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Randomised controlled trial of a psychosocial digital health application to promote coping for caregivers of patients undergoing haematopoietic stem cell transplantation: a study protocol for the BMT-CARE app

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ABSTRACT

Introduction Caregivers of patients undergoing haematopoietic stem cell transplantation (HSCT) experience tremendous psychological distress before, during and after HSCT. However, few interventions are tailