, 2006). Leventhal and colleagues (Leventhal et al., 1997; Leventhal, Nerenz, & Purse, 1984) have described this process in the self-regulatory model which has been applied widely in health-related psychological research (Ogden, 2012; Sharpe & Curran, 2006).

According to the self-regulatory model, helpful mechanisms in the process of adaptation to HSCT may include updating perceptions of the procedure so that they are more in line with its reality and coping strategies (Leventhal et al., 1997; Leventhal, Nerenz, & Purse, 1984; Ogden, 2012; Sharpe & Curran, 2006). Helpful coping strategies might include meaning-making, reprioritising goals, active coping, and promoting helpful health behaviours, both as means of prevention and intervention, leading to a sense of being able to cope (positive coping appraisals) and further adjustment.

The self-regulatory model formed the theoretical basis for developing a psychological intervention to address distress during acute HSCT in the present

project via addressing perceptions of HSCT, coping, and appraisals of coping. The evidence relating both to the relevant theoretical assumptions and the benefits of their application in health populations is discussed below.

3.1.3.1 Illness perceptions

Interpretations of a health difficulty is one of the core components of the self-regulatory model (Leventhal et al., 1997; Leventhal, Nerenz, & Purse, 1984; Ogden, 2012; Sharpe & Curran, 2006). Interpretations is mediated by social messages and reflects understanding of the problem in the form of various perceptions about it (Broadbent, Petrie, Main, & Weinman, 2006; Hagger & Orbell, 2003; Leventhal et al., 1997; Leventhal et al., 1984; Moss-Morris et al., 2002; Ogden, 2012). In the context of HSCT, these perceptions might include:

- Consequences: Beliefs about the effects of HSCT on the patient's life. These consequences may be physical (e.g., disability, pain, etc.), social (e.g., isolation, restricted social life, etc.), and so forth.
- Timeline: Predictions about how long the process (e.g., symptoms, appointments) of HSCT will last, for example, anticipating that the process will end soon after hospitalisation versus continuing over several years.
- Identity: The extent to which the patient constructs HSCT in terms of the side effects and complications surrounding the procedure.
- Concern: The extent to which the patient perceives HSCT as a cause for concern.
- Understanding: The extent to which the patient believes they are able to comprehend the HSCT process.
- Emotional impact: Patients' beliefs about the extent to which HSCT affects them emotionally.
- Cure or control: The degree to which patients believe they or the treatment they receive can control the HSCT process. These perceptions reflect coping appraisals.

These different perceptions may operate on an abstract or concrete level (Leventhal et al., 1997; Leventhal et al., 1984; Ogden, 2012; Sharpe & Curran, 2006). They can change over time under the influence of a range of factors such as knowledge and experience (Sharpe & Curran, 2006), individual differences (e.g. Kohlmann, Ring, Carroll, Mohiyeddini, & Bennett, 2001; Miller, Brody, & Summerton, 1988), mood (Cropley & Steptoe, 2005; Mora, Halm, Leventhal, & Ceric, 2007; Stegen, Van Diest, Van de Woestijne, & Van den Bergh, 2000; Wright, Ebrecht, Mitchell, Anggiansah, & Weinman, 2005), underlying cognitive processes such as focus of attention (Eiser, 2000; Stegen et al., 2000; van Zuuren, 1998), and cultural context (Gureje, Simon, Ustun, & Goldberg, 1997; Minsky, Vega, Miskimen, Gara, & Escobar, 2003; S.-J. Wang et al., 1997).

A breadth of evidence favours the self-regulatory model's conceptualisation of illness perceptions and their role in adjustment (Hagger & Orbell, 2003; Ogden, 2012). Cross-sectional and longitudinal research suggests that illness perceptions are able to predict a range of outcomes including health-related behaviours (e.g., adherence to treatment), emotional wellbeing, social functioning, quality of life, and physical outcomes in a variety of clinical populations (Christensen & Ehlers, 2002; Hagger & Orbell, 2003; Hall, Weinman, & Marteau, 2004; Helder et al., 2002; Parry, Corbett, James, Barton, & Welfare, 2003; Petrie, Broadbent, & Meechan, 2003; Petrie, Cameron, Ellis, Buick, & Weinman, 2002; Sharpe, Sensky, & Allard, 2001; Vaughan, Morrison, & Miller, 2003). However, this evidence is correlational, therefore, a causal link between illness perceptions and the different areas of functioning remains tentative. Furthermore, the extent to which illness perceptions exist prior to the research examining them (i.e. they are "real") as opposed to having been constructed by the research process (e.g., by asking theory-led questions) is unclear (Ogden, 2012) which poses a threat to the internal validity of the findings. On the other hand, the suggestions of the self-regulatory model regarding the role of perceptions in underpinning adjustment are in line with the broader cognitive perspective in psychotherapy, particularly in relation to anxiety, worry, and depression which indicates that reducing threat appraisals (Clark & Beck, 2010) fostering a concrete and realistic representation of the

problem (Watkins, 2008), and addressing negative beliefs (Hollon & Beck, 2013) can be helpful.

3.1.3.1.1 The value of informational input

In light of the above theoretical considerations, providing information on HSCT and its sequelae may foster more accurate and helpful perceptions of the procedure and facilitate adjustment as HSCT progresses. The information could address issues that have been previously identified by HSCT patients as affecting their perceptions of the procedure, for example potential outcomes, recovery times, side effects such as fatigue, potential complications, the availability of medical care, friends' and family's reactions, and so forth (e.g., Andrykowski et al., 1999; Jim et al., 2014).

The benefits of information-based (psychoeducational) interventions about the process of the illness and outcomes have been documented as improving physical and psychological wellbeing in a range of clinical populations including organ transplantation (Engle, 2001), cancer (Beatty, Koczwara, Rice, & Wade, 2010; David, Schlenker, Prudlo, & Larbig, 2013; Fawzy, Fawzy, Arndt, & Pasnau, 1995; Kangas, Milross, Taylor, & Bryant, 2013), surgery preparation (O'Halloran & Altmaier, 1995), and adjustment during recovery several years after HSCT (DuHamel et al., 2010; DuHamel et al., 2000; Gaston-Johansson et al., 2013). Psychoeducation on the emotional response to the illness has been particularly helpful for psychological adjustment to cancer (Greer, Park, Prigerson, & Safren, 2010; Greer et al., 2012; Kangas et al., 2013) and organ transplantation (Hodges, Craven, & Littlefield, 1995) and could be helpful in HSCT in light of the emotional impact of the procedure. Such a component could include discussions relating to anxiety, depression, and their manifestations and day-to-day implications (Greer et al., 2010; Greer et al., 2012; Hodges et al., 1995; Kangas et al., 2013) with an additional therapeutic benefit of providing validation to patients (Elliott, Bohart, Watson, & Greenberg, 2011; Gilbert, 2010; M. J. Lambert & Barley, 2001). The range of physical and emotional outcomes achieved in a small number of sessions when perceptions are targeted according to the self-regulatory model (Petrie et al., 2003; Petrie et

al., 2002) support the use of the model in promoting the needed efficiency in the highly burdened HSCT population.

In sum, there is a breadth of literature documenting the effectiveness of interventions that include an informational component, thus supporting its application in HSCT within the self-regulatory model. However, the informational component was not administered in isolation in the above literature (except in Jones et al., 2001 and Petrie et al, 2002) and control for effects not specific to the intervention such as common factors (Wampold, 2001) was unclear in several of the trials (e.g. Beatty et al., 2010; David et al., 2013; DuHamel et al., 2010; Gaston-Johansson et al., 2013). These limitations raise some doubt regarding the benefits of informational input.

3.1.3.2 Coping

Adaptation in the self-regulatory model is influenced by coping as well as illness perceptions (Leventhal et al., 1997; Leventhal, Nerenz, & Purse, 1984; Ogden, 2012). Coping strategies used by patients can be different for diagnosis, crisis, and the course of illness and can be accompanied by a series of coping appraisals (e.g. “can I cope with this?”) towards increased self-regulation (Folkman & Moskowitz, 2004; Ogden, 2012; Taylor & Stanton, 2007; Tennen, Affleck, Armeli, & Carney, 2000). The use and benefit of coping strategies are also dependent on coping resources of which social support is considered prominent (Taylor, 2007; Taylor & Stanton, 2007). Coping with the stress of a crisis and adaptation may reflect the context of HSCT in particular. The coping literature delineates a range of coping conceptualisations that could apply in this context, of which problem- and emotion-focused and approach versus avoidance have been dominant (Folkman & Moskowitz, 2004; Ogden, 2012).

3.1.3.2.1 Problem and emotion-focused coping

Folkman and Lazarus proposed that coping with stress is primarily problem- or emotion-focussed (Folkman & Lazarus, 1980; Folkman & Moskowitz, 2004). These are complementary with the former addressing the stressor via planning, information-seeking, and so forth, while the latter aims at

alleviating the negative consequences of stress in ways such as seeking emotional support. A large body of evidence has supported the validity of this model. The application of problem- and emotion-focussed styles has been observed in different populations and factors such as type of stressor, age, gender, controllability, and available resources can discriminate meaningfully between the two conceptualisations (Folkman & Moskowitz, 2004; Ogden, 2012; Tennen et al., 2000). The conceptualisations of problem- or emotion-focussed coping provides a helpful guide for developing and organising the content of the coping aspect of the present intervention.

3.1.3.2.2 Approach versus avoidance coping

An alternative conceptualisation to Folkman and Lazarus' (Folkman & Lazarus, 1980; Folkman & Moskowitz, 2004) has been approach versus avoidance coping (Ogden, 2012; Taylor & Stanton, 2007). Approach involves confronting the stressor (e.g. problem-solving, planning, acceptance, use of support, etc.) while avoidance reflects disengaging from it (e.g. denial, distraction, etc.). This model has also received considerable support in the literature and has been found to represent a higher level categorisation relative to problem- versus emotion-focused coping instead of providing a competing model (Tobin, Holroyd, Reynolds, & Wigal, 1989).

What is likely to be helpful in distinguishing between approach and avoidance styles in the intervention is that these coping style groups have been able to predict distress, self-regulation, and adaptation relatively consistently, unlike problem- and emotion-focused coping (Folkman & Moskowitz, 2004; Ogden, 2012; Taylor & Stanton, 2007). On the one hand, avoidant coping strategies may be effective in alleviating distress with short-term, specific, or uncontrollable stressors (Heckman et al., 2004; Ogden, 2012; Taylor & Stanton, 2007) but have been associated with detrimental long-term psychological and physical outcomes. For example, a substantial body of cross-sectional and longitudinal research in various clinical populations indicates that avoidant strategies can predict poorer long-term adjustment and more distress (Holahan, Moos, Holahan, Brennan, & Schutte, 2005; Levine et al., 1987; Rayburn et al., 2005; Stanton & Snider, 1993; Taylor & Stanton, 2007; Young, 1992), less

helpful health behaviours (Weaver et al., 2005), pronounced symptoms (Rosenberger, Ickovics, Epel, D'Entremont, & Jokl, 2004), poorer recovery following surgery (Stephens, Druley, & Zautra, 2002), and worse disease progression/mortality (Epping-Jordan, Compas, & Howell, 1994; Leserman et al., 2000; Murberg, Furze, & Bru, 2004). Similar effects of avoidance coping alongside low levels of support, access to coping resources, and a poor sense of self-efficacy has also been observed during HSCT (Ho, Horne, & Szer, 2002; Hochhausen et al., 2007; Mytko et al., 1996; Wells, Booth-Jones, & Jacobsen, 2009).

Approach coping, on the other hand, can be more helpful for mental and physical wellbeing, particularly in connection with enduring stressors (Billings, Folkman, Acree, & Moskowitz, 2000; de Ridder, Geenen, Kuijer, & van Middendorp, 2008; Keefe et al., 1997; Kneebone & Martin, 2003; Sharkansky et al., 2000; Taylor & Stanton, 2007; Young, 1992). Links between approach coping and physiological processes such as enhanced immune function (Stowell, Kiecolt-Glaser, & Glaser, 2001) and a better-regulated blood circulation during stress (Aschbacher et al., 2005) have also been observed, which would provide additional advantages to the physically challenged HSCT patients (Copelan, 2006).

Nonetheless, the benefits of approach coping in alleviating distress per se have been less robust compared to the pitfalls of avoidant coping (de Ridder et al., 2008; Kneebone & Martin, 2003; Taylor & Stanton, 2007). This could partly reflect contextual constraints on approach coping such poor resources limiting its utility (Taylor & Stanton, 2007). It is also possible that approach coping safeguards against stress via improving positive affect rather than decreasing negative affect (Folkman & Moskowitz, 2000, 2004; Taylor & Stanton, 2007). Consequently, the benefits of approach coping in affective regulation should not be underestimated while taking account of what method of approach coping is feasible for patients remains paramount, particularly in the constraining context of HSCT (isolation, etc.; Copelan, 2006).

3.1.3.2.3 Limitations of coping conceptualisations

Notwithstanding the support for and broad use of problem and emotion-focused and approach versus avoidance coping, the extensive coping literature has featured many different coping mechanisms and conceptualisations (Coyne & Racioppo, 2000; de Ridder, 1997; Folkman & Moskowitz, 2004; Skinner, Edge, Altman, & Sherwood, 2003). This marked lack of consensus has posed a major limitation in the advancement of the coping research and its applications (Coyne & Racioppo, 2000; Folkman & Moskowitz, 2004). Furthermore, different situations can involve different needs, goals, and options for coping therefore coping conceptualisations and styles do not appear to be as fixed as researchers often assume (Coyne & Racioppo, 2000; de Ridder, 1997; Folkman & Moskowitz, 2004). As the self-regulatory model does not endorse any particular conceptualisation (Leventhal et al., 1997), these observations call for caution in the adoption of any coping model in the present project. Furthermore, recognising the importance of exploring in a bottom-up manner what coping styles are helpful in specific clinical populations such as HSCT remains paramount.

3.1.3.2.4 Coping interventions

In spite of extensive theoretical coping research, the application of coping theory into clinical psychology has been limited (Coyne & Racioppo, 2000; de Ridder & Schreurs, 2001; Somerfield & McCrae, 2000). A possible reason may be that coping interventions can be demanding, thereby limiting uptake (Coyne & Racioppo, 2000). Nevertheless, interventions incorporating coping skills training, often within a Cognitive Behaviour Therapy (CBT) framework, have been helpful in a variety of domains including distress tolerance, problem-solving, pain reduction, symptom tolerance, procedural adherence, mortality, and overall health status in a variety of populations (Antoni et al., 2001; Coyne & Racioppo, 2000; Tatrow & Montgomery, 2006; Watson et al., 2013).

Coping-specific interventions have also shown benefits. Coping Effectiveness Training (Folkman et al., 1991), which focuses on coping appraisals, controllability, and encouraging identification of specific coping

strategies, has been effective in ameliorating anxiety and depression (the latter inconsistently) in HIV-positive men (Carrico et al., 2006; Chesney, Chambers, Taylor, Johnson, & Folkman, 2003; Cruess et al., 2002). Mechanisms are thought to involve enhancing coping self-efficacy and approach coping (Folkman et al., 1991).

Coping skills training has also been helpful in a variety of clinical populations. This has included enhanced skills, self-efficacy, and pain control in arthritis (Rhee et al., 2000), enhanced pain tolerance and reduced complications in a sample with sickle cell disease (Gil et al., 2000), and improved social, emotional, and physical functioning in cancer patients (Allison et al., 2004; Beatty, Koczwara, & Wade, 2011; K. M. Carpenter, Stoner, Schmitz, McGregor, & Doorenbos, 2012; David et al., 2013; Gaston-Johansson et al., 2013; S. D. Lambert et al., 2012; Rose, Radziewicz, Bowmans, & O'Toole, 2008). Coping skills training in this literature includes problem-solving, activity scheduling, goal prioritising, identification of specific coping skills, relaxation training, improving communication with staff, and so forth. The purpose is to promote controllability, coping appraisals, and appropriate use of approach and avoidance coping strategies within the context of each illness (Allison et al., 2004; Beatty et al., 2011; K. M. Carpenter et al., 2012; David et al., 2013; Gaston-Johansson et al., 2013; S. D. Lambert et al., 2012; Rose et al., 2008). However, some of the studies combined coping skills training with psychoeducation (e.g. Beatty et al., 2011; Carpenter et al., 2012; Gaston-Johansson et al., 2013), which limits conclusions regarding what contributes to outcome and the benefits of the coping-based component.

An important development in available coping-based interventions involves reduced intensity over time. Many of the recent interventions cited above are delivered via workbooks, the internet, telephone, and so forth. They are, therefore, less demanding than earlier coping interventions involving face-to-face delivery over a series of sessions (Coyne & Racioppo, 2000). Such reduced demands may have resulted in increasing uptake of coping interventions over the years, as suggested by the chronology the literature, and support their suitability for the highly burdened HSCT patients (Copelan, 2006).

In sum, the above evidence indicates that addressing coping in intervention may be beneficial in alleviating distress and physical difficulties in HSCT. Approach strategies may be encouraged in areas where patients can exercise a degree of control, such as planning for transfer to hospital and isolation, identifying activities to engage with, access to staff support and information regarding current and long-term concerns, utilising emotional support, and so forth. Avoidant strategies such as distraction may be identified for use in the short-term in domains which patients are not able to control, though discussing the caveats of continuing to use these strategies as the procedure progresses will need to be highlighted. The lack of conceptual clarity in coping theory and the resulting heterogeneity of styles examined in coping intervention research highlight the need for facilitating exploration and self-determination in identifying helpful coping strategies in HSCT patients. Doing so may be paramount in facilitating positive coping appraisals of personal and care control, within the self-regulatory model.

3.1.3.3 Broader caveats in the self-regulatory model

The model is supported by a breadth of evidence but there are several conceptual inconsistencies. The model assumes that illness perceptions, coping, and coping appraisals interact with each other but does not provide a way of dissociating between them (Odgen, 2012; Sharpe & Curran, 2006). For example, perceiving a characteristic of an illness as less threatening could reflect a coping mechanism such as denial. This lack of dissociation becomes even more problematic when considering that an illness may be seen as threatening when an individual is unable to cope with it and vice versa, as theories of anxiety suggest (Clark & Beck, 2010). Such lack of clarity can limit the model's explanatory power.

A further caveat lies in the centrality of information processing, as the self-regulatory model assumes that cognition precedes emotion in the process of adjustment (Leventhal et al., 1997; Leventhal et al., 1984; Ogden, 2012; Sharpe & Curran, 2006). This hypothesis has received extensive scrutiny in the broader literature on cognitive theories including some supportive experiments (Bennett, Lowe, & Honey, 2003; Kuppens, Van Mechelen, Smits, & De Boeck,

2003; Mathews & MacLeod, 2002; Mathews, Ridgeway, Cook, & Yiend, 2007; Roseman & Evdokas, 2004; C. A. Smith & Lazarus, 1993). Furthermore, cognitive shifts may precede therapeutic breakthroughs and improvement in mood and symptoms (Bieling, Beck, & Brown, 2004; Crits-Christoph et al., 2003; Kuyken, 2004; Tang & DeRubeis, 1999).

However, several findings are contrary to the notion that cognition precedes emotion and the specific role of perceptions in underpinning distress as suggested by the self-regulatory model. Research suggests that the role of cognition in underpinning emotion appears to be much broader than information processing alone (Storbeck & Clore, 2007), which highlights limitations to the scope of the self-regulatory model and its application. Furthermore, the diverse cognitive operations – from perception to reasoning – have been found to be strongly influenced by emotional processes (Phelps, 2006), perceptions have been reported to account for only a minority of variance in emotions, different perceptions often relate to the same emotion, and their effects are confounded with situational exposure (Bennett et al., 2003; Kuppens et al., 2003; Mathews & MacLeod, 2002; Mathews et al., 2007; Roseman & Evdokas, 2004; C. A. Smith & Lazarus, 1993). Finally, there are indications that change in distress may reflect shifts in coping with perceptions rather than cognitive change per se (Adler, Strunk, & Fazio, 2015; Dozois et al., 2009; M. J. Lambert, 2013).

Overall, the evidence raises questions regarding the centrality of cognition in the self-regulatory model and the assumed mechanism of altering perceptions to alleviate distress. Alongside the lack of clarity in the distinction between illness perceptions and coping, these considerations highlight a need to develop the model further. Whilst the limitations suggest that benefits of using the model to guide therapy in the present project could be limited, there is, nevertheless, sufficient evidence to support its current scope and potential as a pragmatic rather than definitive basis for a short and targeted intervention. The theoretical component of the present study focused on the applicability of the model as a basis for intervention in HSCT.

3.1.4 Summary

HSCT is an intensive procedure associated with considerable psychological distress particularly during the acute phase. Relevant interventions are few, show limited benefits, and have failed to address distress at its onset immediately prior to the procedure when the need appears to be highest (Baliousis et al., in press; Lee et al., 2005). An intervention was developed to meet this need.

The lack of effective psychological interventions targeting the acute phase of HSCT may reflect barriers to delivering and evaluating interventions (which remain poorly understood) and a failure to use psychological models to guide interventions in the field. Consequently, the self-regulatory model (Leventhal et al., 1997; Leventhal et al., 1984; Ogden, 2012; Sharpe & Curran, 2006) was used as a basis for the present intervention leading to the inclusion of psychoeducational and coping components. These components purported to address negative perceptions of HSCT, foster realistic expectations, and support patients in identifying helpful coping styles leading to positive coping appraisals. In light of the limitations to the psychological intervention literature in HSCT, the present study aimed both to assess the feasibility of delivering and evaluating the new intervention and to evaluate the applicability of the self-regulatory model as a promising basis for intervention in this clinical population.

3.2 AIMS AND OBJECTIVES

The intensity of HSCT, barriers to accessing interventions, and the many physical needs of patients, highlighted the complexity of delivering psychological interventions and evaluating them in this population. The Medical Research Council's guidance on developing complex interventions emphasises the need to assess feasibility issues and theoretical underpinnings prior to a full trial (Craig et al., 2008). Consequently, the present study had three aims: (a) to evaluate the feasibility of delivering a psychological intervention for distress during acute HSCT; (b) to evaluate the feasibility of conducting a trial to assess the efficacy of the intervention; and (c) to evaluate the applicability of the self-regulatory model (Leventhal et al., 1997; Leventhal et al., 1984; Ogden, 2012; Sharpe & Curran, 2006) in the context of acute HSCT as a basis of the intervention.

A decision was made to proceed with a Phase II trial focusing on preliminary efficacy as well as procedural feasibility (Arain, Campbell, Cooper, & Lancaster, 2010; Stolberg, Norman, & Trop, 2004; D. Wang & Bakhai, 2006), as safety and preliminary acceptability had been established during an earlier pilot of the intervention (see Section 6.2 for details). The objectives of this Phase II study were to assess:

1. The feasibility of delivering the intervention and the trial's procedures for patients and staff. This included examining accrual of referrals, the impact of participant eligibility criteria on accrual, uptake (willingness to participate), willingness to be randomised to and attend the intervention (patients), willingness to recruit participants and facilitate the group (staff), attrition, response rates, and adherence to the protocol.

2. The reliability and validity of assessments since most measures including primary outcomes had not been used in HSCT previously.

3. Sample size calculations by taking account of intraclass correlations (ICCs) for clustered data, outcome variability (standard errors), and effect sizes (i.e., β coefficients and variance).

4. The trajectory of distress over time in order to determine the optimal endpoint for analysis (i.e., transplant day, two weeks, or four weeks).

5. Initial evidence of efficacy with the expectation that individuals allocated to the intervention will report less distress during acute HSCT compared to those allocated to the control group.

The hypotheses regarding the second aim of the study in relation to the applicability of the self-regulatory model (Leventhal et al., 1997; Leventhal et al., 1984; Ogden, 2012; Sharpe & Curran, 2006) were outlined in the journal paper. An additional hypothesis was that lower distress will reflect better adaptation, as suggested by the model.

3.2.1 Epistemological position

The present project approached the research from a logical positivist viewpoint (as discussed in Barker, Pistrang, & Elliott, 2002). Therefore, the investigation was deductive and was pursued on the basis of experimentation rather than personal experience. The project assumed a degree of observable reality and objective measurement, sufficient regularity to enable the study of aggregate effects, and ability to control for contextual influences and threats to validity (e.g. via randomisation). Some uncertainty in the observations was considered inevitable but it was deemed possible to assess this phenomenon to some extent via reliability and validity analyses. Remaining sensitive to information disconfirming expectations was important to prevent the fallacies of naïve realism (Barker et al., 2002).

3.3 EXTENDED METHOD

3.3.1 Participants

Participants were recruited from consecutive referrals in order to minimise the threat of selection bias to internal and external validity (McBurney & White, 2007). For example, a more opportunistic method of recruitment may have resulted in overrepresentation of individuals with more active coping or underrepresentation of patients with avoidant coping, more stress, and so forth (McBurney & White, 2007). Aiming to recruit from consecutive referrals was also important in estimating accrual of eligible patients, uptake to the study, and capture barriers to participation. Both autologous and allogeneic patients were included in light of comparable distress between the two groups despite differences in physical symptomatology (Fife et al., 2000; Lee et al., 2005; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Prieto et al., 1996). However, the earlier pilot of the intervention had taken place with allogeneic patients at one of the sites (see below for details) and had become treatment as usual for that group. Consequently, only autologous patients were able to participate at that site.

The initial target sample size was 60 patients with an estimated drop-out rate of 25% as observed in HSCT and other cancer populations (Billingham, Whitehead, & Julious, 2013; Braamse et al., 2010; DuHamel et al., 2010; Herzog, 2008; S. D. Lambert et al., 2012). To obtain initial evidence of efficacy in this Phase II study (D. Wang & Bakhai, 2006) this target sample size was estimated as sufficient to detect a small to medium intervention effect size. G*Power (Buchner, Erdfelder, Faul, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007) was used, with effect size $f = 0.175$, $\alpha = 0.05$, power = 0.80, and correlation among repeated measures of 0.5. Such a sample size was also considered sufficient and not excessive to gather information on feasibility in line with other feasibility studies in HSCT (Bauer-Wu et al., 2008; Horton-Deutsch et al., 2007; Trask, Jones, & Paterson, 2003).

The target sample size of 60 was also sufficient for meeting the second, theoretical aim of the study. As each patient was expected to contribute up to four time points (as discussed in the journal paper), data for a total of 180 time

points were expected after attrition. This exceeded the 43 participants required to detect a medium effect size.

The cut off of 43 was estimated via the equation $m \times n = N \times [1 + (n - 1)\rho]$; m = number of required participants in the multilevel model; n = 4, number of time points for each participant; N = number of participants according to the nonmultilevel sample size calculation; ρ = intercorrelation coefficient (Twisk, 2006). Essentially, this method adjusts the sample size N based on the assumption that successive data from the same patient are likely to provide diminishing information due to their intercorrelation (Browne, Golalizadeh, & Parker, 2009; Twisk, 2006). An intercorrelation coefficient of 0.7 was assumed among the four measurements of each participant as expected for highly overlapping or equivalent measures (Field, 2013). A sample size N = 55 was estimated as required to detect a medium effect size with independent data in standard, nonmultilevel regression (f^2 = 0.15, α = 0.05, power = 0.80) using G*Power (Buchner et al., 2009; Faul et al., 2007). This method of estimating multilevel sample sizes is considered the most conservative relative to other options (Twisk, 2006).

3.3.2 The intervention

The intervention was a preparation group prior to hospitalisation for HSCT aiming at addressing distress during the acute phase at its point of onset prior to transplantation. Based on the self-regulatory model, the intervention purported to alleviate distress by: (a) reducing negative and threatening 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 that aspects of HSCT are controllable. The information discussed in the group was standardised as it followed the content of The Seven Steps book (Kenyon, 2012). In order to reduce burden, maximise uptake, and enable access to social resources for coping, the intervention was delivered in a single, 90-minute, group session. The sessions took place monthly and were facilitated by the Transplant Coordinator, Clinical Psychologist, and Physiotherapist.

The rationale for the group format was twofold. First, this format has been found to validate the experience of cancer patients (Moyer et al., 2009). Secondly, the group format was aimed at facilitating access to social resources for patients about to undergo transplantation, as the effectiveness of coping is thought to depend on availability of such resources (Taylor & Stanton, 2007).

As the length of the intervention was relatively short, it was essential to include the highest-impact ingredients identified in the relevant literature to maximise benefits, leading to focus on its four core components. Details of these components, their content, aims, delivery methods, and psychological targets are shown in Table 5. The intervention was provided in addition to treatment as usual (TAU) which comprised informal discussions with and support from members of the multi-professional team alongside written information packs.

The intervention was trialled for six months prior to the study with allogeneic patients participating opportunistically at one of the sites. The decision to pilot it to allogeneic patients alone was made due to the increased likelihood of physical complications in this group as a way of fast-tracking the process of formalising delivery and content. As the procedure is similar though less severe in nature for autologous patients, the content of the intervention applied to both patient groups. Patients and staff found the group acceptable and feasible during the trial. Its development over this period focused on structuring the four components based on the theory underpinning the intervention via consensus, peer supervision among facilitators, emerging discussions, and feedback from patients. No adverse effects were identified.

Treatment fidelity between the two sites was also examined. This aimed to ascertain whether the key elements listed in the intervention schedule were included during delivery and whether delivery was broadly comparable across sites. The first group session from one site was recorded and was discussed in peer supervision between the facilitators across sites. Discrepancies from the intervention schedule were identified and delivery was amended accordingly. It was not possible to record the intervention in the second site on ethical grounds, as allogeneic patients participated in the group at that site but had not consented to the use of their information for the study.

Table 5

Schedule of the psychological intervention evaluated 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. *Information on practicalities of the process*: Pretransplant investigations, donor work, transplant day onwards, medication, recovery *Anticipating difficulties & dealing with difficult days/times*: Isolation & implications, what to bring to hospital, what to expect (side effects and complications), going home *Importance of liaising with healthcare staff*: Assistance with symptoms, emotional difficulties, concerns regarding going home, etc.	Challenge myths surrounding HSCT; promote clarity	Reduce negative and threat appraisals in connection with HSCT Facilitate concreteness of the HSCT experience Introduce staff as a coping resource
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) *Identifying previous coping strategies* *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)	Prepare patients for psychological challenge Provide patients with ways of coping	Improve patient's effective use of approach & avoidance coping. Enhance coping appraisals (controllability)
4. Physio-therapy	*Importance of daily routine* (e.g., meals, personal hygiene) *Activity scheduling* *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)	Improve patients' understanding of the role of activity/ exercise & their willingness to use it.	Improve effective use of approach & avoidant coping. Enhance coping appraisals (controllability)
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

3.3.3 Treatment-as-usual

Unlike the psychological intervention, treatment as usual did not aim to address negative appraisals 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 multi-professional team (medical, nursing staff, etc.). Patients were also provided with written information packs about the procedure and the hospital stay, including The Seven Steps book (Kenyon, 2012) that was discussed in the intervention. Specialist nursing staff provided informational and emotional support as required. Patients who experienced considerable distress were referred for psychological input; information on the reasons for referral can be found in Appendix A.

3.3.4 Materials

The study measured psychological distress, HSCT perceptions, coping, and adaptation. The latter was measured with the Brief Resilience Scale (BRS; B. W. Smith et al., 2008). Measures were selected on the basis of their reliability and validity in relation to the relevant concepts. Samples of the materials can be found in Appendices B-F.

3.3.4.1 Proforma

Demographic, illness, and treatment characteristics can predict coping and illness perceptions in general (Folkman & Moskowitz, 2004; Ogden, 2012; Taylor & Stanton, 2007) and adjustment and distress in HSCT (Andersson, Ahlberg, Stockelberg, Brune, & Persson, 2009; Andersson, Ahlberg, Stockelberg, & Persson, 2011; Barata et al., 2014; Braamse et al., 2014; Hefner et al., 2014; Mosher et al., 2009; Prieto et al., 1996; Tecchio et al., 2013). Consequently, demographic and clinical information such as gender, age, disease, transplant type, and so forth, were recorded for each participant. These were also important in evaluating the external validity of the findings (McBurney & White, 2007). The proforma with coding details can be found in Appendix B.

3.3.4.2 Short Depression Anxiety Stress Scales

The Short Depression Anxiety Stress Scales (DASS-21; Appendix C) was selected over alternatives due to its ability to provide a total distress score (thus conserving statistical power in the assessment of efficacy in the present project) and its balanced content. The stress subscale is conceptualised as sustained tension and worry in response to ongoing life challenges rather than a fearful response to threat characterising the anxiety subscale (Lovibond, 1998).

The three-factor structure of the DASS-21 appears suitable for a comprehensive assessment of distress in HSCT relative to other scales often used in cancer populations (Antony, Bieling, Cox, Enns, & Swinson, 1998; Brown, Chorpita, Korotitsch, & Barlow, 1997; Henry & Crawford, 2005; Thekkumpurath, Venkateswaran, Kumar, & Bennett, 2008; Vodermaier, Linden, & Siu, 2009; Yeh, Chung, Hsu, & Hsu, 2014). For example, the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and so forth, appeared too focused for the present project as distress in the self-regulatory model, coping theories, and HSCT, includes depression, anxiety, stress, and negative affect more generally (Fife et al., 2000; Lee et al., 2005; Mitchell, Meader, & Symonds, 2010; Ogden, 2012; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Prieto et al., 2002; Thekkumpurath et al., 2008; Vodermaier et al., 2009; Yeh et al., 2014). In addition, the DASS-21 retains a focus on the psychological experience of distress compared to other general measures of wellbeing used in cancer (Thekkumpurath et al., 2008; Vodermaier et al., 2009; Yeh et al., 2014). For example, the General Health Questionnaire (Goldberg et al., 1997) has some items relating to emotional wellbeing but also examines social functioning and somatic symptoms.

The validity of the DASS-21 and its three-factor structure has received extensive support. Evidence of criterion validity includes significant and meaningful correlations with established clinical measures of psychological distress and overall mental health such as the Beck Depression Inventory, Beck Anxiety Inventory, State-Trait Anxiety Inventory (STAI), Health of the Nation Outcome Scales, and so forth (Antony et al., 1998; Henry & Crawford, 2005; Ng

et al., 2007; Ronk, Korman, Hooke, & Page, 2013). Results from the long version of the DASS extend this evidence to additional measures of distress, for example Hospital Anxiety and Depression Scale (HADS) and the Positive and Negative Affect Scales (Brown et al., 1997; Crawford & Henry, 2003; P. F. Lovibond & S. H. Lovibond, 1995; Page, Hooke, & Morrison, 2007).

Apart from correlations with other instruments, the DASS-21 has good discriminant validity as evidenced by its ability to differentiate between different clinical populations, although this has been more consistent for the stress subscale scale relative to depression and anxiety (Anthony et al., 1998), thereby highlighting a potential threat to validity. In addition, evidence suggests that the depression scale may be susceptible to ceiling effects in populations with depression (Page et al., 2007) but that ought not to be problematic in the present project where lower levels are expected (Lee et al., 2005; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Prieto et al., 2002; Prieto et al., 2006). The factor structure of the DASS-21 has been stable across cultures although subscale inter-correlations may differ (Norton, 2007). Crucially, the moderate sensitivity to clinical change and acceptable to good temporal stability in diverse clinical populations (Brown et al., 1997; Ng et al., 2007; Page et al., 2007; Ronk et al., 2013) were important in ensuring meaningful repeated measurements in the present project.

Notwithstanding extensive support for its validity, there were caveats in the use of the DASS-21 that highlighted the necessity of a feasibility study. The instrument is relatively new compared to the alternatives discussed above and its psychometric properties have not been examined as extensively in cancer populations. Furthermore, some of the items in the DASS-21, for example, “I was aware of dryness of my mouth” and “I experienced trembling”, may reflect somatic side effects of HSCT. This might affect both the construct validity and the reliability of the scale. Consequently, it was important to examine the internal consistency of the DASS-21 in HSCT and collect information from participants regarding whether the somatic items reflected emotional distress versus side effects of HSCT.

3.3.4.3 Brief Resilience Scale

The Brief Resilience Scale (B. W. Smith et al., 2008) assessed the ability to adapt to and recover from a stressor (mainly health-related) such as HSCT. Therefore, it was considered theoretically relevant to the conceptualisation of adaptation within the self-regulatory model (Leventhal et al., 1997; Leventhal et al., 1984). The scale consists of six items rated on a 5-point Likert scale and provides a single score ranging from 6 to 30 (higher scores reflect more resilience; B. W. Smith et al., 2008). It assesses trait adaptation but was amended for measurement over one week as required by the present study (Appendix D).

The BRS is a new instrument but initial research has shown it has good psychometric properties. It has good construct validity both in clinical and nonclinical samples as reflected in meaningful correlations with personal characteristics (e.g., optimism), social relationships, coping, health-related outcomes such as fatigue and other physical symptoms, anxiety, depression, negative affect, and so forth (B. W. Smith et al., 2008; B. W. Smith, Epstein, Ortiz, Christopher, & Tooley, 2013; B. W. Smith, Tooley, Christopher, & Kay, 2010). It also has good internal consistency (Cronbach's $\alpha = 0.78\text{-}0.91$), and acceptable test-retest reliability up to three months ($r = 0.62\text{-}0.69$; B. W. Smith et al., 2008; B. W. Smith et al., 2010). The latter may reflect sensitivity to variability in resilience (a benefit for the present project) or limitations to reliability that could affect statistical validity and power adversely. The psychometric properties of the scale over one week and validity with HSCT patients were examined as part of the study.

The BRS is the briefest scale of its kind and its psychometric properties place it among the highest rated among alternatives (Windle, Bennett, & Noyes, 2011). Compared to alternatives with similar psychometric properties, such as the Connor-Davidson Resilience Scale (Connor & Davidson, 2003) and the Resilience Scale for Adults (Friborg, Hjemdal, Rosenvinge, & Martinussen, 2003), the BRS appears more relevant to the process of adaptation rather than describing protective factors underlying adjustment (e.g., social competence, social support, acceptance of change, self-efficacy, etc.). Consequently, the BRS also overlaps less with coping styles.

In addition, the items of the BRS appear well suited for rewording to measure adaptation over shorter periods of time relative to other measures. For example “I prefer to plan my actions” from the Resilience Scale for Adults (Friborg et al., 2003) or “Can deal with whatever comes” from the Connor-Davidson Resilience Scale (Connor & Davidson, 2003) appear less able to retain the meaning of adaptability when reworded for measurement over the short-term compared to, for example, “I tend to bounce back quickly after hard times” of the BRS.

3.3.4.4 Brief Coping with Problems Experienced questionnaire

The Brief Coping with Problems Experienced questionnaire (Brief COPE; Appendix E) is the short version of the COPE (Carver, Scheier, & Weintraub, 1989). The Brief COPE can be used for different time periods flexibly as required by the present project whilst showing relatively better psychometric properties in comparison to alternatives (Carver et al., 1989; de Ridder, 1997). Of the 14 coping styles, Substance Use and Religion were not included in the present project. This was due to the environmental restrictions during HSCT not permitting substance use, the relatively small number of patients expected to use religious coping due to demographic changes in this domain (Office of National Statistics, 2011), and ethical barriers with addressing religious coping as part of the intervention. It was also important to minimise the burden of the questionnaire as it was the lengthiest in the study.

The Brief COPE was considered suitable for the present study as it is more theoretically flexible compared to alternatives (de Ridder, 1997). It was designed to assess distinct coping styles rather than broader conceptualisations (as in other coping measures; Carver et al., 1989; de Ridder, 1997) that may not apply to HSCT. Some studies have grouped the coping styles of the measure into higher order factors (e.g., problem-, emotion-focused, etc.) in populations such as dementia and inflammatory bowel disease (Coolidge, Segal, Hook, & Stewart, 2000; Cooper, Katona, Orrell, & Livingston, 2006; Knowles, Cook, & Tribbick, 2013). However, such practice is incompatible with the purpose of the scale as it was developed to enable the study between conceptually distinct coping styles and overcome the limitations of problem- and

emotion-focused coping (Carver et al., 1989). In addition, using a priori coping style groups in HSCT does not appear appropriate in light of the general lack of consensus regarding overarching coping styles in the literature (Coyne & Racioppo, 2000; de Ridder, 1997; Skinner et al., 2003) and lack of research regarding the function of coping styles and validity of overarching categories in the context of acute HSCT.

The validity of the Brief COPE has been examined in clinical populations involving both physical and mental health difficulties with meaningful results such as predicting depression, anxiety, burden, positive and negative affect, and differentiating between clinical and nonclinical presentations, (Bautista & Erwin, 2013; Bautista, Rundle-Gonzalez, Awad, & Erwin, 2013; Cooper, Katona, & Livingston, 2008; Cooper et al., 2006; Cooper, Katona, Orrell, & Livingston, 2008; Fletcher, Parker, & Manicavasagar, 2013; Hooper, Baker, & McNutt, 2013; Knowles et al., 2013; Meyer, 2001). It has promising predictive validity in HSCT consistent with the wider literature in indicating that avoidant coping (e.g., denial) predicts worse physical outcomes in the recovery period after HSCT, though the avoidant style grouping does not appear internally consistent (Schoulte, Lohnberg, Tallman, & Altmaier, 2011). However, as the coping styles in the Brief COPE are not specific to HSCT and the challenges facing this patient population, it may be limited in capturing the process of coping in this context.

The evidence on the reliability of the questionnaire appears mixed. Its factor structure appears acceptable (Carver, 1997), relatively low temporal stability has been suggested to reflect meaningful fluctuations in the use of coping styles (de Ridder, 1997), and relatively low coefficients of internal consistency are expected in small scales (Field, 2013) such as the Brief COPE where each coping style is measured by only two items (Carver, 1997). Although Cronbach's α coefficients of the Brief COPE are not ideal for measuring psychological constructs, the COPE appears one of the most reliable measures in the field (de Ridder, 1997). However, low reliability is likely to limit statistical validity and power (Gravetter & Wallnau, 2009; McBurney & White, 2007). It was, therefore, important to assess the reliability of the Brief COPE prior to a full trial.

3.3.4.5 Brief Illness Perceptions Questionnaire

The Brief Illness Perceptions Questionnaire (Brief IPQ) is the short and simplified version of the widely applied, 80-item IPQ-Revised (Broadbent et al., 2006; Moss-Morris et al., 2002; Ogden, 2012; Weinman, Petrie, Moss-Morris, & Horne, 1996). Regarding support for the concurrent, predictive, and discriminant validity of the measure, the evidence includes meaningful concurrent and longitudinal correlations with health behaviours, physical, and mental health functioning, change in illness perceptions following informational input, and ability to distinguish between different illnesses in a variety of populations (Bean, Cundy, & Petrie, 2007; Broadbent, Ellis, Thomas, Gamble, & Petrie, 2009; Broadbent et al., 2006; Knowles et al., 2013; Løchting, Garratt, Storheim, Werner, & Grotle, 2013; Sluiter & Frings-Dresen, 2008).

However, limitations to validity are also present. The findings have been less robust for the individual items of the Brief IPQ (Bean et al., 2007; Broadbent et al., 2009; Broadbent et al., 2006; Knowles et al., 2013; Løchting et al., 2013; Sluiter & Frings-Dresen, 2008), suggesting some caution. The literature also indicates comparable results to the original IPQ-Revised but further corroboration is required since the Brief IPQ was developed primarily by summarising the items from the IPQ-Revised but the correlations between the two instruments (coefficients between 0.32 and 0.63) were not as high as expected if they measured the same constructs (Broadbent et al., 2006; Field, 2013). Furthermore, the validity of the version of the Brief IPQ in the present project may be compromised as it assesses perceptions of a procedure rather than an illness.

The Brief IPQ has variable reliability. Cronbach's α coefficients suggest mixed albeit acceptable internal consistency. The modest test-retest reliability coefficients indicate fluctuating stability (potentially affected by illness progression). These could limit statistical validity and power in the present study (Gravetter & Wallnau, 2009; McBurney & White, 2007) and emphasised a need to examine the internal consistency of the present adaptation of the Brief IPQ for HSCT.

3.3.5 Design

Overall, a prospective 2x4 mixed between-within-subjects randomised controlled trial (RCT) design was adopted (D. Wang & Bakhai, 2006). The within-subjects factor was time, with four levels (four time points: prior to HSCT, on the day of the transplant, two, and four weeks after the transplant). The two levels of the between-subjects factor were intervention plus TAU versus TAU alone (control). Primary outcome was distress (DASS-21) while HSCT perceptions (Brief IPQ), coping (Brief COPE), and adaptation (BRS) were secondary outcomes.

An RCT design appears important in improving the quality of the intervention evidence in HSCT (Baliousis et al., in press). The presence of a control group can mitigate individual differences and covariates that have not or cannot be assessed reliably, which can compromise the analysis and has been a major limitation in coping research (Coyne & Racioppo, 2000; McBurney & White, 2007; Tabachnick & Fidell, 2013; D. Wang & Bakhai, 2006). Furthermore, a control group involving therapeutic contact without the active ingredients of the intervention can mitigate the maturation and common factor effects that limit current HSCT intervention literature (Baliousis et al., in press; Bauer-Wu et al., 2008; Horton-Deutsch et al., 2007; Lounsberry et al., 2010).

However, the randomised trial design can be demanding, many trials fail to be completed timely due to infeasibility, and cancer populations often do not accept randomisation (Bower, Wilson, & Mathers, 2007; Howard, de Salis, Tomlin, Thornicroft, & Donovan, 2009; Moyer et al., 2009; Sully, Julious, & Nicholl, 2013; Toerien et al., 2009). The many potential barriers immediately prior to and during acute HSCT may increase the challenges of implementing an RCT. Therefore, examining the feasibility of such a design was important prior to a full study.

The purpose of including four time points in the within-subjects factor was threefold. The evidence on distress during HSCT (Dakanalis et al., 2013; Fife et al., 2000; F. Keogh et al., 1998; Lee et al., 2005; McQuellon et al., 1998; Molassiotis et al., 1996; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Prieto et al., 2002; Tecchio et al., 2013) suggests considerable variability and a need for frequent measurement. Furthermore, frequent measurement in

the project facilitated an accurate estimation of attrition at different time points and, therefore, was useful for estimating a target sample size for the full trial. Data for multiple time points were also helpful in increasing statistical power for the theoretical component in light of the small sample (Field, 2013; Tabachnick & Fidell, 2013).

Block randomisation with block size of four and one-to-one sequential allocation ratio with separate randomisation codes for each site was used to ensure the resulting groups were equal in size (Altman & Bland, 1999; Schulz & Grimes, 2002b; D. Wang & Bakhai, 2006). Randomisation codes were computer-generated prior to recruitment with Random Allocation software (Saghaei, 2004a). The software has been found to be reliable in producing random sequences using a pseudorandom method based on the computer timer as numerical seed (Saghaei, 2004b). The codes were stored in digital files that were password protected by an NHS medical professional not involved in the study otherwise. These files were held by the outcome assessor who did not possess the password. Upon receipt of consent and allocation of participant number, each code was made available to the interventionists (who possessed the password) in order to allocate participants and invite them to the intervention as appropriate. The professional who generated the codes kept a log of participant numbers and codes as the latter ones were released to interventionists in order to ensure that the allocation was adhered to. The outcome assessor and participants were intended to be blind to the allocation.

3.3.6 Procedure

Participants were invited using the sheet in Appendix G. The timing of the initial approach was before the transplant at the discretion of the multi-professional team. Interested patients were then able to review the study material in the participant information sheet shown in Appendix H at their convenience. The consent form is presented in Appendix I. Baseline measures were completed as soon as practically possible after enrolment but prior to the intervention. Participants were then randomised, were invited to the intervention via letter, and confirmed attendance or otherwise via telephone. Subsequent data collection took place over the telephone by the outcome

assessor who made up to three attempts to collect data per day up to two weeks following each time point. During the telephone calls to fill in the questionnaires, participants were reminded frequently that all questions referred to their experience over the past week. Participants were asked for feedback on the procedure (calls, timing, burden, etc.) and materials (comprehensibility, ease of completion, etc.) at the end of the final telephone call. If participants made relevant comments throughout data collection, these comments were also noted. Breaches of assessor blinding were noted to assist with the evaluation of feasibility and internal validity.

3.3.7 Data analysis

3.3.7.1 Computations

Total and subscale scores were computed by adding up constituent items, reversed as appropriate. This included the DASS-21 total and subscale score (Henry & Crawford, 2005), total score of the BRS (B. W. Smith et al., 2008), total score of the Brief IPQ (Knowles et al., 2013), and coping styles of the Brief COPE (Carver, 1997).

3.3.7.2 Initial and feasibility analyses

Assumption violations were examined as discussed by Field (2013), Pallant (2005), and Tabachnick and Fidell (2013):

1. ***Accuracy of input and outliers*:** Out of range values and the plausibility of means and standard deviations were examined. Univariate and multivariate outliers were set at $\alpha = 0.001$ (Field, 2013). Multivariate outliers were detected via Mahalanobis distance in χ^2 distribution (Pallant, 2005). Care was exercised not to exclude possible outliers due to nonnormal distributions so as not to render samples unrepresentative.
2. ***Normality*:** Normality was assessed visually via histogram, normality plots, and distributions of residuals (for multivariate analysis of variance, MANOVA), the Kolmogorov-Smirnov test, and skewness and kurtosis significant at $\alpha = 0.001$ (Field, 2013; Tabachnick & Fidell, 2013). For

MLM, the normality of residuals, intercepts, and slopes was examined via visual inspection of their histograms (Rasbash, Steele, Browne, & Goldstein, 2015; Twisk, 2006). Transformations were attempted for nonnormal data (Field, 2013) but were not possible due to different distributions across time points.

3. ***Linearity*****:** Linearity was evaluated via examination of multilevel bivariate scatter plots of continuous variables whose relationships were examined in main analyses. These included outcome variables (BRS score, DASS-21 total and subscales) plotted against predictors (Brief IPQ total and subscales, Brief COPE styles, days from transplantation, and time points).
4. ***Homogeneity of variance and homogeneity of covariance matrices*****:** These assumptions were examined via Levene's test and Box's test ($\alpha = 0.001$; Field, 2013).
5. ***Multicollinearity and singularity*****:** Two indicators were examined – bivariate correlations with $r>0.70$ and tolerance approaching zero (in the range of 0.1) or condition index exceeding 30 coupled with variance proportions greater than 0.5 for at least two different variables (Belsey, Kuh, & Welsch, 1980; Tabachnick & Fidell, 2013).
6. ***Missing data in MLM*****:** Missing data can be tolerated well in MLM particularly when either missing completely at random (MCAR, Little's test is not significant) or missing at random (MAR; Goldstein, 2003; Rasbash, Steele, Browne, & Goldstein, 2009; Tabachnick & Fidell, 2013). MAR can be assumed when Little's test is significant but data are missing in a predictable pattern which is unrelated to the outcome variables (Snijders & Bosker, 2012; Tabachnick & Fidell, 2013). Missing value analysis (Tabachnick & Fidell, 2013) was conducted for outcomes measured at each time point to determine Little's test and examine whether missing data were related to demographic and clinical characteristics, baseline measures, or outcomes measured at previous time points.

Descriptive statistics in relation to feasibility variables focused on accrual and uptake to the study and intervention, reasons for declining participation,

attendance, reasons for nonattendance, response rates (attrition), and reasons for attrition.

Group differences between participants randomised to intervention versus control on demographics, clinical characteristics, and baseline measures were examined in order to assess the success of randomisation (Lewis & Warlow, 2004). Differences between participants who attended the intervention versus those who did not (overall and from those participants randomised to the intervention only) were also examined to assess sampling bias. Chi-square tests (with continuity correction for 2x2 tables and Fisher's exact test when expected frequencies did not exceed five; Field, 2013), robust independent *t*-tests (with Bonferroni corrections, $\alpha = 0.01$, and bias-corrected bootstrapping with 1000 samples), and robust MANOVA (for theoretically related variables such as distress, coping, and HSCT perceptions subscales) were used. Use of robust statistics and bootstrapping aimed at mitigating the influence of potential outliers and assumption violations (Field, 2013; Wilcox, 2012; Wilcox & Keselman, 2003).

3.3.7.3 Efficacy and psychological processes

Randomisation (intervention versus control) and its interaction with time were entered as predictors to the baseline model (which contained only time). Sensitivity analyses also examined the effect of actual group attendance versus nonattendance (instead of randomisation). 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 estimations took account of the observed nonresponse rates. The standard sample size calculation was adjusted for the multilevel data structure using the method described in Section 6.1. However, the results of different methods for estimating sample size in MLM can vary considerably depending on the method (Twisk, 2006); therefore, caution is required regarding their interpretation.

In light of limited attendance to the intervention (see Section 7.1.1), multilevel single case analysis (Huber, Klein, Moeller, & Willmes, 2015) was also used to triangulate the results of the main analysis and allow for the

detection of small effects that may not be possible due to lack of power. The intervention aimed to secure lower increases in distress during acute HSCT (time points 2-4) compared to baseline than might be expected otherwise; therefore, single case analysis examined the change in distress of intervention attendees relative to nonattendees. To conduct the multilevel single case analysis, each case was dummy-coded in the multilevel model. The change of each case compared to nonattendees (β coefficient) was then examined.

The method of using multilevel models for repeated measures has been shown to be mathematically and statistically equivalent to the *t*-test often used in single-measure methods (Crawford & Garthwaite, 2002; Crawford & Howell, 1998; Huber et al., 2015). A two-tailed test was selected since the study was the first evaluation of the intervention which was, therefore, not assumed to be effective (this is in line with Phase II trial practice; Craig et al., 2008). The within-subjects nature of the comparison was a weak design for establishing causality and control but frequent lower increases in distress in attendees were considered initial evidence of effectiveness prior to further evaluation for the purpose of the present study.

3.3.7.4 MLM configuration

The multilevel data structure was defined with time points as Level 1 (*i*) units and participants as Level 2 (*j*) units. With the exception of days from the transplant (zero for transplant day), all continuous Level 1 predictors (those measures at each time point) were centred around the grand mean in order to aid interpretation and improve the stability of the model by mitigating the potential multicollinearity (Twisk, 2006). Predictors were entered first as fixed and then, if the model improved significantly, random at Level 2. Results from random effects models were reported when improvements were significant. The R_1^2 provided an estimation of the variance that was explained by the predictors and random effects added at each stage. The R_1^2 was computed as percentage of $1-((\sigma_2^2+\tau_2^2)/(\sigma_1^2+\tau_1^2))$ where σ^2 and τ^2 represent Level 1 and Level 2 variance respectively between two successive models (Snijders & Bosker, 2012). Negative change in variance is generally not interpretable (Snijders & Bosker, 2012). Bootstrap estimation (nonparametric, bias-

corrected, with five sets of 500 iterations) was used to mitigate bias from nonnormal distributions and the small sample size (Rasbash, Steele, et al., 2015)

3.3.7.5 Software

Robust MANOVA was conducted using the mulrank() function (Wilcox, 2012) on R (Version 3.2.2; R Core Team, 2015). An example of the robust MANOVA code testing for differences between the groups as randomised on the distress subscales is provided in Appendix J. MLM was conducted using MLwiN software (Version 2.34; Rasbash, Browne, Healy, Cameron, & Charlton, 2015), power analysis and sample size estimations were conducted using MLPowSim software (Version 1.0; Browne & Golalizadeh, 2009), and SPSS software (Version 22; IBM Corp, 2013) was used in all other analyses. Unless specified otherwise, α was 0.05.

3.3.8 Ethics

The study was registered with ClinicalTrials.gov (NCT02212236). Approval documents by the NRES Committee East Midlands - Nottingham 1 are included in Appendix K. The Participant Information Sheet and Consent documents adhered to the British Psychological Society (2009, 2011) and Health Research Authority (National Research Ethics Service, 2011) guidance. The decision to participate was voluntary and participants had the right to withdraw without negative consequences. These were made clear in the Participant Information Sheet and were reiterated prior to obtaining consent.

Participants were also informed that their responses would remain strictly confidential, anonymous, and securely stored. Medical records for participant and procedural information were accessed only on site by the researchers. Data were stored in secure facilities at the University of Nottingham adhering to the University's policies (The University of Nottingham, 2013). Password protected and NHS-approved encrypted digital media were used for temporary storage. Personal data (address, telephone number) will be kept for 12 months after the end of the study for participant debriefing regarding the findings (unless participants advise that they do not wish to be contacted). All research

data will be kept securely for seven years and will be disposed of securely afterwards.

No adverse effects were anticipated from participating in the present study or the new intervention (following the initial pilot preceding this study). The participants' Consultant Haematologist was also notified prior to their participation in the event of concern. In addition, withholding the intervention from the control group was not considered ethically controversial, as there was no convincing evidence of the intervention's efficacy at the time of the study and the intervention would not have been made available to prospective participants outside of the study.

As it is recognised that patients undergoing HSCT are under considerable strain, every effort was taken to minimise any additional burden by participating in the study. This was reflected in the brevity of the intervention and the use of short and targeted measures. If needed, participants were able to access support readily by nursing staff and the clinical psychologist on either site who were also involved in the study.

It was not possible to inform participants of the condition they were allocated to during their participation in order to preserve binding (D. Wang & Bakhai, 2006) though it was recognised that in practice blinding of participants taking part in psychological interventions may not be feasible. All participants were debriefed at the end of their participation and were provided with the researcher's contact details should they wish to seek further information at a future time. Participants will receive a brief written summary of the results within 12 months following completion via post or email according to their preference.

3.3.9 Service user involvement

A patient panel at one of the sites was consulted on the content of the intervention, outcomes, and measures and provided feedback on acceptability and feasibility. This led to several adjustments:

1. Use of the same anchor for the 4-point Likert scales of the DASS-21 and Brief COPE.

2. Recognising the need to clarify some of the questions such as Item 19 of the DASS-21 verbally over the telephone as required.
3. Provide a hard copy of the questionnaires as sample including a large print of the scales to facilitate completion over the telephone.
4. Remain mindful of ethical concerns (e.g., stigma, shame) in relation to obtaining consent for disclosure of physiological problems within certain communities.
5. The site psychologist to remain mindful of the need to provide emotional support to patients who had not been randomised to the intervention group should they become aware of their allocation at the end of their participation.

3.4 EXTENDED RESULTS

3.4.1 Initial analyses

3.4.1.1 Feasibility

Bone marrow transplant coordinators were able to approach participants at one site but not the other due to resourcing demands (participants were recruited by the clinical psychologist at the other site). 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 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 (Figure 5). The need to randomise half of the patient to the control group hindered accrual for more frequent interventions. The probability of nonresponse across all time points was 22%.

Randomisation remained concealed as planned. 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. Most participants were unlikely to have remained blind as information about the nature of the intervention was provided unsystematically during recruitment. The outcome assessor remained blind to randomisation in all but one case where a participant commented on having attended the group over the telephone. The outcome assessor became aware that two participants did not attend the group prior to completing data collection, as these participants returned their signed consent after the final group had taken place.

Regarding fidelity of intervention, peer supervision indicated that all core elements of the intervention were included. However, delivery was found to be more directive at one site compared to the other (where the group had been

originally developed). The resulted in relevant changes to delivery such as asking more exploratory questions and eliciting information from the group.

Overall, participants provided favourable feedback on the procedure. The majority (80%) commented on the noninstrusiveness of the procedure and found the questionnaires of sufficient length. The majority (60%) also suggested that flexibility with telephone calls was helpful in allowing them to continue participating. Four participants (9%) reported that some questions did not apply to them and that this made it difficult to follow what was asked. Approximately 10% of participants indicated that rating adaptation (i.e., how well or quickly they were recovering from the transplant process) on the day of the transplant was ambiguous. Two participants (4%) indicated that being asked questions about distress and their experience with the transplant made them reflect on their experience and feelings between time points.

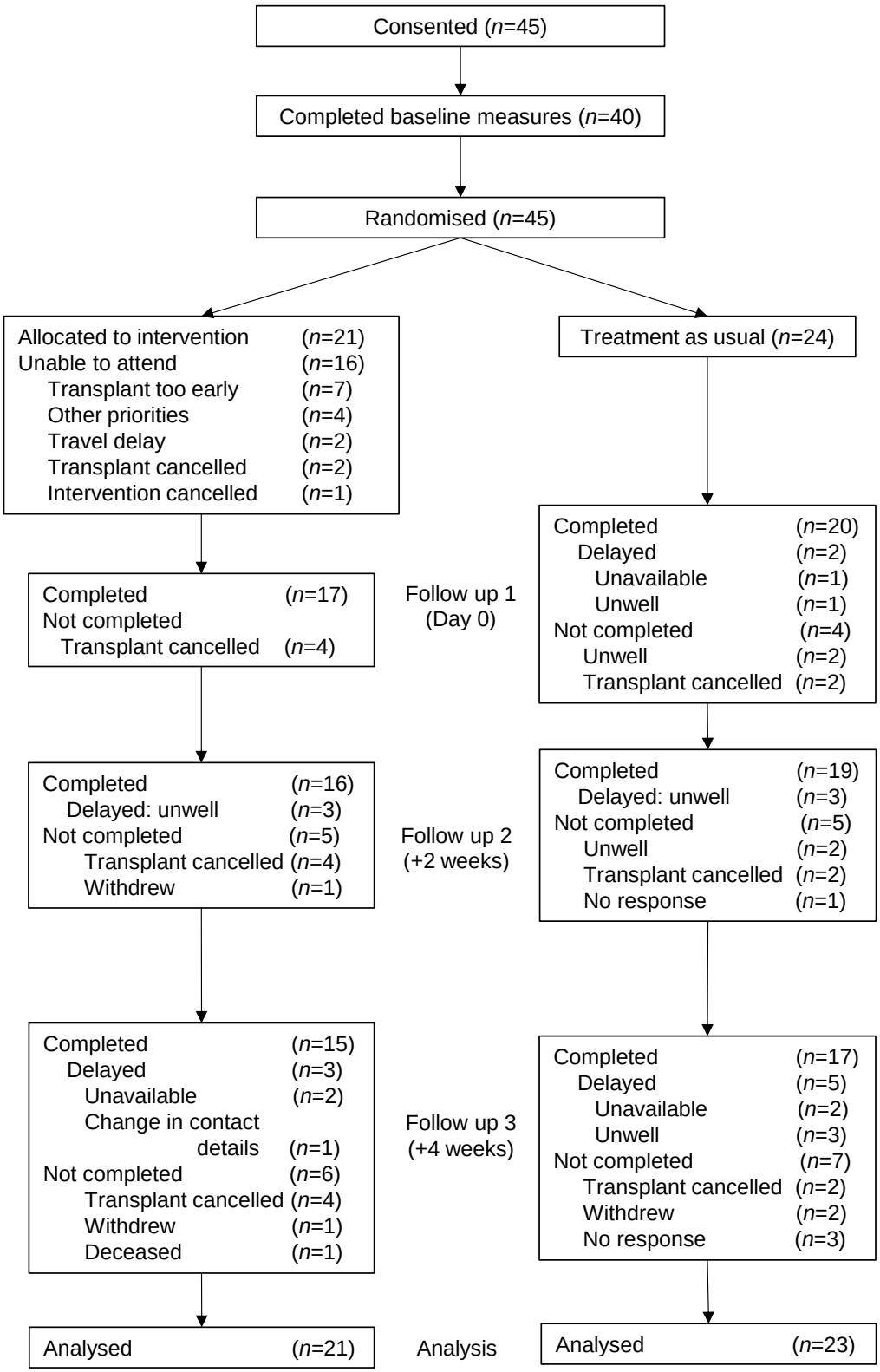

Figure 5. CONSORT diagram of participant flow. Missing baseline measures were not returned following consent. Procedural burden involved primarily competing appointments. The complexity of the procedure included length and

data collection via telephone rather than face to face. All collected data were included in analyses. Day 0 = Day of transplantation.

3.4.1.2 Reliability coefficients

Cronbach's α coefficients are shown in Table 6. Removal of both Items 3 and 4 from the Brief IPQ increased Cronbach's α to between 0.67 and 0.73 across time points.

Table 6

Cronbach's α coefficients prior to removing anxiety items confounded by side effects of haematopoietic stem cell transplantation

Scale	**Time point**			
	T1	T2	T3	T4
Distress				
Total distress	0.95	0.83	0.90	
Stress	0.90	0.78	0.92	0.86
Anxiety	0.78	0.54	0.46	0.47
Depression	0.91	0.72	0.79	0.92
Adaptation	0.76	0.56	0.81	0.87
Negative HSCT perceptions	0.63	0.64	0.63	0.68
Coping				
Self-distraction	0.46	0.65	0.42	0.57
Denial	0.87	No variance	-0.14	0.18
Behavioural disengagement	0.77	-0.05	0.90	0.39
Venting	0.59	0.67	0.27	0.48
Self-blame	0.44	0.65	0.23	0.78
Active coping	0.61	0.80	0.70	0.75
Emotional support	0.76	0.86	0.60	0.79
Instrumental support	0.68	0.64	0.73	0.71

Positive reframing	0.54	0.60	0.36	0.63
Planning	0.77	0.77	0.72	0.86
Humour	0.86	0.94	0.81	0.92
Acceptance	0.80	0.23	0.53	0.81

Note. T1-4=Time points 1-4.

3.4.1.3 Assumption checks

Overall, assumption violations supported the use of robust tests and bootstrap estimation. Most distributions deviated from normality (Table 7). Transformations were not successful due to different distributions across time points. One possible outlier was detected for number of recurrences and another for hospital stay. The latter was related to intensive care admission for a patient who eventually died, therefore, his hospital stay was not taken into consideration. At baseline, one possible outlier was detected for total distress, anxiety, and depression, another for adaptation, and a further outlier for care control. A few possible outliers were detected in denial, venting, behavioural disengagement, acceptance, and self-blame coping styles. However, all these values did not appear unrepresentative as histogram inspection did not suggest they were remote based on the degree of skewness and kurtosis. Removing these values was, therefore, likely to render the dataset unrepresentative and result in incorrect estimates of standard errors from the robust tests (Wilcox, 2012). No additional outliers were identified when data were examined by intervention and control groups. Outliers were not examined for the group of participants who attended the intervention due to the small sample size.

Table 7

Results of statistical screening for normality in measures treated as continuous data

Measure	**Skewness**	**Kurtosis**	**K-S test**
Age	-1.43**	1.78**	0.14*
	(0.38)	(0.74)	
Disease recurrences	1.89***	3.32***	0.42***
	(0.35)	(0.70)	

Years since diagnosis	1.93***	2.45***	0.39***
	(0.35)	(0.70)	
ECOG	0.48(0.49)	-0.58(0.77)	0.31***
Length of admission	-0.17(0.38)	0.04(0.75)	0.12
Time point 1	(*SE*=0.40)	(*SE*=0.78)	
Days from transplant	-0.82*	0.07	0.15*
Distress	(*SE*=0.37)	(*SE*=0.73)	
Total	2.07***	5.18***	0.22***
Depression	1.96***	4.40***	0.22***
Anxiety	3.18***	12.23***	0.28***
Stress	1.46***	1.68*	0.18***
Adaptation	1.89***	7.69***	0.13
HSCT perceptions	0.12	1.76*	0.13
Consequences	-0.51	-0.62	0.18***
Timeline	0.31	-1.01	0.17***
Personal control	1.01**	0.78	0.17***
Treatment control	-2.00***	4.03***	0.34***
Identity	-0.04	-0.96	0.13
Concern	0.01	-0.76	0.11
Understanding	-0.51	-0.69	0.17**
Emotional impact	0.54	0.03	0.13
Coping			
Self-distraction	0.13	-0.97	0.19**
Denial	2.56***	5.81***	0.42***
Behavioural disengagement	3.16***	10.67***	0.49***
Venting	2.22***	5.12***	0.33***
Self-blame	1.90**	3.90***	0.34***
Active coping	0.54	-0.14	0.23***
Emotional support	-0.20	-1.01	0.14*
Instrumental support	0.52	-0.90	0.19**
Positive reframing	0.50	-0.13	0.16*

Planning	0.77*	-0.78	0.24***
Humour	0.56	-0.89	0.20***
Acceptance	-0.97**	0.15	0.18***
Time point 2	(*SE*=0.39)	(*SE*=0.76)	
Days from transplant	4.38***	21.82***	0.31***
Distress			
Total distress	0.51	-0.06	0.12
Depression	0.88*	-0.22	0.18**
Anxiety	1.43***	1.65*	0.24***
Stress	0.11	-1.13	0.19**
Adaptation	0.09	-0.77	0.10
HSCT perceptions	-0.51	-0.22	0.14
Consequences	-1.09**	0.19	0.24***
Timeline	0.19	-0.13	0.15*
Personal control	0.77*	-0.71	0.21***
Treatment control	-1.70***	2.40**	0.27***
Identity	0.35	-0.59	0.15*
Concern	-0.34	-1.09	0.16*
Understanding	-1.46***	2.05**	0.23***
Emotional impact	0.23	-1.26	0.15*
Coping			
Self-distraction	-0.24	-1.05	0.14
Denial	3.33***	11.64***	0.50***
Behavioural disengagement	4.78***	23.57***	0.53***
Venting	2.02***	4.26***	0.35***
Self-blame	2.42***	6.60***	0.36***
Active coping	0.45	-1.11	0.16*
Emotional support	-1.14**	-0.48	0.39***
Instrumental support	-0.11	-1.13	0.11
Positive reframing	-0.19	-1.18	0.14
Planning	0.65	-0.84	0.21***

Humour	-0.20	-1.39	0.18**
Acceptance	-0.44	-1.36	0.29***
Time point 3	(*SE*=0.40)	(*SE*=0.78)	
Days from transplant	1.88***	2.03***	0.35***
Distress			
Total distress	1.14**	0.73	0.17*
Depression	1.11**	1.13	0.13
Anxiety	0.51	-0.97	0.20**
Stress	1.45***	1.99***	0.18**
Adaptation	-0.34	-0.95	0.11
HSCT perceptions	-0.28	0.57	0.13
Consequences	-1.41***	1.88***	0.22***
Timeline	0.13	-0.14	0.16*
Personal control	0.95*	0.03	0.24***
Treatment control	-1.98***	3.69***	0.28***
Identity	-0.62	0.37	0.14
Concern	-0.28	0.53	0.17*
Understanding	-0.68	0.01	0.16*
Emotional impact	0.01	-1.24	0.13
Coping			
Self-distraction	0.53	-0.02	0.25***
Denial	2.40***	5.03***	0.49***
Behavioural disengagement	4.08***	17.95***	0.50***
Venting	0.90*	-0.35	0.33***
Self-blame	1.54**	0.78	0.45***
Active coping	0.65	-0.79	0.20**
Emotional support	-0.99*	-0.31	0.30***
Instrumental support	0.13	-1.25	0.15*
Positive reframing	0.34	-0.84	0.17*
Planning	0.88*	-0.71	0.27***
Humour	0.45	-1.04	0.21**

Acceptance	-2.02***	5.26***	0.34***
Time point 4	(*SE*=0.41)	(*SE*=0.81)	
Days from transplant	1.14**	6.08***	0.28***
Distress			
Total distress	1.26**	1.20	0.19**
Depression	1.27**	0.98	0.21**
Anxiety	1.07**	0.21	0.28***
Stress	1.02*	0.72	0.15
Adaptation	-0.17	1.26	0.15
Negative HSCT perceptions	-0.20	0.06	0.09
Consequences	-0.66	-0.36	0.18*
Timeline	0.11	-0.55	0.13
Personal control	0.31	-0.91	0.19**
Treatment control	-1.46***	1.90*	0.22***
Identity	-0.18	-0.64	0.11
Concern	0.09	-0.89	0.15
Understanding	-0.98*	1.23	0.17*
Emotional impact	-0.15	-1.16	0.14
Coping			
Self-distraction	0.09	-0.75	0.15
Denial	2.13***	3.26***	0.48***
Behavioural disengagement	1.98***	2.93***	0.47***
Venting	0.79	-0.31	0.26***
Self-blame	3.03***	9.50***	0.44***
Active coping	0.59	-0.39	0.25***
Emotional support	-1.28**	0.30	0.35***
Instrumental support	-0.10	-0.89	0.15
Positive reframing	0.38	-0.98	0.19**
Planning	0.56	-1.12	0.23***
Humour	0.38	-0.88	0.20**

Acceptance	-0.96*	-0.18	0.29***

Note. SE = Standard error, also in parentheses; ECOG = Performance status on the Eastern Cooperative Oncology Group scale*;* HSCT = Haematopoietic stem cell transplantation; K-S = Kolmogorov-Smirnov.

***P<0.001; **P<0.01; *P<0.05

Regarding homogeneity of variance, Levene's test (relevant to both t-tests and MANOVA) was significant for several variables and this varied across group comparisons. For participants randomised to intervention versus control, Levene's test was significant for age, distress subscales, denial, self-blame, and personal control, *Ps*≤0.025. For participants who attended the intervention versus those who did not (regardless of randomisation), Levene's test was significant for number of recurrences, years since first diagnosis, emotional support, humour, and self-blame, *Ps*≤0.04. Finally, for participants who attended the intervention versus those who did not from those who were randomised to the intervention, Levene's test was significant for number of recurrences, emotional support, humour, and acceptance, *Ps*≤0.048.

Additional variance assumptions for MANOVA and multivariate normality also appeared violated. Box's test (heterogeneity of covariance matrices) was significant for distress subscales, *Ps*<0.001. One potential multivariate outlier was detected for distress subscales but removal did not alter results. Most residuals did not appear normally distributed (visual inspection). There was no evidence of multicollinearity as correlation coefficients between distress subscales, coping styles, and illness perceptions were below 0.70 (except perceived emotional impact and concern, r=0.76), tolerance exceeded 0.26, and condition index was below 5.

Regarding linearity, bivariate scatterplots revealed approximately linear relationships between distress and psychological processes (negative HSCT perceptions and coping). Days from transplantation showed a linear relationship with total distress and depression, a curvilinear relationship with anxiety, and no observable pattern with stress.

3.4.1.4 Success of randomisation and group comparisons

Randomisation appeared successful as participants randomised to intervention were comparable to those randomised to the control group on demographics, clinical variables, baseline distress, negative perceptions of HSCT, coping style use, and adaptation (Tables 8 and 9). Results were comparable for intervention attendees versus nonattendees except that attendees were from the same site and more likely to be ambulatory (ambulatory treatment was only available at that site), $\chi^2(1)=5.10$, $P=0.02$.

Table 8

Demographic and clinical characteristics of participants and 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%)	Amb (6, 27%)	$\chi^2(1)=0.02$
	7.40 (4.28)	9.50 (7.01)	*ts*(9-25)≤1.55
	Nonamb (12, 71%)	Nonamb (16, 73%)	
	19.4 (3.5)	22.3 (6.3)	

Note. SD = Standard deviation; ECOG=Performance status on the Eastern Cooperative Oncology Group scale; NHL = Non-Hodgkin's lymphoma; Amb = Ambulatory, autologous patients initially attending day ward; Fisher's exact test replicated χ^2 for counts below five; 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 9

Baseline means and standard deviations (SDs) for outcomes and predictors of participants and groups as randomised

Measure	Overall	Intervention	Control	Test
Distress				
Total distress	9.84(10.93)	7.25(8.72)	6.79(4.84)	*t*(26)=0.01
Depression	3.84(4.60)	4.92(6.09)	2.86(2.39)	*F*=0.41 (robust MANOVA)
Anxiety	1.45(2.49)	2.05(3.39)	0.90(1.04)	
Stress	4.55(4.94)	5.79(6.49)	3.43(2.60)	
Adaptation	3.75(0.72)	3.93(0.66)	3.96(0.65)	*t*(26)=0.17
Negative HSCT perceptions	35.8(11.1)	34.1(7.06)	31.1(10.8)	*t*(26)=0.86
Consequences	6.10(2.97)	6.95(2.66)	5.30(3.10)	*F*=0.46 (robust MANOVA)
Timeline	5.82(2.81)	5.89(2.98)	5.75(2.71)	
Personal control	3.18(2.60)	2.79(1.90)	3.56(3.13)	
Treatment control	8.79(1.98)	8.68(2.36)	8.90(1.59)	
Identity	4.18(2.79)	4.32(2.91)	4.05(2.74)	
Concern	5.13(3.01)	5.32(2.81)	4.95(3.25)	
Understanding	7.44(2.20)	7.26(2.35)	7.60(2.09)	
Emotional impact	3.94(2.61)	4.24(3.06)	3.65(2.13)	
Coping				
Self-distraction	2.15(1.73)	1.95(1.68)	2.33(1.80)	*F*=0.40 (robust MANOVA)
Denial	0.55(1.24)	0.84(1.61)	0.29(0.72)	

Behavioural disengagement	0.30(0.82)	0.32(1.00)	0.29(0.64)
Venting	0.75(1.26)	1.05(1.54)	0.48(0.87)
Self-blame	0.88(1.38)	1.26(1.73)	0.52(0.87)
Active coping	1.63(1.53)	1.53(1.43)	1.71(1.65)
Emotional support	3.73(1.74)	3.53(1.93)	3.90(1.58)
Instrumental support	2.20(1.88)	2.11(2.05)	2.29(1.76)
Positive reframing	1.83(1.52)	2.05(1.65)	1.62(1.40)
Planning	1.83(1.99)	1.89(2.18)	1.76(1.84)
Humour	2.40(2.11)	2.47(2.22)	2.33(2.06)
Acceptance	4.25(1.84)	4.32(1.83)	4.19(1.89)

Note. HSCT = Haematopoietic stem cell transplantation; MANOVA = Multivariate analysis of variance.

***P<0.001; **P<0.01; *P<0.05.

3.4.1.5 Effects of time and participant characteristics on distress

The intercepts-only models highlighted intraclass correlations between 0.49 and 0.62, with significant variance in intercepts across participants, $\sigma_{0j}^2 \geq 2.47$, $\chi^2(1) \geq 11.9$, $P \leq 0.001$. Such variability across participants justified the use of MLM (Twisk, 2006).

As discussed in the journal paper, there was a significant main effect of time on total distress, anxiety, and depression. There were also significant random effects (variability in intercepts and slopes across participants) for depression, anxiety, and stress. For depression, there was significant variance in intercepts but not slopes across participants, $\sigma_{0j}^2=11.9$, $\chi^2(1)=13.0$, $P<0.001$, and, $\sigma_{1j}^2=7.83$, $\chi^2(1)=3.39$, $P=0.07$. Slopes and intercepts did not covary significantly with the intercepts, $\sigma_{01j}^2=5.25$, $\chi^2(1)=3.14$, $P=0.08$. For anxiety, there was significant variance in intercepts and slopes across participants, $\sigma_{0j}^2=4.06$, $\chi^2(1)=15.3$, $P<0.001$, and, $\sigma_{1j}^2=2.09$, $\chi^2(1)=4.44$, $P=0.04$, respectively. The slope-intercept covariance was not associated with a significant improvement and was not retained for parsimony. For stress, the

effect of time on depression showed significant variance in intercepts and slopes across participants, σ_{0j}^2=21.0, $\chi^2(1)$=15.9, P<0.001, and, σ_{1j}^2=9.69, $\chi^2(1)$=4.65, P=0.03. The slopes also covaried significantly with the intercepts, σ_{01j}^2=-12.5, $\chi^2(1)$=9.71, P=0.002. Days from baseline confirmed the results regarding the effect of time: stress was stable and total distress, anxiety, and depression increased from baseline (Table 10).

Table 10

Summary of final multilevel model results for distress scores with days from transplantation and participant characteristics as predictors

Predictor	**Total distress**			**Depression**			**Anxiety**			**Stress**		
	$\Delta\chi^2$	R_1^2	β(*SE*)	$\Delta\chi^2$	R_1^2	β(*SE*)	$\Delta\chi^2$	R_1^2	β(*SE*)	$\Delta\chi^2$	R_1^2	β(*SE*)
Days	12.2***	4%	0.08(0.02)***	17.2***	8%	0.05(0.01)***	4.6*	2%	0.013(0.006)*	2.64	1%	0.020(0.012)
Age	4.58*	7%	0.18(0.08)*	5.19*	10%	0.08(0.04)*	1.3	3%	0.02(0.02)	0.45	2%	0.03(0.04)
Gender	4.82*	6%	-6.38(2.88)*	10.7**	13%	-3.73(1.08)**	12.4***	15%	-2.20(0.58)***	4.4*	nil	-2.49(1.14)*
Marital status	2.40 (Δ*df*=4)	4%	-9.65(6.54) to -3.39(6.62)	2.00 (Δ*df*=4)	2%	-3.54(2.67) to -1.63(1.82)	3.40 (Δ*df*=4)	4%	-2.21(1.49) to -0.61(1.46)	3.88 (Δ*df*=4)	6%	-3.89(2.48) to -2.07(2.49)
Education	1.03 (Δ*df*=2)	nil	1.69(2.33) -1.08(3.22)	0.91 (Δ*df*=2)	nil	-0.13(11.5) 0.48(1.37)	0.61 (Δ*df*=2)	nil	0.38(0.45) -0.14(1.11)	4.82 (Δ*df*=2)	1%	0.63(1.60) -1.11(1.30)
Diagnosis	0.30 (Δ*df*=2)	nil	3.56(3.32) 3.94(5.18)	2.72 (Δ*df*=2)	2%	1.62(1.44) 2.35(2.22)	0.48 (Δ*df*=2)	nil	0.77(0.83) 1.04(1.12)	5.51 (Δ*df*=2)	nil	1.95(1.15) -0.28(3.85)
Years since diagnosis	2.35	4%	-0.60(0.39)	2.35	4%	-0.24(0.16)	0.71	2%	-0.08(0.09)	2.36	4%	-0.23(0.15)
Transplant	1.00	2%	-4.35(4.31)	0.40	1%	-1.14(1.76)	0.76	2%	-0.89(1.00)	1.82	3%	-2.26(1.65)
Conditioning	2.88	5%	6.33(3.66)	2.10	3%	2.20(1.49)	1.77	4%	0.85(0.62)	3.64	6%	3.53(1.82)
ECOG	4.99*	12%	6.19(2.38)**	3.59	7%	1.74(0.88)	10.55**	26%	1.35(0.39)**	5.78*	8%	2.68(1.09)*
Site	0.22	nil	1.31(2.76)	0.22	nil	-0.55(1.12)	nil	nil	0.02(0.64)	0.94	nil	1.02(1.04)
Ambulatory	2.49	4%	3.58(2.23)	1.14	2%	1.00(0.92)	0.72	1%	0.33(0.38)	1.00	3%	1.13(1.12)

Length of admission	0.35	1%	-0.08(0.14)	0.30	nil	-0.03(0.06)	0.04	nil	0.01(0.02)	1.04	1%	-0.07(0.07)

Note. $\Delta\chi^2$ = -2log Likelihood change compared to baseline (time as categorical predictor), Δdf = 1 unless specified otherwise; R_1^2 = Variance explained compared to baseline; β = Fixed parameter estimate; *SE* = Standard error; ECOG = Performance status on the Eastern Cooperative Oncology Group scale.

***P<0.001; **P<0.01; *P<0.05.

3.4.2 Efficacy

The analysis did not reveal a significant main effect of group or group x time interaction for either set of comparisons (participants randomised to intervention versus control and participants who attended the group versus those who did not, Table 11 and Table 12). Whilst the intervention group showed significantly less depression on the day of the transplant (time point 2) compared to baseline, the overall model improvement was not significant.

Power analysis used the parameter estimates from the acute phase only (time points 2-4, Table 13). The probability of nonresponse during this period was 0.13. Results indicated that sample sizes of 105, 70, over 1000, and 145 (for total distress, depression, anxiety, and stress, respectively) would be required to detect a significant main effect of group between participants randomised to intervention versus control.

Of the three intervention attendees who received transplants, no individual demonstrated change in distress that was significantly different to the control group after Bonferroni correction (Table 14). Distress decreased during the acute phase for two patients and increased for the third participant. However, the latter also had poorer performance status which was found to contribute to distress in the covariates analysis.

Table 11

Fixed parameter estimates and standard errors for the main effects of time, randomisation, and their interaction in relation to distress using multilevel modelling

Measure	**$\Delta\chi^2$**	***R_1^2***	**β(*SE*)**						
			T2	T3	T4	Randomisation	Randomisation x Time		
							T2	T3	T4
Total distress	3.48	nil	0.02	3.72*	2.72	2.15			
			(0.37)	(1.50)	(1.53)	(2.18)			
	8.21	nil	2.19	4.35*	5.00*	4.65	-4.60	-1.39	-4.77
			(2.11)	(1.94)	(2.11)	(3.17)	(2.82)	(2.80)	(2.95)
Depression	0.43	<0	-0.85	1.58**	3.51**	0.92			
			(0.71)	(0.51)	(0.84)	(1.22)			
	9.14	3%	0.39	1.63*	3.11**	1.61	-2.72*	-0.13	-2.00
			(0.73)	(0.78)	(1.06)	(1.28)	(1.18)	(2.14)	(1.61)
Anxiety	3.10	1%	0.45	1.52***	0.15	1.13			
			(0.30)	(0.38)	(0.29)	(0.65)			
	4.82	5%	0.41	1.56**	0.14	1.12	0.10	-0.15	0.001
			(0.30)	(0.49)	(0.26)	(0.63)	(0.62)	(0.50)	(0.004)
Stress	-0.61	<0	-0.03	0.63	0.69	-0.11			
			(0.33)	(0.63)	(0.68)	(1.24)			
	2.63	2%	1.15	0.94	1.54	1.97	-2.55	-0.68	-1.83

	(1.04)	(0.85)	(1.00)	(1.65)		(1.47)	(1.31)	(1.43)

Note. T2-4=Time points 2-4; $\Delta\chi^2$ = -2log Likelihood change compared to baseline, Δdf = 1 for Randomisation and 4 when the interaction was included; R_1^2 = Variance explained compared to baseline or previously improved model; β = fixed parameter estimate; Shading = Model improved with predictor set random at Level 2.

***P<0.001; **P<0.01; *P<0.05.

Table 12

Fixed parameter estimates and standard errors of main effects of time, actual group attendance, and their interaction in relation to distress using multilevel modelling

Measure	**$\Delta\chi^2$**	**R_1^2**	**β(*SE*)**						
			T2	T3	T4	Attendance	Attendance x Time		
							T2	T3	T4
Total distress	3.19	5%	0.06	3.73**	1.74	7.81			
			(1.37)	(1.39)	(1.43)	(4.32)			
	3.58	6%	0.23	3.90**	3.03*	8.93	-1.81	-1.81	-2.94
			(1.43)	(1.46)	(1.51)	(4.73)	(4.75)	(4.76)	(4.78)
Depression	3.01	5%	-0.79	1.63**	2.18**	3.09			
			(0.57	(0.58)	(0.66)	(1.76)			
	3.79	6%	-0.64	1.70**	2.22**	3.69	-1.72	-0.72	-0.46
			(0.60)	(0.61)	(0.82)	(1.93)	(1.98)	(1.98)	(2.64)
Anxiety	1.08	2%	0.48	1.51***	0.16	1.37			
			(0.28)	(0.37)	(0.29)	(1.02)			
	1.70	3%	0.51	1.78***	-0.71	1.62	-0.31	-0.71	-0.70
			(0.29)	(0.37)	(1.29)	(1.08)	(0.96)	(1.29)	(1.00)
Stress	3.69	4%	0.02	0.65	0.68	3.39			
			(0.76)	(0.63)	(0.65)	(1.74)			
	3.77	4%	0.04	0.67	0.74	3.52	-0.15	-0.19	-0.59

	(0.80)	(0.66)	(0.69)	(2.42)		(2.52)	(2.16)	(2.16)

Note. T2-4 = Time points 2-4; $\Delta\chi^2$ = -2log Likelihood change compared to baseline, Δdf = 1 for Attendance and 4 when the interaction was included; R_1^2 = Variance explained compared to baseline or previously improved model; β = fixed parameter estimate; Shading = Model improved with predictor set random at Level 2.

***P<0.001; **P<0.01; *P<0.05.

Table 13

Parameter estimates used in power analysis

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

Note. β = fixed parameter estimate of the difference from the control group; σ_{0j}^2 = Level 2 variance; σ_{0ij}^2 = residual variance.

Table 14

Results of single case analysis examining whether change in distress during the acute phase of HSCT was different in participants who attended the intervention attendees relative to those who did not

Case	β(*SE*)	$\chi^2(1)$	*P*
1	-5.75(4.85)	1.40	0.24
2	10.46(4.75)	4.85	0.03
3	-5.17(5.04)	1.06	0.30

Note. β = fixed parameter estimate of the difference from the control group; *SE* = standard error.

3.4.3 Psychological processes

3.4.3.1 HSCT perceptions and coping

As discussed in the journal paper, overall negative HSCT perceptions and use of self-distraction, active coping, emotional and instrumental support, humour, and positive reframing increased during the acute phase of HSCT. The fixed parameter estimates are shown in Table 15. Random effects models did not result in further improvements.

Table 15

Model improvements and fixed parameter estimates with time as categorical predictor of HSCT perceptions and coping using multilevel modelling

Measure	**$\Delta\chi^2$**	**R_1^2**	**β(*SE*)**		
			T2	T3	T4
Negative HSCT perceptions	31.4***	2%	-0.19(1.15)	8.12*** (1.69)	5.14** (1.83)
Consequences	6.61	nil	29.6(18.5)	30.9(17.6)	31.4(18.6)
Timeline	2.52	1%	28.0(18.43)	29.8(19.5)	31.6(21.4)
Personal control	3.34	1%	29.3(19.6)	29.5(20.0)	31.8(20.5)
Treatment control	3.30	1%	29.4(19.5)	29.6(19.9)	30.6(20.5)
Symptom identity	3.80	1%	29.1(19.5)	33.5(19.9)	33.9(20.5)
Concern	3.37	1%	29.3(19.6)	30.9(20.0)	31.0(20.5)
Understanding	3.42	1%	29.8(19.5)	30.2(19.9)	31.7(20.5)
Emotional impact	3.41	1%	29.1(19.5)	30.5(19.9)	31.9(20.5)
Coping					
Self-distraction	8.42**	3%	0.79** (0.29)	0.61* (0.31)	0.70* (0.30)
Denial	2.14	4%	-0.18(0.14)	-0.17(0.14)	-0.14(0.15)
Behavioural disengagement	4.31	2%	-0.18(0.14)	-0.04(0.14)	0.12(0.14)
Venting	2.23	nil	0.15(0.24)	0.26(0.25)	0.36(0.25)
Self-blame	4.96	4%	-0.02(0.20)	-0.30(0.20)	-0.37(0.21)
Active coping	8.69**	3%	0.71* (0.31)	0.63* (0.31)	0.90** (0.32)
Emotional support	23.9***	10%	1.26*** (0.28)	1.24*** (0.29)	1.11*** (0.30)
Instrumental support	18.2***	1%	1.21*** (0.30)	1.11*** (0.30)	1.02** (0.31)
Positive reframing	23.8***	6%	1.45*** (0.31)	1.11*** (0.30)	0.60 (0.33)

Planning	1.75	nil	0.29(0.32)	0.38(0.32)	0.38(0.33)
Humour	11.0*	1%	0.77** (0.28)	0.18(0.28)	-0.13(0.30)
Acceptance	7.48	5%	0.41(0.29)	0.83** (0.30)	0.44(0.31)

Note. $\Delta\chi^2$ = -2log Likelihood change compared to baseline, Δdf = 3; R_1^2 = Variance explained compared to baseline or previously improved model; β = fixed parameter estimate; *SE* = standard error; T2-T4 = Time points 2-4. ****P*<0.001; ***P*<0.01; **P*<0.05.

HSCT perceptions and several coping styles predicted distress. Setting these as random predictors improved the models in several instances. The slopes varied significantly and often covaried with intercepts across participants (Table 16).

Table 16

Variance and standard errors of intercepts (σ_{0j}^2), slopes (σ_{1j}^2), and intercept-slope covariance (σ_{01j}^2) for random effects models with distress as dependent variables and HSCT perceptions and coping as predictors

Scale	**Total distress**			**Depression**			**Anxiety**			**Stress**		
	σ_{0j}^2	σ_{1j}^2	σ_{01j}^2	σ_{0j}^2	σ_{1j}^2	σ_{01j}^2	σ_{0j}^2	σ_{1j}^2	σ_{01j}^2	σ_{0j}^2	σ_{1j}^2	σ_{01j}^2
Negative HSCT	43.6**	0.08	1.27*	8.19**	0.01	0.27	1.29**	0.008*	0.09*	10.38***	0.02	0.28
perceptions	(12.8)	(0.04)	(0.61)	(2.65)	(0.01)	(0.16)	(0.49)	(0.004)	(0.04)	(2.92)	(0.01)	(0.15)
Consequences	428.8	0.34	12.4	10.6***	nc	nc	2.44**	nc	nc	148.1	0.17	4.97
	(245.4)	(0.41)	(10.0)	(2.94)			(0.73)			(93.4)	(0.13)	(3.44)
Timeline	1867.9*	3.79	83.4	254.3	0.45	10.5	126.0**	0.27**	5.82**	324.1	0.62	13.90
	(947.2)	(2.01)	(43.4)	(180.6)	(0.35)	(7.88)	(45.4)	(0.10)	(2.13)	(170.9)	(0.35)	(7.63)
Personal	64.3***	ns	ns	10.4***	nc	nc	117.6**	0.27**	5.59**	13.03***	ns	ns
control	(17.0)			(2.95)			(42.3)	(0.10)	(2.01)	(3.47)		
Treatment	64.9***	ns	ns	10.4***	ns	ns	2.52**	nc	nc	13.15***	ns	ns
control	(18.3)			(2.95)			(0.73)			(3.49)		
Identity	868.8**	1.32*	33.2*	11.9***	ns	ns	37.8	0.06	1.45	208.0*	0.34*	8.25*
	(360.6)	(0.64)	(15.0)	(3.17)			(20.4)	(0.04)	(0.86)	(86.8)	(0.16)	(3.70)
Concern	1058.0**	1.73*	42.8*	191.2*	0.30*	7.53*	49.9*	0.09*	2.09*	248.2	0.41	10.01
	(384.5)	(0.71)	(16.5)	(80.7)	(0.15)	(3.50)	(21.0)	(0.04)	(0.94)	(130.5)	(0.24)	(5.55)
Understanding	1940.1	5.09	98.6	9.26**	ns	ns	123.8	0.35	6.56	12.47***	nc	nc
	(1149.0	(2.92)	(57.7)	(2.84)			(70.3)	(0.19)	(3.60)	(3.50)		

Emotional impact	426.3 (261.0)	0.57 (0.52)	15.7 (11.6)	4.75** (1.77)	nc	nc	43.9 (24.3)	0.08 (0.05)	1.88 (1.09)	6.41** (2.02)	nc	nc
Coping												
Self-distraction	57.2*** (15.2)	ns	ns	9.77*** (2.81)	ns	ns	2.44** (0.71)	ns	ns	11.48** (3.33)	ns	ns
Denial	30.1** (11.2)	8.29 (6.59)	-5.60 (6.66)	4.44** (1.70)	ns	ns	1.05* (0.49)	0.56 (0.62)	0.38 (0.78)	9.63** (2.98)	ns	ns
Behavioural disengagement	36.2*** (11.0)	13.2 (11.4)	exc	5.47** (1.97)	2.95 (2.64)	exc	1.13* (0.53)	1.10 (0.93)	0.22 (1.00)	11.87*** (3.22)	ns	ns
Venting	46.5*** (12.7)	7.02 (4.31)	-0.22 (1.98))	13.4*** (3.73)	1.47 (0.90)	-2.03 (1.40)	1.80** (0.56)	ns	ns	8.35** (2.48)	1.34 (0.84)	ns
Self-blame	24.9* (9.86)	14.3 (7.73)	4.89 (6.81)	6.16* (2.49)	2.10 (1.45)	1.08 (1.86)	0.77 (0.45)	0.83 (0.53)	0.52 (0.42)	7.78** (2.44)	ns	1.71 (1.27)
Active coping	58.4*** (15.3)	ns	ns	9.90*** (2.83)	ns	ns	2.48** (0.72)	ns	ns	11.75*** (3.20)	ns	ns
Emotional support	59.6*** (16.7)	ns	ns	9.56** (2.93)	ns	ns	2.50** (0.73)	ns	ns	12.57*** (3.47)	ns	ns
Instrumental support	48.4*** (13.1)	nc	nc	8.48** (2.75)	nc	nc	2.55** (0.76)	ns	ns	10.15** (2.93)	ns	ns
Positive reframing	60.3*** (15.7)	ns	ns	10.4*** (2.90)	ns	ns	2.41** (0.70)	ns	ns	12.21*** (3.28)	ns	ns

Planning	49.5***	ns	ns	9.53**	ns	ns	2.16**	ns	ns	5.59*	1.09*	0.53
	(13.8)			(2.84)			(0.65)			(2.31)	(0.53)	(0.62)
Humour	62.4***	ns	ns	10.9***	ns	ns	1.40*	0.29	0.43	13.17***	ns	ns
	(16.2)			(3.02)			(0.65)	(0.16)	(0.23)	(3.48)		
Acceptance	63.0***	ns	ns	10.4***	ns	ns	2.49**	ns	ns	13.21***	ns	ns
	(16.3)			(2.94)			(0.72)			(3.51)		

Note. ns = No significant improvement by including random parameter; nc = no convergence; exc = Term excluded when model fit did not deteriorate significantly without bootstrapping in order to achieve convergence during bootstrapping.

3.4.3.2 Adaptation to HSCT

Higher reported adaptation to HSCT was significantly associated with lower distress (Table 17).

Table 17

Model improvements, fixed, and random parameter estimates with adaptation to HSCT as predictor of distress

Measure	**$\Delta\chi^2$**	**R_1^2**	**β(*SE*)**	**σ_{0j}^2**	**σ_{1j}^2**	**σ_{01j}^2**
Total distress	68.2***	36%	-4.99***	42.6***	6.33	-15.1**
			(0.75)	(11.1)	(4.51)	(5.68)
Depression	95.6***	45%	-2.73***	6.79***	1.98	-3.02**
			(0.36)	(1.86)	(1.09)	(1.13)
Anxiety	11.9***	11%	-0.66***	2.01**	ns	ns
			(0.19)	(0.61)		
Stress	32.4***	20%	-1.61***	10.99***	0.96	-3.19*
			(0.38)	(2.92)	(1.07)	(1.40)

Note. $\Delta\chi^2$ = -2log Likelihood change compared to the baseline model, Δ*df* = 1 for fixed predictors and 3 for random; R_1^2 = Variance explained compared to the intercepts-only model; β = Fixed parameter estimate; *SE* = Standard error; Shading = Model improved with predictor set random at Level 2; σ_{0j}^2 = intercept variance; σ_{1j}^2 = slope variance; σ_{01j}^2 = intercept-slope covariance; ns = No significant improvement by including random parameters.

***P<0.001; **P<0.01; *P<0.05.

3.5 EXTENDED DISCUSSION

HSCT is an intensive procedure posing considerable challenges for patients particularly during the acute phase. As a result, it has been associated with distress potentially affecting physical wellbeing and recovery. There is a need for robust research in psychological intervention, further understanding into underlying psychological processes underpinning distress, and a careful assessment of feasibility issues particularly in relation to preparing patients and evaluating interventions during the acute phase. Consequently, the present study sought to evaluate the feasibility of delivering and evaluating a psychological intervention aiming to prepare patients for HSCT in an RCT design. It also sought to assess the relevance of the psychological theory used to develop the intervention. Findings indicated considerable feasibility issues but were supportive of the theory.

3.5.1 Feasibility

The results indicated considerable barriers to the evaluation of the preparatory psychological intervention. Several reasons curtailed uptake and attendance including insufficient time prior to transplantation, burden in light of other priorities (e.g., other appointments), being unwell, travel distance, and so forth. Uptake was slower than studies of inpatient interventions during HSCT and cancer (Bauer-Wu et al., 2008; Jarden, Baadsgaard, Hovgaard, Boesen, & Adamsen, 2009; Moyer et al., 2009) though more in line with outpatient intervention studies, particularly those randomising (DuHamel et al., 2010; Goodwin et al., 2000; Lounsberry et al., 2010), highlighting procedural burdens and lack of integration with the clinical process (primarily due to the trial setup) as possible barriers. The experience of lower distress prior to HSCT may have contributed to lower prioritisation by patients (Moyer et al., 2009). Time point 3 may be the optimal endpoint of analysis for anxiety in a full trial and time point 4 for depression, as these were the time points when each distress subscale was highest. Findings were mixed regarding other feasibility issues regarding the research procedure, the intervention, and the assessment used, as discussed below.

3.5.1.1 Procedure and intervention

Most aspects of the procedure appeared feasible but the use of randomised control appeared to pose a major barrier to conducting the research. Inability to attend the intervention prior to the transplant was a main reason both for not consenting to participate and not attending the intervention after consent was obtained. As attendance had not been a problem during the earlier pilot of the intervention (prior to this study), the present findings highlighted a feasibility issue posed by allocating only 50% of participants to the intervention at each site. It appears that this impacted on accrual of patients for the group, which was no longer sufficient to hold the intervention frequently enough to allow participants to attend prior to their transplant. Such effects of randomised control are reported in psychooncology more generally (Goodwin et al., 2000; Mills et al., 2006) but appear to be completely neglected as a potential issue in HSCT feasibility studies, which do not tend to factor in such procedures (Bauer-Wu et al., 2008; Bevans et al., 2010; Horton-Deutsch et al., 2007; Lounsberry et al., 2010). The impact on accrual highlights randomised control within each site as a potentially major barrier to conducting RCTs of group interventions in HSCT alongside already limited uptake in this population.

The predominance of limited timeframes as reason for not consenting to the study and not attending the intervention may have overshadowed subsequent feasibility issues with delivering the intervention. Psychological interventions in cancer care including HSCT vary considerably on the level of participation they require but limited adherence has been observed across the field (Baliousis et al., in press; Moyer et al., 2009; Newell, Sanson-Fisher, & Savolainen, 2002). For example, participants have been found to neglect self-help materials or even show resistance to engage with interventions (Cunningham et al., 1998; Cunningham et al., 2000; Edgar, Rosberger, & Collet, 2001; Trask et al., 2003). Had available timeframes in the present study provided participants with the opportunity to attend the intervention prior to the transplant, such factors may have emerged in this project also.

Other aspects of the procedure, such as the process of randomising participants, allocation concealment, assessor blinding, and collecting data over

the telephone during the acute phase of HSCT appeared feasible. Attrition was in line with HSCT studies using remote data collection but higher compared to those collecting data on site (DuHamel et al., 2010; Lee et al., 2005; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005). Reasons for attrition were not known (except in one case where the participant died) but may reflect some of the reasons leading to delays in data collection (e.g., feeling unwell and unavailability due to other commitments). It is possible that direct rather than telephone contact might enable outcome assessors to assist participant with completing the questionnaires and foster rapport and engagement. This approach may partly circumvent reasons for attrition but may increase the chance of deblinding the outcome assessor.

Participant blinding was more difficult to achieve. This was because information about the intervention was disclosed inadvertently in the course of recruitment and suggests that participant blinding may not be possible in a full trial. Recruiters may have to be more mindful of deblinding potential participants this way. However, the difficulties with participant blinding for interventions whose nature is not concealed (Schulz & Grimes, 2002a), means that it may not be an essential part of the design or technically possible.

The primary outcome was total distress with the subscales of depression, anxiety, and stress. The estimated required sample size of up to 145 participants to detect an intervention effect for distress, depression, and stress may be feasible. However, the required sample size for an effect on anxiety exceeded 1000 participants and did not appear feasible. However, these estimations may be inaccurate in light of limited attendance to the intervention and mixed findings of efficacy when single-case data were examined.

Overall, findings on the feasibility of the procedure and the intervention indicated that barriers to delivering the intervention were compounded by those of the RCT design suggesting that such a mode and timing of intervention may be very difficult to evaluate using randomised control within each site. The impact of RCT procedures has been neglected in other feasibility studies in HSCT (Bauer-Wu et al., 2008; Lounsberry et al., 2010) but are important in informing research towards more robust evidence base.

3.5.1.2 Assessments

Findings were mixed regarding the appropriateness of the assessments used in the study. The DASS-21 total distress, depression and stress subscales appear applicable to HSCT. However, two items of the anxiety subscale appear confounded by physical symptoms of the procedure and reliability coefficients for this subscale decreased over time as physical symptoms increased (Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005). Other anxiety scales (e.g., Hospital Anxiety and Depression Scale) have better reliability in HSCT (Gaston-Johansson et al., 2013; Jarden et al., 2009; Lee et al., 2005; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 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 anxiety subscale (Antony et al., 1998; Crawford & Henry, 2003). It follows that the construct measured by the anxiety subscale of the DASS-21 appears be more difficult to assess in HSCT due to confounding with physical symptomatology. In light of the infeasibility of accruing a required sample size in excess of 1000 participants to detect an intervention effect on anxiety (as measured by the DASS-21), it seems reasonable to exclude this subscale from the full trial altogether.

The adapted Brief IPQ showed acceptable internal consistency. However, the coping appraisal items (personal and care control) may be less applicable to HSCT or may not capture the relevant theoretical processes of the self-regulatory model adequately (Leventhal et al., 1997; Leventhal et al., 1984; Ogden, 2012; Sharpe & Curran, 2006) as they reduced the reliability of the scale. The care control item ("How much do you think the care you receive can help you through the transplant process?") appears particularly problematic. The issue with this item may have arisen due to social desirability as the question was asked by the researcher who worked with members of the care team and participants could have interpreted the item in terms of rating satisfaction with care. It is also possible that the item led participants to focus on nursing than overall care (including medication, etc.). To bring the item more in line with the self-regulatory model in rating the ability of the treatment as well as care to help control the HSCT process, an adjustment to the item's wording

may be helpful, for example “How much do you think the care and treatments you receive can help you through the transplant process?”.

Low reliability coefficients were observed in coping styles acceptance, positive reframing, behavioural disengagement, denial, self-blame, self-distraction, and venting. Such coefficients are often expected with small scales and have been common in coping research (de Ridder, 1997; Field, 2013; Folkman & Moskowitz, 2004) but the findings suggest potentially limited applicability of the above items to HSCT. However, previous research in HSCT using a priori coping categories (emotion-focussed, problem-focussed, and avoidance coping) that contain more items also reported very modest reliability coefficients (Schoulte et al., 2011), which suggests a broader problem with coping assessment in HSCT. It follows that improving reliability of measurement, for example by deriving higher-order coping categories in a bottom up manner (e.g., factor analysis with a sufficiently large sample) that reflect the context of HSCT, may be helpful in improving the reliability of assessment (de Ridder, 1997) and, therefore, analysis in a full trial.

The BRS was adapted from a trait measure (B. W. Smith et al., 2008) to assess the degree of adaptation to HSCT over one week. It showed comparable reliability to the original version (B. W. Smith et al., 2008) except at time point 2 where internal consistency appeared modest. Measurement at this time point was on or soon after Day 0 (the beginning of the acute phase of HSCT) and some participants found the questions about bouncing back from the transplant process ambiguous in this context. The ambiguity may have resulted in mixed ratings and, therefore, the lower internal consistency of the scale at that time point. Consequently, it may be beneficial to clarify the transplant process as including the preparatory pretransplant period and to refine the wording of the items so that it captures participants’ experience over the preceding week better. For example, “so far, I have been bouncing back quickly since this hard time began” could be adapted as “I have been bouncing back quickly from this hard time over the past week.”

In sum, findings indicate considerable barriers to conducting an RCT during the acute phase of the procedure, to the extent that such an approach may not be suitable to evaluate preparatory group interventions in HSCT.

However, results also suggest feasibility in some procedures (e.g., data collection). Measures appear mostly suitable but some adjustments may be required for the full trial. There are some limitations to the reliability of coping appraisal items in the Brief IPQ, coping subscales of the Brief COPE, and the anxiety subscale of the DASS-21. The DASS-21 anxiety subscale could be omitted from the full trial whilst refining some items and deriving higher order coping categories may be helpful.

3.5.2 Psychological processes

The present findings suggest that diverse negative perceptions of HSCT and apparent ineffectiveness of coping may explain distress during the acute phase of the procedure. Whilst these may reflect wider processes and causal pathways are yet to be firmly established, they highlight the potentially unique contribution of HSCT perceptions and coping to the development and maintenance of distress in this population, with implications for further development of the intervention.

3.5.2.1 Perceptions of HSCT

Patients reporting more emotional distress appeared to perceive HSCT as a prolonged and poorly understood process with severe physical, social, and emotional impact on their lives, many side effects, and a cause for concern. Overall perceptions of HSCT became more negative as the procedure progressed (reflecting the increase in distress) but the change in individual subscales did not reach significance. The diversity of relevant perceptions and the findings of an overall rather than subscale increase over time suggest that the negative HSCT perceptions and their effect on distress may be cumulative.

The intensity and complications of HSCT and the disruption they cause to patients' lives appears to reflect the complex pattern of negative perceptions. Admission to hospital for HSCT and isolation to prevent infections result in loss in many life domains such as social contact, employment (most participants function well physically and are often employed prior to transplantation), and leisure (Antin & Raley, 2013; Copelan, 2006). The consequences of the physical complications of the procedure (e.g., pain, fatigue) are diverse

including physical suffering and disability, inability for self-care and engaging with valued-activities, sexual dysfunction, relationship conflict, and so forth, particularly in the earlier stages of the procedure (Jim et al., 2014; Mosher et al., 2009). Furthermore, these sequelae are often unexpected as patients differ in their reactions to HSCT and the course of recovery whilst pretransplant information frequently fails to prepare patients adequately (Anderson et al., 2007; Copelan, 2006; Jim et al., 2014; Larsen et al., 2004; Lee et al., 2005; Mosher et al., 2009; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Xuereb & Dunlop, 2003). Focus on the breadth of complications, their impact, and lack of suitable preparation are likely to contribute to negative perceptions of the procedure in terms of consequences, defining symptoms, length and degree of recovery, and comprehensibility (e.g, Jim et al., 2014).

All subscales of the Brief IPQ (except coping appraisals) were highly correlated with depression, less so with anxiety, and fewer subscales were associated with stress. Initially, negative perceptions may reflect a sense of threat to wellbeing as the severe negative sequelae of HSCT emerge resulting in the fearful anxiety response observed in the present study (see Rachman, 2013 for discussion on perceptions and appraisals associated with anxiety). This appeared relatively short-lived, which may explain the smaller associations between perceptions and anxiety. Compounded and persistent losses and suffering over time is likely to result in increasing hopelessness and the depression that was observed both in the present project and other studies in HSCT (Fife et al., 2000; Hjermstad et al., 1999; Lee et al., 2005; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005). The pervasiveness of negative perceptions associated with depression in the present study are consistent with literature suggesting a ubiquitous pattern of negative beliefs underpinning this emotional response (Blackburn, James, & Flitcroft, 2006). Finally, perceiving negative consequences (including emotional ones), cause for concern, and a lengthy recovery appear to characterise stress. This suggests a sense of sustained challenge during HSCT and supports the conceptualisation of the DASS-21 stress subscale as tension and worry in the context of ongoing demands, as opposed to the fearful anxiety response measured by the anxiety subscale (Lovibond, 1998).

Notwithstanding the issues with coping appraisals, the present findings highlight the relevance of negative HSCT perceptions in explaining distress but these could reflect a broader appraisal style. For example, perceiving the procedure more negatively may reflect a broader cognitive bias or schema about the world, self, and others based on early experiences (Beck & Haigh, 2014; Padesky, 1994). Negative perceptions may also reflect insecure attachment models that render the person more susceptible to environmental stressors and loss, with limited skills to cope and regulate emotions (Brethreton & Munholland, 2008; Dykas & Cassidy, 2011). A dominant professional discourse about HSCT emphasising challenges over resilience and hope once the procedure is underway (Copelan, 2006; Xuereb & Dunlop, 2003) may also influence patients' focus on negative outcomes and difficulties. Attending to negative HSCT perceptions in psychological intervention may be useful in alleviating distress but the above considerations suggest potential benefits in targeting broader appraisal styles and mechanisms in order to be more effective.

In spite of the overall robust findings regarding HSCT perceptions, there is a need for cautious interpretation regarding their mediating role in maintaining distress. As discussed in the extended background (Section 4.3.3), the self-regulatory model assumes primacy of cognition over emotion (Leventhal et al., 1997; Leventhal et al., 1984; Ogden, 2012; Sharpe & Curran, 2006) but contemporary theoretical literature suggests they are likely to influence each other (Barnard, Duke, Byrne, & Davidson, 2007; Duncan & Barrett, 2007; Gazzaniga, 1998; Ochsner & Gross, 2005; Phelps & LeDoux, 2005; Salzman & Fusi, 2010; Storbeck & Clore, 2007). The extent and precise mechanism of the relationship between perceptions and distress in HSCT remains unclear in light of the correlational nature of the present study.

3.5.2.2 Coping

The present findings provided some support for the role of unhelpful coping in underpinning distress, as predicted by the self-regulatory model though some patterns deviated from what was expected. Avoidance-based and what are broadly considered unhelpful coping styles such as self-distraction,

denial, disengagement, venting, and self-blame (Carver et al., 1993; Stanton, Danoff-Burg, & Huggins, 2002; Taylor & Stanton, 2007), were associated with higher distress in the present study, with similar reports in other literature including HSCT (Folkman & Moskowitz, 2004; Mytko et al., 1996; Ogden, 2012; Schoulte et al., 2011; Taylor & Stanton, 2007). In contrast, approach-based coping, such as planning and seeking instrumental and emotional support, are generally considered helpful styles (Folkman & Moskowitz, 2004; Taylor & Stanton, 2007) but the opposite appeared to occur in the present study.

Avoidance-based coping styles can be helpful with transient stressors and the short-term because they can divert attention from distress and its causes until both diminish naturally (Folkman & Moskowitz, 2004; Ogden, 2012; Taylor & Stanton, 2007). The acute phase of HSCT is relatively short-term, hospitalisation has a relatively clear end at first, and patients may be unprepared to cope with complications initially (Anderson et al., 2007; Copelan, 2006; Jim et al., 2014; Xuereb & Dunlop, 2003). Consequently, patients may rely heavily on avoidance-based coping mechanisms at first but, as complications mount rather than diminish, may also persist with using such mechanisms (Mah et al., 2008) which could become counterproductive as they fail (by definition) to address the situation.

In contrast, approach-based coping, such as planning and seeking instrumental and emotional support, purports to resolve the problem and has generally been found to predict lower distress (Folkman & Moskowitz, 2004; Taylor & Stanton, 2007). However, such coping in HSCT and other cancer populations with acute or long-term difficulties has not been consistently beneficial (Carver et al., 1993; Mytko et al., 1996; Schoulte et al., 2011). In the present study, planning and seeking instrumental and emotional support were associated with more distress during HSCT. This suggests a possible interaction with the circumstances of the procedure, as detailed below.

The effectiveness of approach-based coping (in the solution-focused sense) often depends on the availability and appropriateness of social and practical resources (Ogden, 2012; Taylor & Stanton, 2007). HSCT can be very challenging, particularly in the first few weeks, with complications and consequences (e.g., side effects, fatigue, social isolation) that cannot be controlled easily and whose impact often worsens in spite of a range of possible

solutions available to patients (e.g., medication, access to activities such as physiotherapy, etc.; Antin & Raley, 2013; Copelan, 2006; Jacobsen et al., 2014). Furthermore, hospitalisation and physical disability often means that HSCT patients lack social support during the procedure and often the support they receive is poor match for their needs (Antin & Raley, 2013; Copelan, 2006; Schulz-Kindermann et al., 2002; Wells et al., 2009). Consequently, attempts to resolve difficulties during acute HSCT via seeking support may be rendered counterproductive. Planning without sufficient information (as reported by patients; Jim et al., 2014) is also unlikely to be effective. Persisting with the use ineffective coping strategies (approach- or avoidance-based) may lead to more cognitive focus on the challenges surrounding HSCT, prevent the exploration of alternative coping strategies, exacerbate negative perceptions of the procedure, and – ultimately – psychological distress (Cheng, Lau, & Chan, 2014; Harris, 2009; Hulbert-Williams, Storey, & Wilson, 2015).

The present findings highlight the ineffectiveness of the coping strategies in the Brief COPE but other strategies may be more effective. For example, coping via cognitive acceptance[V] of and engagement with the distressing experience (as in Mindfulness or Acceptance and Commitment Therapy) has been found to reduce distress in clinical populations suffering from lack of control, prolonged struggle, and a disabling impact on patients' lives (e.g., chronic pain, and other long-term physical conditions; Carlson, Speca, Patel, & Goodey, 2004; Hulbert-Williams et al., 2015; Ott, Norris, & Bauer-Wu, 2006). It has also shown promise in HSCT (Bauer-Wu et al., 2008; Horton-Deutsch et al., 2007). Such a strategy is different from the approach-based coping styles of the present study in being less dependent on the social context and not seeking to resolve the challenging situation patients are in. Instead, it is thought to operate via allowing patients to act more in line with what they consider important in their life rather than focusing on struggling to resolve a challenging situation ineffectively (Hulbert-Williams et al., 2015).

[V] Acceptance in the Brief COPE was not related to distress but the style is conceptualised as resignation and opposite to denial rather than psychologically engaging with the distressing experience (Carver, 1997; Hulbert-Williams et al., 2015).

Overall, the present findings highlight the role of negative HSCT perceptions and use of some coping strategies in the development and maintenance of distress during the acute phase of the procedure. These findings are also in line with research from a range of other clinical populations where the self-regulatory model has been applied successfully, such as heart failure, epilepsy, and Huntington's disease (Arran, Craufurd, & Simpson, 2013; Bridges & Smith, in press; Hagger & Orbell, 2003; Knibb & Horton, 2008; Morgan, Villiers-Tuthill, Barker, & McGee, 2014; Rizou, De Gucht, Papavasiliou, & Maes, 2015). Psychological interventions within HSCT relative to other health populations have been unforthcoming (Baliousis et al., in press; Newell et al., 2002; Nicassio, Meyerowitz, & Kerns, 2004; O'Halloran & Altmaier, 1995; Rueda, Sola, Pascual, & Subirana Casacuberta, 2011; Semple et al., 2013), perhaps due to an over-focus on the physiological rather than psychological predictors of distress. The present findings provide a promising step towards a more nuanced psychological understanding of distress in HSCT that supports the rationale for the present intervention and could help guide further development of psychological interventions for this population.

3.5.3 Distress and adaptation to HSCT

The self-regulatory model is concerned with adaptation to illness of which psychological distress is one of several possible outcomes (Hagger & Orbell, 2003; Leventhal et al., 1997; Leventhal et al., 1984; Ogden, 2012; Sharpe & Curran, 2006). As the present project used the model for the first time to understand distress in HSCT, some evidence that distress reflected adaptation in this population as conceptualised by the self-regulatory model was important in supporting such an application of the model.

The concept of adaption to health-related difficulties as measured by the BRS and assumed by the self-regulatory model is multifaceted. The aspects of the concept are diverse, for example psychological distress, depression, anxiety, stress, a sense of purpose in life, social functioning, role functioning (ability to fulfil one's role), and so forth (Hagger & Orbell, 2003; Sharpe & Curran, 2006; B. W. Smith et al., 2008; B. W. Smith et al., 2013; B. W. Smith et al., 2010; Windle et al., 2011). Relevant variables are highly correlated with adaptation as measured by the BRS (B. W. Smith et al., 2008; B. W. Smith et

al., 2013; B. W. Smith et al., 2010), as expected by variables that reflect aspects of the same construct (Field, 2013). Such correlations between adaptation to HSCT and distress were replicated in the present project and suggest that distress is likely to reflect adjustment to the procedure. This supports the secondary hypothesis of the project about the close relationship between distress and adaptation and the application of the model to understand distress in HSCT.

The correlations with depression and stress suggest the greatest overlap with the concept of adaptation in HSCT. This indicates that experiencing depression and stress during the procedure may reflect limited ability to adapt to its circumstances, consistent with the observations of ineffective coping in this context. In contrast, the modest correlation with DASS-21 anxiety suggests less overlap with adaptation. This finding may reflect the nature of the concept of DASS-21 anxiety, that is, a fearful response to a threat (Lovibond, 1998; S. H. Lovibond & P. F. Lovibond, 1995) likely to precede (or even trigger) the process of adaptation (Rachman, 2013) rather than represent a facet of it. It follows that the anxiety subscale of the DASS-21 may be less relevant to the self-regulatory model. This conclusion is also consistent with the smaller correlations between DASS-21 anxiety and HSCT perceptions and coping and further justifies the rationale for the exclusion of this anxiety subscale from a full trial. However, the smaller correlation between anxiety and adaptation may also reflect the possible confounding by physical symptomatology in the former.

3.5.4 Strengths and limitations

There is a lack of suitably evaluated psychological interventions aiming at preparing patients for distress during acute HSCT (Baliousis et al., in press). This project makes an empirical contribution to the field through the novel application of the self-regulatory model to acute HSCT. It also extends the current literature on distress in the procedure, which is largely focused on medical and demographic factors (Ahles, Tope, Furstenberg, Hann, & Mills, 1996; Fife et al., 2000; Meyers et al., 1994; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Schulz-Kindermann et al., 2002; Tecchio et al., 2013). The project also highlights some of the barriers regarding the feasibility

of evaluating and delivering psychological interventions for this population, and help to inform future research and intervention in this area. In addition, the study provides preliminary psychometric data relating to two new adaptations of the Brief IPQ and BRS scales for HSCT populations.

3.5.4.1 Strengths

Key strengths of this research included: multisite involvement; a prospective design; examination of efficacy as well as process; detailed examination of feasibility issues; inclusion of key RCT features; attempts to control for sampling bias alongside broad inclusion of HSCT patients; and the method of analysis. Further detail regarding these strengths is provided below.

3.5.4.1.1 Multisite involvement and longitudinal design

HSCT is a standardised procedure (Antin & Raley, 2013) but there can be variations in care across sites, as in the present project, potentially contributing to variability in findings between studies. For example, ambulatory care in one site resulted in somewhat later admission compared to the other site and may have attenuated the impact of isolation, delayed the emergence of anxiety, and so forth. Significant variability between sites was not detected in the present study (no significant differences between them in terms of distress) but power for those analyses was limited and findings are potentially more representative of the wider population by using more than one site.

A key advantage of the longitudinal design was evidence for reliable change in distress during HSCT. This may permit a causal link to be inferred (though not established as manipulation was not possible due to the nature of the transplantation procedure). The longitudinal association between HSCT perceptions, coping, distress, and resilience also strengthens support for the underlying theory across the acute phase.

3.5.4.1.2 Process

Diverse factors may contribute to outcome in psychotherapy research, such as those present across modalities (e.g., therapeutic alliance), those specific to theory (e.g., cognitive change in CBT), or those that provide a

context for therapy (e.g., structure and coherence; Wampold, 2001). It is, therefore, important that intervention research examines process as well as outcome to inform further development but this is missing from the HSCT literature (Baliousis et al., in press). The present study provided the first attempt to evaluate a psychological intervention in HSCT whilst incorporating some evidence for the specific theoretical factors that were assumed to be operating, namely HSCT perceptions and coping. This information can help generate targeted recommendations for developing the intervention further in terms of both content and delivery. For example, the findings on HSCT perceptions indicated specific targets for intervention whilst the findings on coping can guide on what styles to promote, what styles to minimise, and on extending the social context of patients to improve the effectiveness of coping styles.

3.5.4.1.3 Feasibility focus

Clinical trials are often faced with considerable feasibility issues but there is little understanding regarding specific barriers to and strategies for their successful completion (Bower et al., 2014; M. Campbell, Snowdon, Francis, Elbourne, & McDonald, 2007; Howard et al., 2009). This can be compounded in HSCT as the challenges facing patients together with the physical burden of the procedure and illness can pose considerable barriers to uptake and retention (Baliousis et al., in press; Bauer-Wu et al., 2008; Mosher et al., 2010). Feasibility studies in HSCT focus primarily on efficacy (Bauer-Wu et al., 2008; Bevans et al., 2010; Horton-Deutsch et al., 2007; Lee et al., 2005; Lounsberry et al., 2010; Trask et al., 2003) thus failing to document feasibility issues to evaluating intervention using RCT designs.

In contrast, the present study placed a detailed focus on feasibility issues during the acute phase of HSCT. The many barriers that were identified are likely to enhance research and further development of interventions in the field. They are also able to facilitate better decision-making regarding the overall feasibility of the research and possible threats to validity that have been missed from the literature to date.

A particular aspect of RCTs that has been neglected in HSCT feasibility trials concerns the aspect of randomised control (Bauer-Wu et al., 2008; Bevans et al., 2010; Horton-Deutsch et al., 2007; Lounsberry et al., 2010). This is in spite of it being considered the method of choice for confounder control (McBurney & White, 2007) and its potentially negative impact on recruitment in cancer populations (Moyer et al., 2009). Randomised control within each site could be particularly problematic for HSCT studies in light of the present findings, where accrual of patients for the intervention was halved due to the procedure. The possibility that participants may be assigned to the control group at random and have to go through the research process without any tangible benefit when they are already strained may have also impacted negatively on uptake to the study. It follows that results of prior feasibility studies of psychological interventions in HSCT may have underestimated recruitment and accrual challenges. The uptake observed in the present project is likely to be more representative of the field.

A further benefit of incorporating randomised control in the present study was to assess its potential in producing groups that are comparable on usual confounders such as age, diagnosis, performance status, and so forth (Andersson et al., 2009; Andersson et al., 2011; Barata et al., 2014; Braamse et al., 2014; Hefner et al., 2014; Mosher et al., 2009; Prieto et al., 1996; Tecchio et al., 2013). Consequently, there was no need to include additional variables in the statistical models thereby limiting loss of power in the study and improving the accuracy of sample size estimates. Furthermore, by assessing the feasibility of allocation concealment and blinding, which are also neglected in full and feasibility trials in HSCT (Baliousis et al., in press; Bauer-Wu et al., 2008; Bevans et al., 2010; Horton-Deutsch et al., 2007; Lounsberry et al., 2010), the study provides further evidence regarding the applicability of randomised control designs for evaluating psychological interventions in HSCT.

3.5.4.1.4 Sampling bias

Sampling bias can limit a study's internal and external validity (McBurney & White, 2007). This can become particularly problematic in HSCT in light of the many recruitment challenges and attrition that were observed in the study

and reluctance to engage with mental health services in this population (Mosher et al., 2010). In addition, stringent inclusion criteria can render samples unrepresentative of naturalistic settings in psychotherapy research (Kazdin, 2008). Consequently, setting broad inclusion criteria and approaching patients consecutively as they entered the service are likely to have made the present sample more representative of the HSCT patient population. Alongside recording reasons for nonconsent, these methods also permitted a detailed examination of sampling bias. The evaluation of external validity was enhanced further by recording reasons for nonattendance and comparing attendees versus nonattendees from those participants randomised to the intervention.

3.5.4.1.5 Analysis

Use of MLM and robust statistics offered several advantages. The study involved data collection from a highly burdened population resulting in missing data and unequal intervals between time points. In addition, the comparison between group attendees and nonattendees was highly unbalanced. These would have been problematic with traditional ANOVA which requires balanced designs and complete datasets resulting in considerable loss of participants following listwise deletion (Field, 2013). Indeed, prior research in the field has suffered considerably from such loss of outcome data (Baliousis et al., in press), a problem also prominent in trials generally (Gravel, Opatrny, & Shapiro, 2007; Hollis & Campbell, 1999). However, MLM in the present project provided partial control for these issues by permitting the inclusion of all available data thereby enhancing statistical validity. MLM also enabled control for significant variance in intercepts and slopes across participants. This provided a more valid representation of the observed effects in light of such heterogeneity in the population. Additionally, using bias-corrected (bootstrap and robust) tests allowed for more accurate estimations of effects and sample calculations for a fully-powered efficacy study. Overall, robust analyses suggested more accurate results and better maintenance of nominal Type I error rates notwithstanding assumption violations. This reflected a consistent strength of the present project relative to other studies in HSCT and psychotherapy more generally (Baliousis et al., in press; Erceg-Hurn & Mirosevich, 2008; Wilcox, 2012).

3.5.4.2 Limitations

In spite of several methodological strengths, the study also contained a number of limitations that potentially impact on the validity of the research. Four types of threats to research validity are discussed: internal, external, construct, and statistical (McBurney & White, 2007).

3.5.4.2.1 Threats to internal validity

Internal validity refers to the extent to which a study provides credible evidence for the effects under scrutiny (particularly in relation to causality in experiments) whilst minimising the plausibility of alternative explanations (D. T. Campbell, Stanley, & Gage, 1963; McBurney & White, 2007). Notwithstanding a number of steps to control for confounding variables in the present study it was not possible to rule out alternative explanations and several threats to the internal validity of the research remained. In fact, the feasibility component provided evidence for a range of additional confounders. Threats to internal validity included limitations to the manipulation, ambiguous temporal precedence, factors outside the study, a limited scope of psychological processes, effects of the method of collecting data, and attrition. Further detail regarding these limitations is provided below.

3.5.4.2.1.1 Manipulation and temporal precedence

Manipulation of attendance to intervention aimed to establish a causal link between the intervention and its assumed mechanisms of change but this was not feasible. Consequently, the design of the study became exclusively correlational. Whilst the longitudinal component evinced the often close relationship of distress with HSCT progression, HSCT perceptions, and coping, it was not possible to establish which preceded which. In the case of HSCT perceptions and coping, this means that a causal link with distress, as suggested by the self-regulatory model, could only be inferred and the opposite pattern remained plausible (as discussed in Section 8.2.1).

3.5.4.2.1.2 Confounding variables and control

Apart from inability to establish direct causal links between the different variables, an additional caveat with correlational evidence involves the potentially causal contribution of factors not measured in the study (McBurney & White, 2007). Distress may be associated with progression through HSCT but the procedure is diverse and multifaceted (Copelan, 2006). Consequently, many factors may have changed how the procedure was perceived, coping, and distress such as tests following transplantation, uncertainty regarding going home, staff availability, physical needs, and so forth (Antin & Raley, 2013; Copelan, 2006). A range of other psychological processes may have also mediated the relationship between the distress, perceptions of HSCT, and coping, as discussed earlier (e.g., discourses, attachments, etc.). This limits conclusions regarding the nature of the relationship between distress and the psychological variables examined in the study.

The range of potentially confounding processes also highlights a limitation in TAU as control condition. TAU was not standardised and consisted of ad hoc informational and supportive input from clinical staff. This input may have overlapped with the intervention, as patients who did not attend the intervention were able to seek support should they wished, but the extent to which this occurred was unclear. This support could include information and advice on coping similar to what was addressed during the intervention, albeit with less shared exploration with peers (due to isolation and lack of facilitated contact).

Furthermore, most participants were aware of the nature of the intervention and, therefore, did not remain blind regarding which groups they had been allocated to. This awareness may have influenced their expectations of experiencing distress and, therefore, their responses to the questionnaires. It may have also caused participants to compensate for not receiving the intervention by seeking alternative support, as observed often in cancer populations (Moyer et al., 2009). Cancer patients who receive interventions have also been found to seek additional assistance (Moyer et al., 2009), which may have introduced further bias in the findings. These possibilities highlight patient agency as an important contributor to intervention outcome (Carey &

Stiles, in press; M. J. Lambert, 2013). However, patient agency may be difficult to assess due to the uniqueness and diversity of participants' personalities (Carey & Stiles, in press). Consequently, this factor may be difficult to control in clinical trials whilst its inadvertent interaction with randomisation when participants cannot be blind to the allocation (such as in psychological interventions) may compromise internal validity.

A further limitation of TAU was that it was not equivalent to the intervention in terms of attention to participants. For example, attending the intervention group was likely to have strengthened the alliance between patients and the staff team conferring additional benefits to addressing HSCT perceptions and coping. Control for such common (e.g., therapeutic alliance) or contextual factors (e.g., coherence; M. J. Lambert, 2013; Wampold, 2001) were not adequately controlled for in the study with effects in favour of the intervention due to reasons other than the assumed mechanism of change.

Overall, these considerations highlight limitations to the control strategy, the scope of processes that were examined, and the quantitative approach that measures relationships between variables to evince effects more generally. These limitations also characterise the wider HSCT research and the randomised clinical trial (RCT) paradigm more generally (Baliousis et al., in press; Carey & Stiles, in press; Kazdin, 2008), with several implications for improvement, as discussed in Section 8.6.

3.5.4.2.1.3 Study and instrumentation effects

The influence of the questionnaire interviews on participants and floor effects in the instruments posed additional threats to internal validity. As two participants indicated, the process of going through questionnaires prompted them to reflect on their experience and emotional reactions. It is, therefore, possible that participants' reports of distress, resilience, HSCT perceptions, and coping across time points may have been influenced by drawing attention to these experiences. Regarding floor effects, most DASS-21 scores were below clinical cut-offs; consequently, notwithstanding previous validation of the instrument, loss of sensitivity was possible, making intervention effects difficult to detect.

Additional limitations relating to the procedure included data collected retrospectively and social desirability. Recall of events can be inaccurate (Coughlin, 1990; Kruijshaar et al., 2005; Raphael, 1987) and biased by a range of factors such as emotional states, expectations, accessibility, and so forth (Eysenck & Keane, 2015; Schwarz, Kahneman, & Xu, 2009). Recall of coping appears especially affected by these issues (Schwartz, Neale, Marco, Shiffman, & Stone, 1999). Participants reported on their distress, resilience, HSCT perceptions, and coping based on their recall over the preceding week; therefore, their responses may have been biased by such factors. Furthermore, many questions were related to personal experiences and some questions requested feedback on the performance of clinical staff (e.g., distress, coping styles such as "I've been expressing my negative feelings", the treatment control item from the Brief IPQ "How much do you think the care you receive can help you through the transplant process?"). Participants may not have wished to disclose personal struggles to a stranger (outcome assessor) over the telephone or voice criticism towards clinical staff, resulting in socially desirable responding (Carnrike, 1997; Krumpal, 2013) and, therefore, additional bias.

3.5.4.2.1.4 Attrition

Baseline stress appeared to predict subsequent missing data. Whilst this does not mean that missing data resulted from higher stress at the time they were due, it highlights the possibility that this may have been the case. If so, any effects and relationships implicating stress may have been inaccurate, which threatens the internal validity of relevant findings. Furthermore, whilst no other relationships between missing data and outcome variables reached significance, the samples were small so that bias in the findings was difficult to assess fully and replication remains necessary. Attrition may also threaten external validity, as discussed below.

3.5.4.2.2 Threats to external validity

Threats to the external validity of the findings arose primarily due to sample characteristics, sampling bias, and the limited number of sites involved. Participants were entirely White-British, mostly males, older individuals,

married, with a diagnosis of multiple myeloma, and autologous transplants. Other subgroups were underrepresented so that results may not generalise to them and differences may have been missed in light of their small size. As distress, health concerns, and coping may manifest differently across cultures (Alonso et al., 1998; Ballenger et al., 2001; Minsky et al., 2003; Piccinelli & Simon, 1997), results may also not generalise to individuals of non-White-British background. Furthermore, reasons for not consenting to the study were noted but were not comprehensive and the characteristics of patients who did not consent were not recorded. Consequently, some of these patients may have been from distinct populations who were not represented in the study. Finally, results may also not generalise to individuals with higher stress or poorer physical functioning (performance status) as missing data may have been due to these factors.

In addition to sampling issues, the study was undertaken in the British NHS under times of unprecedented financial pressure affecting frontline services (Appleby, Galea, & Murray, 2014), which may have influenced care provision at the participating sites and, therefore, patients' distress and coping resources. Consequently, it is unclear whether findings would generalise to other countries, healthcare systems, and times. Such reasons may also contribute to the variability in distress trajectories reported across studies of distress in HSCT (Fife et al., 2000; Lee et al., 2005; Prieto, Atala, Blanch, Carreras, Rovira, Cirera, & Gastó, 2005; Schulz-Kindermann et al., 2002).

3.5.4.2.3 Threats to construct validity

These involve threats to validity due to limitations of the ability of instruments to measure the constructs they were intended for (McBurney & White, 2007). A range of measures were employed in the present project for measuring variables in connection with the hypotheses. All have received reasonable levels of validation across different populations but their application in the emerging field of HSCT has been minimal. Furthermore, items were open to interpretation by participants, which is inherent in such use of questionnaires despite standardisation (McBurney & White, 2007). In addition, some physiological items on the DASS-21 relating to anxiety appear

confounded with physical side-effects of HSCT. These items were removed but it is possible that the rest of the subscale may partly reflect physical functioning as well as anxiety in HSCT, unlike the populations in which the subscale was originally validated. Furthermore, the Brief IPQ and BRS are novel adaptations. In light of the lack of fit of the care control items with the rest of the Brief IPQ, it is possible that the constructs measured by these items is different compared to the original versions. Finally, the list of coping styles in the Brief COPE is not exhaustive and a bottom-up exploration in order to identify higher-order coping constructs in this population was not possible in the present study. It follows that many aspects of the construct validity of the instruments used in the study remains uncertain.

3.5.4.2.4 Threats to statistical validity

A range of statistical analyses were conducted and concerns with reliability of measurement, sample size, power, parametric assumptions, and some shortcomings of MLM threatened the validity of findings. A major limitation was the relatively low (and at times very low) internal consistency of some scales, for example, anxiety at later time points, resilience on the day of the transplant, and several coping styles. It is possible that this increased measurement error and resulted in wider confidence intervals thereby underestimating effects and inflating Type II error (Field, 2013; McBurney & White, 2007). The relatively small number of participants (Level 2 units in MLM) may have also inflated Type II error and biased parameter estimates, particularly in analyses relating to participant characteristics (Field, 2013; Snijders & Bosker, 2012).

There were parametric assumption violations in the data with those of normality particularly widespread. Whilst bootstrapping, nonparametric, and robust tests may have partly mitigated violations and biases due to the small sample size, the effectiveness of bootstrapping for MLM in particular is less clear. Indeed, it has shown promise in providing unbiased estimates for fixed effects when samples are large but may be less effective in doing so for random effects or small samples (J. R. Carpenter, Goldstein, & Rasbash, 2003; Maas & Hox, 2004; Seco, García, García, & Rojas, 2013; Snijders & Bosker, 2012). In

addition, ANOVA tests are exact whilst those in MLM are approximate (Snijders & Bosker, 2012) yielding results that may be less accurate. This may have been more prominent for the few models that did not converge when random effects were examined, since it was not possible to obtain parameter estimates adjusted for variability across participants. Finally, the process of examining assumption violations in MLM is not as rigorous as for classic statistics and it is not always clear whether clustering (repeated measurements by each participant) is fully controlled for (Field, 2013; Snijders & Bosker, 2012).

A final note concerning Type I error is necessary. Measurement error, loss of power, conservative and robust analyses, and evaluating overall model improvements in MLM prior to examining specific effects (fixed and random parameters) may have partly mitigated probability of Type I error. Nevertheless, the number of tests that were conducted was large and it is possible to have identified effects where none were present. Consequently, replication of the current findings remains necessary.

3.5.4.3 Summary

The study demonstrated several methodological strengths that support the validity of findings including two-site involvement, examination of psychological processes, detail of feasibility variables, assessment of sampling bias, and robust analyses. However, the study also contains a number of limitations. Inability to establish causality, the number of possible uncontrolled confounders and covariates, procedural effects (e.g., going through the questionnaires influencing participants' responses), limitations to the instruments, and attrition may limit the internal validity of the research. In addition, sample and site characteristics together with a demanding NHS context may restrict external validity whilst lack of clarity regarding the validity of the assessments and a nonexhaustive coping list indicate limitations to construct validity. Finally, limited reliability of some measurements, small sample sizes, lack of power, assumptions violations, and lack of clarity regarding the ability of MLM to control for these threaten statistical validity. Consequently, caution remains essential when considering the present findings.

Notwithstanding these issues, the findings have several clinical and research implications, discussed below.

3.5.5 Clinical implications

The findings indicate limitations to the feasibility in delivering the intervention (though confounded with limited feasibility of conducting the trial itself) but provided some support for its purpose. This support is reflected in the complex emotional needs that emerged during HSCT and the role of HSCT perceptions and coping in underpinning distress. In light of the barriers to uptake and attendance, it appears that a preparatory intervention could be better integrated with current care provision alongside some outreach.

A range of methods could be employed to address negative perceptions of HSCT. The intervention has drawn primarily on psychoeducation and exploration but the findings on the range of specific negative perceptions of HSCT underpinning distress suggest that teaching patients to identify and challenge these might be of benefit. Such applications of the self-regulatory model extending beyond psychoeducation but remaining brief and targeted to specific perceptions have shown promise in alleviating distress and improving coping (Broadbent et al., 2009; K. M. Keogh et al., 2011).

The intervention also purported to facilitate more helpful coping by increasing approach-based and decreasing avoidance-based coping. The latter is supported by the findings. In contrast, aspects of the intervention relating to approach-based coping may need to be developed further in light of the ineffectiveness of planning and support seeking. Enhancing social resources may be a way of improving the effectiveness of these styles, as discussed in Section 8.2.2. A viable way of doing so could be via peer mentoring, as initial literature on its usefulness has highlighted that HSCT patients view it as a valued resource and it can help them plan for the procedure better (Rini et al., 2007). It can also help attenuate fears in relation to HSCT (Rini et al., 2007), thus addressing some of the negative perceptions of the procedure. Allowing peer mentors to contribute to the intervention and enabling patient contact with this resource throughout the acute phase of HSCT could be options for augmenting the intervention helpfully.

Promoting cognitive acceptance of and engagement with the distressing experience (Hulbert-Williams et al., 2015) could provide a helpful alternative, emotion-focussed strategy when resources are lacking. Such methods have often involved mindfulness in HSCT (Bauer-Wu et al., 2008; Horton-Deutsch et al., 2007). As this literature is uncontrolled, the advantages of mindfulness in HSCT have not been established, but well-documented benefits in other clinical populations (Carlson et al., 2004; Hulbert-Williams et al., 2015; Ott et al., 2006) suggest that such methods may be valuable approach-based additions to coping with HSCT. The intervention could introduce the practice of mindfulness as an alternative coping mechanism when resources are limited as well as facilitating other types of approach-based coping when resources are available.

In sum, both the feasibility and theoretical findings of the present project provided indications for the development of the intervention. A preparation group that is well-integrated with clinical care, aims to offer psychoeducation relating to HSCT perceptions and coping, widens the coping styles of patients to include mindfulness-based methods, and facilitates peer support may be particularly helpful.

3.5.6 Research implications

Findings on the feasibility issues and the role of negative HSCT perceptions and unhelpful coping in underpinning distress together with weaknesses in the study have several implications for further research. These implications include adjustments to the design and procedure to improve feasibility and areas of further investigation in relation to HSCT perceptions, coping, mechanisms of change in the intervention, and physical outcomes. Further detail regarding these implications is provided below.

3.5.6.1 Design and procedure

An alternative design could circumvent some of the feasibility issues whilst enhancing the control condition and addressing sampling and attrition issues may mitigate some threats to internal validity. A cluster randomised design with crossover (D. Wang & Bakhai, 2006) could help address some barriers to conducting the trial posed by randomised control and the recruitment

procedure at each site. With this method, each site (cluster) would be randomly allocated to intervention or control. Consequently, prospective participants could be provided with information about the study and be invited to the group upon referral to the service (at sites allocated to the intervention), thus reducing the length of the recruitment and allocation process. All consenting patients would also be able to participate in the intervention at the relevant sites. The resulting higher accrual rates could allow groups to take place more frequently, prior to patients' transplantation dates. However, cluster randomisation could introduce a higher risk of outcome assessor bias, since deblinding regarding one participant could result in deblinding regarding all other participants at the same site.

A disadvantage of a cluster randomised design is that potential differences between clusters (sites) could unbalance the samples (D. Wang & Bakhai, 2006). Differences between sites may not be significant (as in the present findings) but this may not be replicated if additional sites are used and if power increases with larger samples. Potential confounding could be controlled by reversing the condition allocated to each site once a crossover point is reached, for example, when 50% of the target sample has been recruited (D. Wang & Bakhai, 2006). The problems with outcome assessor bias in the event of deblinding could be further mitigated if the outcome assessor is also blind of the crossover point. Introducing more than one crossover point (e.g., when 25% of the target sample has been recruited), may mitigate this risk further but doing so could burden the staff teams administratively (e.g., change the scheduling of the group) thereby increasing the likelihood or procedural error.

Three other adjustments could enhance the control condition and improve control for sampling and attrition bias to address threats to internal validity. The control condition could be more structured than TAU in the present study, to match the intervention both in form and staff attention to participants. The amended control condition could include a preparatory group meeting with focus on communicating empathy and building alliance with staff (common factors; Wampold, 2001) without the assumed active ingredients of the intervention, that is, challenging negative HSCT perceptions and facilitating helpful coping. However, maintaining these boundaries may be challenging as patients may ask for further information or advice during the meeting and it may

be unethical (or infeasible) for staff to deny such requests. Furthermore, inviting the heavily burdened HSCT patients to participate in a group which does not aim to offer direct benefits may not be easily justifiable ethically.

The final two adjustments may help 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 of their illness and treatment (Moyer et al., 2009) and this may be more prominent during acute HSCT due to the intensity of the procedure (Antoni et al., 2001; Copelan, 2006). Identifying characteristics of patients who decline to participate may help assess the representativeness and accuracy of findings. Developing rapport with participants and supporting them with completing the questionnaires via direct contact may reduce attrition and stress (particularly due to the added burden of the research procedure) with similar benefits, though it may also increase the likelihood of deblinding the outcome assessor.

3.5.6.2 HSCT perceptions and coping

Future research should elucidate the role of HSCT perceptions and coping in underpinning distress further. The present findings highlight a range of negative HSCT perceptions that appear to underpin distress. However, HSCT is complex and has many complications (Antoni et al., 2001; Copelan, 2006) but the relevant questions of the Brief IPQ were broad and, therefore, it was not possible to examine how these complications interacted with perceptions (e.g., what consequences patients perceive on their lives) in detail. Such an investigation could provide further evidence for the applicability of the self-regulatory model and could help accelerate the process of identifying and addressing specific negative perceptions in intervention. The task is likely to benefit by qualitative inquiry which is able to provide a more nuanced level of detail than the Brief IPQ.

Further validation of the novel Brief IPQ for HSCT is needed to verify findings and particularly clarify the relationship between coping appraisals and distress. The lack of relationship may be accurate but the role of coping

appraisals in underpinning distress in HSCT may also be complex and not captured in the present study or the null result may be due to limitations of the Brief IPQ. Further validation of the coping appraisal items could involve examining convergent validity, for example, by correlating these items with measures of self-efficacy (Hagger & Orbell, 2003).

Further research on coping in HSCT is needed to explore higher-order categories, reasons for the ineffectiveness of planning and support seeking, and the usefulness of mindfulness-based coping. As the outcomes and groupings of coping styles differ across populations, exploring higher-order categories in a bottom-up manner is considered essential (Folkman & Moskowitz, 2004; Ogden, 2012; Taylor & Stanton, 2007). Doing so in HSCT may allow a better understanding of the general types of coping patients use and their outcomes, mitigate limitations to the reliability of measurement (since larger scales are likely to be more reliable; Field, 2013), and conserve statistical power (by conducting fewer tests; Field, 2013). Examining the resources available to patients and their interaction with coping styles may help elucidate reasons for the ineffectiveness of planning and support seeking and help develop alternative ways of supporting patients to cope. As the present findings in conjunction with prior literature (Bauer-Wu et al., 2008; Horton-Deutsch et al., 2007; Schoulte et al., 2011) indicate that mindfulness-based coping may be more helpful to HSCT patients relative to other strategies, incorporating this strategy in future investigations appears necessary in the process of exploring how to improve coping in this population.

3.5.6.3 Mechanism of change

Common therapeutic factors (e.g., therapeutic alliance) have been found to contribute to intervention outcome in various populations including HSCT (Applebaum et al., 2012; M. J. Lambert, 2013). It follows that future investigations into the effectiveness of the intervention may benefit by examining the contribution of common factors to outcome alongside the effects of addressing negative HSCT perceptions and unhelpful coping. Such comprehensive process examinations remain largely absent from the HSCT literature (Baliousis et al., in press) but could strengthen conclusions regarding

the mechanism of change and inform further development of interventions. However, in light of the feasibility findings, any added burden on participants may compromise uptake and retention.

3.5.6.4 Physical outcomes

There is a need to improve physical outcomes in HSCT (Anderson et al., 2007; Antoni et al., 2001; Bhatia et al., 2007; Copelan, 2006; Mosher et al., 2009). Distress can predict physical burden and mortality following the procedure (Prieto et al., 2002; Pulgar, Garrido, Alcala, & Reyes del Paso, 2012; Schulz-Kindermann et al., 2002) whilst negative perceptions and unhelpful coping may predict physical status and behaviours promoting recovery (e.g., medication adherence) in various clinical populations (Cherrington, Moser, Lennie, & Kennedy, 2004; Hagger & Orbell, 2003; Zoeckler, Kenn, Kuehl, Stenzel, & Rief, 2014; Zyrianova, Kelly, Sheehan, McCarthy, & Dinan, 2011). It follows that the present intervention for distress may be helpful in in improving physical outcomes also. Such an effect was not assessed in the present study but could be examined in future research to ascertain the extent to which the intervention can meet the broader needs of HSCT patients and help maximise the benefits of the intervention.

In sum, future research could address feasibility issues and threats to validity by adopting a cluster randomised design with crossover, enhancing the control condition, and other adjustments. Further research on theoretical aspects could explore the relationship between the circumstances of HSCT and patients' perceptions of the procedure, the role of coping appraisals in underpinning distress, the validity of the Brief IPQ, the nature of coping in HSCT and reasons for ineffectiveness, and mechanisms of change. Focus on physical outcomes may be helpful towards meeting the broader needs of patients. Overall, replication and further exploration in different patient subgroups, other cultures, and settings remains necessary.

3.5.7 Conclusions

The present study examined the feasibility of delivering and evaluating a group-based psychological intervention to alleviate distress during acute HSCT. The study also assessed the applicability of the self-regulatory model in this population. The findings highlight considerable feasibility issues with delivering the intervention and conducting the research. These issues suggest a need to integrate the intervention better within routine care and adopt an alternative design such as cluster randomisation with crossover. Control for sampling and attrition bias could also improve. Other aspects of the research procedure and most assessments appear feasible and appropriate for a full trial.

The findings support the self-regulatory model as a basis for the intervention. HSCT perceptions and coping appear to underpin distress as a facet of adjustment to the procedure. A range of negative perceptions of HSCT (e.g., consequences, length, etc.) and several coping styles including those considered helpful in other populations seem to predict more distress. The intervention could aim to address specific negative perceptions, reduce avoidance-based coping, extend access to resources and information for effective use of approach-based coping, and promote mindfulness-based coping. Overall, replication in other samples and settings remains necessary.

3.5.8 Reflections

The three years of training in clinical psychology have provided a unique opportunity to develop professionally and personally. The research component has been a major contributor to this. I believe that applying psychological theory and research methods as part of the present study has been instrumental in furthering my insights into the processes of research and service development in clinical psychology. This section discusses some of these reflections.

3.5.8.1 Research process

New insights involved the process of formulating research questions, recognising ethical implications of the power imbalance between professional and participant (especially for those who are also patients), and reappraising

the methodological approach to the present project and its epistemological assumptions.

3.5.8.1.1 Formulating research questions

At the beginning of the doctoral programme, I noticed that I experienced difficulty developing a research question, finalising the psychological intervention, and identifying a theoretical background to inform its development. Consequently, I drew extensively on supervisors' experience and guidance. This was in contrast to methodological aspects where I found myself better able to generate and reflect on ideas. At first, the difficulty with the conceptual aspect of the research had alarmed me as I believed at the time that I lacked an essential skill in clinical psychology and in being able to engage in research.

As the project progressed, I developed detailed familiarity with the population and its difficulties via reflecting on the literature, conversations with colleagues and participants, and analysing the data. This resulted in a keen interest in making a difference as a clinical psychologist in HSCT, which resulted in identifying numerous questions about how this might be achieved. For example, I became curious about how patients experience distress, why might their coping be helpful or otherwise, whether empathy and unconditional positive regard during their times of vulnerability might also play a role in alleviating distress, whether distress predicts physical recovery and mortality in the longer-term, and so forth.

All of these questions could be translated into research. Coming to this realisation, highlighted the importance of developing a nuanced clinical understanding of the population and the research area for guiding investigations. This experience also delineated the distinctions between the procedure and substance of research in clinical psychology, where the former involves its mechanics and can be learnt whilst the latter reflects an authentic interest in investigation towards a clinical end.

3.5.8.1.2 Power imbalance and research ethics

An ethical dilemma emerged early during the project and provided a useful opportunity to explore relevant processes, personal assumptions, and

develop more person-centred participant engagement skills. As I called participants to complete the questionnaires during the acute phase of HSCT, several were unable to respond to the initial attempts or repeatedly requested that we reschedule. At first, my interpretation was that I was harassing them when they wished to withdraw and that they were reluctant to say so due to the power differential between practitioner and patient. I saw continuing the attempts to contact participants under these circumstances as against my ethical principles of professional benevolence and avoiding harm and, ultimately, as oppressive. These beliefs cause me anxiety and led me to avoid making further telephone calls after initial unsuccessful attempts.

This solution highlighted a barrier to conducting research both in the present and future projects and indicated a need to explore the issue in supervision. My supervisors, who were experienced in conducting clinical trials, highlighted that continuing the attempts to call participants in a collaborative manner until participants express a wish to withdraw reflects standard practice. Following this conversation, I experimented by adopting such an approach whilst communicating the right to withdraw to participants empathically in conversations or via messages as appropriate. Doing so appeared to address partly the power differential and allow some participants to withdraw consent gratefully. It also allowed the project to continue without unnecessary loss of data.

This experience also enabled me to review my assumptions regarding how participants viewed the research procedure. When asked about their feedback regarding telephone calls and potential intrusiveness, no participant described the procedure in such terms. There may have been some influence of social desirability but the feedback appeared genuine as participants volunteered comments on my flexibility as interviewer and on feeling no pressure to respond. For example, participants expressed appreciation for being allowed to determine the timing of subsequent calls or withdraw from the study and for my willingness to work around their schedules. This feedback disconfirmed my initial beliefs that participants were becoming frustrated and oppressed by participating in the research. Such beliefs are now less likely to pose a barrier to conducting future research with highly distressed participants.

3.5.8.1.3 Methodological and epistemological considerations

The quantitative methodology in the present project reflected my familiarity with and value of this approach upon beginning the doctoral training. This quantitative orientation was embedded within the medical context of my previous research work within psychiatry. However, my perspective began to shift as barriers to conducting an RCT emerged in the present project and as my familiarity with the topic and alternative research methods (e.g., qualitative, single case) increased during training. I also became more person-centred and appreciative of multiple perspectives in clinical practice, which allowed me to note that the present research data is unable to capture the nuance of participants' experiences. As a result, I concluded that many of my research questions in relation to psychological distress in HSCT (such as those described in the reflections earlier) might be answered less easily via quantitative methods and I have become more reserved towards the realist perspective that often underpins such methods (Carey & Stiles, in press; Deacon, 2013; Donmoyer, 2012; Gottdiener, 2011). In contrast, I have valued increasingly the contribution of alternative approaches that enable more incisive, interpretative, qualitative exploration fit for revealing the nuance of psychological experience, even when evaluating and developing psychological interventions.

3.5.8.2 Service development and clinical psychology

Having begun a Doctorate in Clinical Psychology upon submitting a PhD thesis, my ambitions regarding a three-year research project extended beyond a feasibility study. However, I decided to focus on the present project (a feasibility study) in recognition that I had little idea about the process of developing interventions and probably underestimated the importance of exploring feasibility issues in conducting relevant research.

Indeed, feasibility issues were abounding in the present project, which, in turn, allowed me to recognise the ubiquity of unintended consequences when implementing plans. This insight coincided with my nascent interest in organisational theory and particularly Complexity theory (Cilliers, 1998) in the context of service development in clinical psychology. Complexity theory

highlights the limitations of traditional conceptualisations of service development as a planned, top-down process determined by the persons who appear to engineer it (Weick & Quinn, 1999), in this case myself and the clinical psychologists involved in the project. Instead, it suggests that the process of development emerges from unique and iterative contributions by a range of agents (including its assumed engineers) and factors involved, as appeared to occur in the present study.

Using this perspective to make sense of my research experience enabled me to appreciate the range of possible factors that influenced the implementation of the present project. To name but a few, colleagues were unable to recruit participants as planned due to resource cuts, there were delays with starting recruitment, transplants were cancelled unpredictably, I was willing to contact participants outside standard working hours so that I could complete my doctoral training, and so forth. In my eyes, unintended consequences became an inherent part of service development and now I consider feasibility studies a necessity in exploring the nature and impact of such unexpected outcomes. Overall, I learnt to view the role of clinical psychology as key in coordinating the process of change with the core skills of communication, assessment, meaning-making (formulation), intervention, reflection, and scientist-practitioner working as vital parts of the work.

3.5.9 Epilogue

Overall, engaging in doctoral-level research as part of clinical psychology training has highlighted the many ways in which such activity is important to the role and its added value. During the training programme, my ultimate research aim was to produce findings whose implications would bear direct relevance to clinical work. I believe I have achieved this in light of how my ideas about supporting HSCT patients developed and how the practice of my field supervisors has changed.

However, I have also become acutely aware of the barriers to such activity in a pressured NHS. Having completed a PhD with sole focus on research just prior to the current training which allocates one day per week to research, I realised that time and resource limitations to this type of work can

restrict the impact of research considerably. During the training programme, I found myself contributing considerably more time than what was timetabled for the research. In light of the pressures facing services currently, resourcing demands are likely to increase further and risk diminishing this part of the role as direct clinical work becomes prioritised. I found this prospect concerning for the profession as it appears to strip what I have come to see as an essential component of its added value. If prolonged, this eventuality may alter the discourse about what clinical psychologists can contribute to services and pave the way for devaluation.

At the same time, I am unwilling to forego such a rewarding and seemingly essential component of the role and have contemplated on different ways of working. Drawing on the ideas of Complexity theory and social constructionism, I have wondered whether discursive “interventions” that aim to promote questioning in staff teams, foster a reflective process, critique, exchange of ideas, and so forth, could highlight the importance of scientific investigation and promote greater research engagement within the wider system. In this context, the focus in the work of clinical psychologists could be on a conceptual level in a more facilitative than engineering role. However, in light of a changing context of service delivery and the apparent inevitability of unintended consequences when implementing plans, it is unclear how such “interventions” might play out. Perhaps this calls for a feasibility study to understand the process better.

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4 APPENDICES

Appendix A

Guidelines for Referral to Clinical Psychology Service for Patients with Haematological Cancer

Referrals can be made from Haematology Consultants, Haematology Specialist Registrars (following discussion with Consultant) and Haematology Clinical Nurse Specialists.

Patients will normally be offered an appointment at the out-patient area within the Haematology Unit. Patients offered an assessment and up to six appointments, depending on their needs. Each appointment will usually last between 30 - 50 minutes and appointments may be offered on a weekly, fortnightly or monthly basis.

Please ensure that the reason for referral is discussed with the patient and that consent to the referral is obtained.

Referrals can be made in writing to Dr. [name], Clinical Psychologist, [address].

Alternatively a Clinical Psychology referral form can be completed.

Please highlight any access issues or communication needs so that I can actively support patients to engage with the service.

Examples of appropriate referrals

This service is funded to work with people struggling to cope with haematological cancer or other issues arising as a result of their disease, where the health professionals involved feel unable to provide the level of emotional support needed.

Some examples of the issues I work with are:

1. Patients who have difficulty coping with the stress of their illness or related issues

2. Patients who have difficulty coping with feelings of anxiety, panic or depression arising from their illness

3. Patients who re-live or remember past traumatic experiences associated with their illness

4. Patients who are struggling with body image issues arising from their illness

5. Patients who are struggling to cope psychologically where this impacts on treatment concordance

6. Psychological components of pain, fatigue or anticipatory nausea and vomiting associated with their illness

7. Fear about impending medical procedures where this impacts on treatment

8. Loss and adjustment issues related to having cancer

Patients **not suitable** for a referral to the Haematology Clinical Psychology Service

1. Mental Health Emergency. A working definition of a mental health emergency is when a person's thoughts and feelings are beyond their control. This may include:

- *Posing a serious risk to themselves or others*
- *Actively suicidal / self harming*
- *Psychotic episode*

The Psychology Service is not an emergency service and cannot respond to an emergency or cancel planned patient appointments to respond to an emergency. **In case of emergency, please contact Liaison Psychiatry.**

2. Difficulties relating to longstanding severe mental health problems such as psychosis, bipolar disorder, severe mood disorders and personality disorders.

3. Active alcohol and drug difficulties or misuse

4. Less severe mental health difficulties that are not related to issues arising from their cancer. However I can undertake an assessment with a view to onward referral to a mental health service.

Many of these patients will be linked with mental health teams or psychiatric services, therefore speaking directly with the teams involved (with patient consent) may be of most benefit.

I am available to discuss cases with the team. Please contact me on [extension]

Pro-forma	*ID:*	*Date:*
Demographics		
1	Age:	_____ years
2	Gender:	1-Male 2-Female
3	Ethnicity:	1/2-White (British/other) 3/4-Asian (British/other) 5/6-Black (British/other) 7-Mixed 8-Chinese 9-Middle Eastern 10-Other: _____ 998-Prefer not to say
4	Marital status:	0-Divorced or separated 1-Married/civil partnership/ cohabiting 2-Single 3-Widowed 998-Prefer not to say
5	Educational background:	0-Mainstream 1-Further 2-Higher 3-Other: _____
Procedural		
1	Disease:	_____
2	Number of recurrences:	_____
3	Type of recurrences:	_____
4	Year of 1st diagnosis:	_____
5	Type of transplant:	0-Autologous 1-Allogeneic
6	Conditioning intensity:	0-Reduced intensity conditioning 1-Myeloablative
7	Baseline Performance Status?	___
8	Length of hospital stay for transplantation:	_____ days
9	Referral to psychologist during transplantation:	0-No 1-Yes
10	Non-concordant events	
	- Leaving isolation room:	0-No 1-Yes: _____ days
	- Intensive care admission:	0-No 1-Yes: _____ days
11	Disease status	0-Complete remission 1-Partial remission 2-Stable 3-Progressive disease
12	Other:	_____

Appendix C

DASS21	*ID:*	*Date:*			

Please read each statement how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

Appendix D

Brief Resilience Scale

ID: *Date:*

The following questions are about how your transplant process have affected you ***over the past week***. Use the following scale and **circle** one number for each statement to indicate how much you disagree or agree with each of the statements.

The rating scale is as follows:
1 Strongly Disagree
2 Disagree
3 Neutral
4 Agree
5 Strongly Agree

1	So far, I have been bouncing back quickly since this hard time began……	1	2	3	4	5
2	I have had a hard time making it through this stressful event……	1	2	3	4	5
3	It has not been taking me long to recover from this stressful event…….…….	1	2	3	4	5
4	It has been hard for me to snap back since this happened……...……..	1	2	3	4	5
5	So far, I have come through this difficult time with little trouble..……..…….	1	2	3	4	5
6	I have been taking a long time to get over this set-back in my life……..……..…….	1	2	3	4	5

Brief COPE

ID: *Date:*

These items deal with ways you've been coping with the stress in your life *over the past week*. There are many ways to try to deal with problems. These items ask what you've been doing to cope with this one. Obviously, different people deal with things in different ways, but I'm interested in how you've tried to deal with it. Each item says something about a particular way of coping. I want to know to what extent you've been doing what the item says. How much or how frequently. Don't answer on the basis of whether it seems to be working or not-just whether or not you're doing it. Use these response choices. Try to rate each item separately in your mind from the others. Make your answers as true FOR YOU as you can.

The rating scale is as follows:
1 I haven't been doing this at all
2 I've been doing this a little bit
3 I've been doing this a medium amount
4 I've been doing this a lot

1	I've been turning to work or other activities to take my mind off things.	1	2	3	4
2	I've been concentrating my efforts on doing something about the situation I'm in.	1	2	3	4
3	I've been saying to myself "this isn't real.".	1	2	3	4
5	I've been getting emotional support from others.	1	2	3	4
6	I've been giving up trying to deal with it.	1	2	3	4
7	I've been taking action to try to make the situation better.	1	2	3	4
8	I've been refusing to believe that it has happened.	1	2	3	4
9	I've been saying things to let my unpleasant feelings escape.	1	2	3	4
10	I've been getting help and advice from other people.	1	2	3	4
12	I've been trying to see it in a different light, to make it seem more positive.	1	2	3	4
13	I've been criticizing myself.	1	2	3	4
14	I've been trying to come up with a strategy about what to do.	1	2	3	4
15	I've been getting comfort and understanding from someone.	1	2	3	4
16	I've been giving up the attempt to cope.	1	2	3	4
17	I've been looking for something good in what is happening.	1	2	3	4
18	I've been making jokes about it.	1	2	3	4
19	I've been doing something to think about it less, such as watching TV, reading, daydreaming, or sleeping.	1	2	3	4
20	I've been accepting the reality of the fact that it has happened.	1	2	3	4
21	I've been expressing my negative feelings.	1	2	3	4

23	I've been trying to get advice or help from other people about what to do.	1	2	3	4
24	I've been learning to live with it.	1	2	3	4
25	I've been thinking hard about what steps to take.	1	2	3	4
26	I've been blaming myself for things that happened.	1	2	3	4
28	I've been making fun of the situation.	1	2	3	4

Brief IPQ

ID: *Date:*

For the following questions, please indicate the number that best corresponds to your views about the process of your transplant *over the past week*:

1 **How much does the transplant process affect your life?**

0 1 2 3 4 5 6 7 8 9 10

no effect at all — severely affects my life

2 **How long do you think the transplant process will continue?**

0 1 2 3 4 5 6 7 8 9 10

a very short time — forever

3 **How much control do you feel you have over the transplant process?**

0 1 2 3 4 5 6 7 8 9 10

Absolutely no control — extreme amount of control

4 **How much do you think the care you receive can help you through the transplant process?**

0 1 2 3 4 5 6 7 8 9 10

not at all — extremely helpful

5 **How much do you experience symptoms from the transplant process?**

0 1 2 3 4 5 6 7 8 9 10

no symptoms at all — many severe symptoms

6 **How concerned are you about the transplant process?**

0 1 2 3 4 5 6 7 8 9 10

not at all concerned — extremely concerned

7 **How well do you feel you understand the transplant process?**

0 1 2 3 4 5 6 7 8 9 10

don't understand at all — understand very clearly

8 **How much does the transplant process affect you emotionally? (e.g., does it make you angry, scared, upset or depressed?)**

0 1 2 3 4 5 6 7 8 9 10

not at all affected emotionally — extremely affected emotionally

Appendix G

Development and evaluation of a psychological intervention to alleviate distress during haematopoietic stem-cell transplantation

An invitation to participate

You are invited to take part in a research study. The study aims to find out whether a new programme of psychological support prior to haematopoietic stem-cell transplantation helps people cope better psychologically with the treatment.

The study compares the new programme of support with the support currently available. So, if you participate, you may or may not be offered the new programme in addition to the support currently available. The results of this study will help clarify whether the new programme provides an added benefit. This may enable us to make it routinely accessible to patients like you in the future. Your transplant itself will not be affected in any way by your decision whether to participate in this study.

Participation in the study will involve four 15-minute conversations over the telephone over a period of approximately six weeks beginning shortly prior to your transplantation. During these interviews, a researcher will ask you a series of questions about your experience and how you are coping. Some participants will be asked to attend a meeting of several patients awaiting a transplant at [*Site*] for approximately one hour. During this meeting a clinical psychologist, physiotherapist and bone marrow transplant coordinator will discuss how to cope with the transplant. Some participants may also be invited to take part in a longer telephone interview (up to half an hour) asking about your experiences.

For more information about the study and taking part please contact your bone marrow transplant coordinator or site clinical psychologist who will be happy to provide further details, answer your questions, and enrol you in the study. Their contact details are below:

[*Clinical Psychologist and Bone Marrow Transplant Coordinator contact details*]

Appendix H

Participant Information Sheet
(Draft Version 1.0: 9th May 2014)

Title of Study: Development and evaluation of a psychological intervention to alleviate distress during haematopoietic stem-cell transplantation.

Name of Researcher(s): Dr Michael Baliousis, Dr Michael Rennoldson, & Dr Roshan das Nair.

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

The purpose of the study is to evaluate a new programme of psychological support developed to facilitate tolerance of distress in patients undergoing haematological stem-cell transplantation.

Why have I been invited?

You are being invited to take part because you will be undergoing haematological stem-cell transplantation for a haematological cancer soon. We are inviting 60 individuals like you to take part.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?

Your involvement in the study will begin a short while prior to the transplantation and will end approximately four weeks following transplantation. As part of your participation, you will be offered the support already available to all patients during transplantation and may or may not be offered the new programme which is being evaluated in the study. However, we will not be able to let you know whether you have been offered the new intervention until the end of your participation as this may affect your responses in the meantime. All support and interventions will be delivered by the members of your transplant team at the location of your transplantation.

During your participation, you will be contacted four times over the telephone by one of the researchers (Michael Baliousis) who will ask you some questions about your

feelings, thoughts and actions over the preceding week. The interviews will take place prior to the transplant, on the day of the transplant, two weeks following transplantation, and four weeks following transplantation. Each call will last approximately 15 minutes. While you are an inpatient, the researcher will gain permission from a member of staff looking after you on the day of each telephone call to ensure that it will not inconvenience you. Once these interviews have taken place, you may be invited to take part in a longer telephone interview (up to half an hour) asking about your experiences of the intervention and how you used what you learnt.

Expenses and payments

It is not anticipated that you will incur any expenses as a result of participating in the study and no travel will be required. It is not possible to pay participants to participate in the study.

What are the possible disadvantages and risks of taking part?

This study involves receiving different types of support in preparation for the transplantation procedure. The types of support available to date have been used extensively and have not posed any risks. The new programme has already been piloted with patients like you and no negative effects have been reported.

What are the possible benefits of taking part?

You may or may not be offered the new type of support as a result of taking part in the study but, should you receive it, we cannot promise that it will provide you with additional benefits to support already on offer. Indeed, it is the information we will get from this study that will show us whether the new programme is helpful to patients like you and, if so, it would enable us to make it more widely available to patients in the future.

What happens when the research study stops?

You will continue to be seen regularly by you bone marrow transplant team.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers or the clinical psychologist at your clinic who will do their best to answer your questions. The researchers' and clinical psychologist's contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by following the local complaints procedure. The Patient Liaison and Advice Service will be able to support you with this. Their contact details are also provided at the end of this document.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for 12 months after the end of the study so that we are able to contact you about the findings of the study (unless you advise us that you do not wish to be contacted) after which they be disposed of securely. All anonymised research data will be kept securely for 7 years and then will also be disposed of securely. During the 7 years, all precautions will be taken by all those involved to maintain your confidentiality and only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the Consultant Haematologist

Should you consent to take part in the study, we will notify your Consultant Haematologist of your participation.

What will happen to the results of the research study

The results of the study are likely to be presented in conferences and be submitted for publication in scientific journals relevant to clinical psychology and/or the field of clinical haematology within two years of its completion. The study will also be written up as part of a Doctorate in Clinical Psychology with the University of Nottingham. Any reported results will be aggregate and you will not be identified in any publication.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the NHS Health Education East Midlands via the Trent Doctoral Programme in Clinical Psychology.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by East Midlands Research Ethics Committee – Nottingham 1.

Further information and contact details

For further information or complaints please contact the researchers involved in the study or the clinical psychologist at your clinic who will do their best to assist you.

[*Contact details of Principal Investigator, Research Supervisors, site Clinical Psychologist, and Patient Liaison and Advice Service*]

Appendix I

CONSENT FORM
(Final Version 2.0 : 27th September 2014)

Title of Study: Development and evaluation of a psychological intervention to alleviate distress during haematopoietic stem-cell transplantation

REC ref: 14/EM/1095

Name of Researcher: Michael Baliousis

Name of Participant: **Please initial**

1. I confirm that I have read and understand the information sheet version number 1.0 dated 4th July 2014 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

5. I understand that some of my conversations as part of the support I receive by taking part in the study may be recorded. The researchers may listen to them for quality purposes and to improve the support that is provided. I understand that my personal details will be kept confidential. ☐

6. I agree to my Consultant Haematologist being informed of my participation in this study. ☐

7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent **(if different from Principal Investigator)**	Date	Signature
_____	_____	_____
Name of Principal Investigator	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

Appendix J

R code for robust MANOVA

```
#To load SPSS files:
library(foreign)
#To use melt and cast commands:
library("reshape")
#WRS is the package for robust MANOVA:
library(WRS)
#Load SPSS file and assign rows (variable “row):
BaseData<-read.spss("BaseRDistressRandArm.sav",use.value.labels=TRUE,
to.data.frame=TRUE)
BaseData$row<-c(1:24,1:21)
#Restructure data into long format, then rename columns to match variables.
baseMelt<-melt(BaseData, id = c("RandArm", "row"), measured =
c("Stressb","Anxietyb","Depressb"))
names(baseMelt)<-c("RandArm", "row", "Outcome_Measure", "Score")
#Restructure data into wide format and remove variable "row".
baseRobust<-cast(baseMelt, row ~ RandArm + Outcome_Measure, value =
"Score")
baseRobust$row<-NULL
#Robust MANOVA function:
mulrank(2, 3, baseRobust)
```

Appendix K

Research ethics committee approval letters

NHS
Health Research Authority
NRES Committee East Midlands - Nottingham 1

Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839428

22 August 2014

Dr Thomas Schröder
Associate Professor in Clinical Psychology & Co-Director
University of Nottingham
Division of Psychiatry and Applied Psychology
YANG Fujia Building, University of Nottingham
Jubilee Campus
NG8 1BB

Dear Dr Schröder

Study title:	**Development and evaluation of a psychological intervention to alleviate distress during haematopoietic stem-cell transplantation (HSCT)**
REC reference:	**14/EM/1095**
Protocol number:	**14069**
IRAS project ID:	**150976**

The Research Ethics Committee reviewed the above application at the meeting held on 12 August 2014. Mr Michael Baliousis attended to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager, Liza Selway, NRESCommittee.EastMidlands-Nottingham1@nhs.net.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

1. Ensure correct spelling of the word haematopoietic throughout documentation

2. Ensure consistent use of correct research title on the participant information sheet and invitation to participate.

3. Submission of valid insurance certification.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on question 2 of the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet been completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Summary of discussion at the meeting

Mr Michael Baliousis joined the meeting.

The Committee thanked the researcher for attending and presenting an interesting study.

Recruitment arrangements and access to health information, and fair participant selection

The Committee noted the Consultant Haematologist has the final approval on who participates within the study and queried what criteria would be used for this decision.

The researcher advised this was an additional safeguard for the participant in case the consultant knew of a reason why a particular patient might not be suitable to participate in the study that the multi-disciplinary team were unaware of.

Other general comments

Members of the Committee noted the insurance certificate was out of date.

The Committee noted the term haematopoietic is misspelt in a number of places in the documentation.

The Committee asked the Researcher whether the interview referred to was actually a questionnaire

The Researcher explained they are question type interviews but there will be some open ended interview questions for a sub group of 15 Participants.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]	1.0	04 July 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor insurance letter]		31 July 2013

GP/consultant information sheets or letters [Consultant letter]	1.0	04 July 2014
Interview schedules or topic guides for participants [Final interview schedule]	1.0	04 July 2014
IRAS Checklist XML [Checklist_21072014]		21 July 2014
Letter from sponsor [Sponsor letter]		07 July 2014
Letters of invitation to participant [Leaflet invitation to participate]	1.0	04 July 2014
Non-validated questionnaire [Demographics pro-forma]	1.0	04 July 2014
Other [Second Supervisor Summary CV]	1.0	24 July 2013
Participant consent form [Consent form]	1.0	04 July 2014
Participant information sheet (PIS) [Participant Information Sheet]	1.0	04 July 2014
REC Application Form [REC_Form_21072014]		21 July 2014
Research protocol or project proposal [Protocol]	1.0	04 July 2014
Summary CV for Chief Investigator (CI) [Chief Investigator Summary CV]	1.0	18 February 2013
Summary CV for student [Student Summary CV]	1.0	04 July 2014
Summary CV for supervisor (student research) [Supervisor Summary CV]	1.0	18 May 2013
Validated questionnaire [Appendix B - Brief Resilience Scale]	1.0	04 July 2014
Validated questionnaire [Appendix C - Brief COPE questionnaire]	1.0	04 July 2014
Validated questionnaire [Appendix A - Depression Anxiety Stress Scales - 21]	1.0	04 July 2014
Validated questionnaire [Appendix D - Brief Illness Perceptions Questionnaire]	1.0	04 July 2014

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

14/EM/1095	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Carl Edwards
Chair

E-mail: NRESCommittee.EastMidlands-Nottingham1@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Mrs Angela Shone,*
Ms Anna Leesley, Sheffield Teaching Hospitals NHS Foundation Trust

NHS
Health Research Authority
NRES Committee East Midlands - Nottingham 1
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839428

01 September 2014

Mr Michael Baliousis
Trent Doctorate in Clinical Psychology
Division of Psychiatry and Applied Psychology
YANG Fujia Building
University of Nottingham
Jubliee Campus
Nottingham
NG8 1BB

Dear Mr Baliousis,

Study title:	**Development and evaluation of a psychological intervention to alleviate distress during haematopoietic stem-cell transplantation (HSCT)**
REC reference:	**14/EM/1095**
Protocol number:	**14069**
IRAS project ID:	**150976**

Thank you for your letter of 1st September 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 22 August 2014

Documents received

The documents received were as follows:

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering letter on headed paper		01 September 2014
Covering letter on headed paper [Cover letter]	1.0	04 July 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		29 July 2014
GP/consultant information sheets or letters [Consultant letter]	1.0	04 July 2014

Interview schedules or topic guides for participants [Final interview schedule]	1.0	04 July 2014
IRAS Checklist XML [Checklist_21072014]		21 July 2014
Letter from sponsor [Sponsor letter]		07 July 2014
Letters of invitation to participant	2	01 September 2014
Non-validated questionnaire [Demographics pro-forma]	1.0	04 July 2014
Other [Second Supervisor Summary CV]	1.0	24 July 2013
Participant consent form [Consent form]	1.0	04 July 2014
Participant information sheet (PIS) [Participant Information Sheet]	1.0	04 July 2014
REC Application Form [REC_Form_21072014]		21 July 2014
Research protocol or project proposal [Protocol]	1.0	04 July 2014
Response to Request for Further Information		01 September 2014
Summary CV for Chief Investigator (CI) [Chief Investigator Summary CV]	1.0	18 February 2013
Summary CV for student [Student Summary CV]	1.0	04 July 2014
Summary CV for supervisor (student research) [Supervisor Summary CV]	1.0	18 May 2013
Validated questionnaire [Appendix A - Depression Anxiety Stress Scales - 21]	1.0	04 July 2014
Validated questionnaire [Appendix B - Brief Resilience Scale]	1.0	04 July 2014
Validated questionnaire [Appendix D - Brief Illness Perceptions Questionnaire]	1.0	04 July 2014
Validated questionnaire [Appendix C - Brief COPE questionnaire]	1.0	04 July 2014

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/EM/1095 **Please quote this number on all correspondence**

Yours sincerely

Miss Liza Selway
REC Manager

E-mail: NRESCommittee.EastMidlands-Nottingham1@nhs.net

Copy to: *Dr Thomas Schröder, University of Nottingham*
Mrs Angela Shone
Ms Anna Leesley, Sheffield Teaching Hospitals NHS Foundation Trust

NHS
Health Research Authority

NRES Committee East Midlands - Nottingham 1
Royal Standard Place
Nottingham
NG1 6FS
Tel: 01158839390

28 October 2014

Dr Thomas Schröder
Associate Professor in Clinical Psychology & Co-Director
University of Nottingham
Division of Psychiatry and Applied Psychology
YANG Fujia Building, University of Nottingham
Jubilee Campus
NG8 1BB

Dear Dr Schröder

Study title:	**Development and evaluation of a psychological intervention to alleviate distress during haematopoietic stem-cell transplantation (HSCT)**
REC reference:	**14/EM/1095**
Protocol number:	**14069**
Amendment number:	**SA#01**
Amendment date:	**24 October 2014**
IRAS project ID:	**150976**

The above amendment was reviewed on 28 October 2014 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP) [150976/685487/13/834/34691]		24 October 2014
Participant consent form	2.0	27 September 2014

Membership of the Committee

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

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/EM/1095:	**Please quote this number on all correspondence**

Yours sincerely

Dr Carl Edwards
Chair

E-mail: NRESCommittee.EastMidlands-Nottingham1@nhs.net

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

Copy to: *Ms Anna Leesley, Sheffield Teaching Hospitals NHS Foundation Trust*
Mrs Angela Shone

NHS
Health Research Authority
NRES Committee East Midlands - Nottingham 1
Royal Standard Place
Nottingham
NG1 6FS

Tel: 0115 8839697

02 June 2015

Mr Michael Baliousis
YANG Fujia Building
The University of Nottingham
Jubilee Campus
Wollaton Road
Nottingham
NG8 1BB

Dear Mr Baliousis

Study title:	**Development and evaluation of a psychological intervention to alleviate distress during haematopoietic stem-cell transplantation (HSCT)**
REC reference:	**14/EM/1095**
Protocol number:	**14069**
Amendment date:	**15 May 2015**
IRAS project ID:	**150976**

Thank you for your letter of 15 May 2015, notifying the Committee of the above amendment.

The Committee does not consider this to be a "substantial amendment" as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Notice of Minor Amendment [Extended data collection]		15 May 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

14/EM/1095:	**Please quote this number on all correspondence**

Yours sincerely,

Rachel Nelson
Acting REC Manager

Email: NRESCommittee.EastMidlands-Nottingham1@nhs.net

Copy to: *Ms Anna Leesley*

Dr Thomas Schröder

Ms Angela Shone

Intervention for distress during stem-cell transplantation: Feasibility issues and theoretical underpinnings

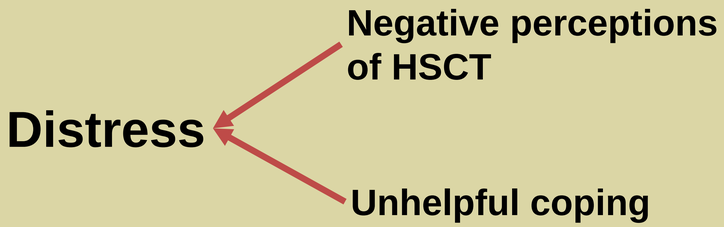
Michael Baliousis*, Michael Rennoldson, Dave Dawson, Jayne Mills, & Roshan das Nair

Trent Doctorate in Clinical Psychology

***Email: lwxmb8@nottingham.ac.uk**

Background

- The first weeks of haematopoietic stem-cell transplantation (HSCT) can be very distressing.[1]
- Feasibility issues and failure to draw on psychological models has hampered development of effective interventions.[2]
- We used the *self-regulatory model* [3] to develop such an intervention:



- Informational and coping components aimed to address negative HSCT perceptions and unhelpful coping.

Objectives

- Assess the feasibility of the intervention and methodology.
- Test the applicability of the self-regulatory model to HSCT.

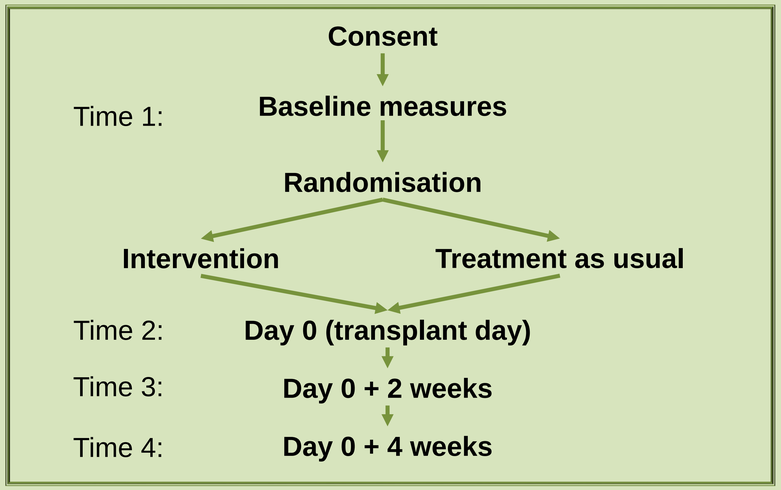
Method

Participants

- Recruited from consecutive referrals over 10 months.

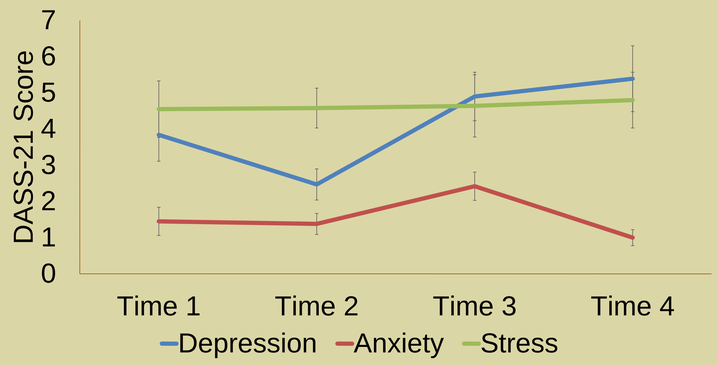
Measures

- *DASS-21*: Total distress, depression, anxiety, & stress.
- *Brief IPQ*: Negative perceptions of HSCT – consequences, duration, identity (HSCT's label and symptoms), understanding, concern, & emotional impact.
- *Brief COPE*: Helpful (e.g., active coping, seeking support) and unhelpful coping styles (e.g., denial, self-blame, etc.).

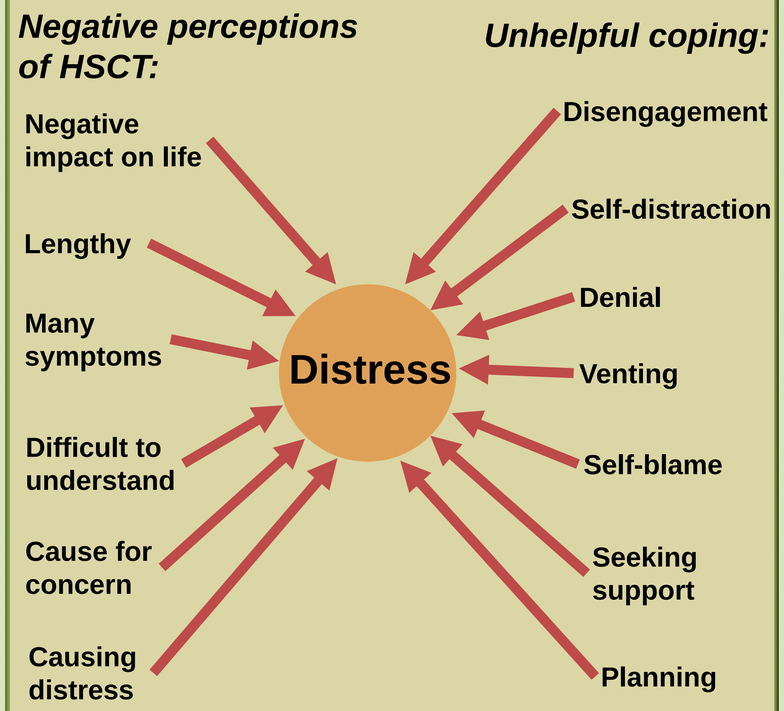


Results

- Forty-five of 99 approached patients consented: Unable to consent prior to transplant (*n*=18), procedure burden (*n*=18), unwell (*n*=7), no benefit (*n*=4), taking part in other studies (*n*=3), distressed (*n*=1), none given (*n*=3).
- Five of 21 patients randomised to the intervention attended: transplant too early (*n*=7), other priorities (*n*=4), travel delay (*n*=2), transplant cancelled (*n*=2), & intervention cancelled (*n*=1).
- Anxiety peaked at Time 3 but decreased thereafter.
- Depression increased continually.
- Clinical levels of distress in 42% of patients.



- No significant differences between participants randomised to intervention versus control, $\Delta\chi^2(\Delta df \leq 4) \leq 9.14$, $Ps > 0.05$. Similar results for attendees versus nonattendees.
- HSCT perceptions & coping predicted distress strongly:



Conclusions

- Complex psychological needs during acute HSCT.
- HSCT perceptions and coping underpin distress.
- Considerable barriers to conducting a randomised controlled trial and delivering a group intervention.
- Need of alternative research procedure and delivery.

References

1. Prieto, J. M., Atala, J., Blanch, J., Carreras, E., Rovira, M., Cirera, E., & Gastó, C. (2005). Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation. *Bone Marrow Transplantation, 35(3), 307-314. doi:10.1038/sj.bmt.1704788*
2. Baliousis, M., Rennoldson, M., & Snowden, J. A. (2015). Psychological interventions for distress in adults undergoing haematopoietic stem cell transplantation: a systematic review with meta-analysis. *Psycho-Oncology. doi:10.1002/pon.3925*
3. Ogden, J. (2012). *Health psychology (5th ed.). Maidenhead, England: Open University Press.*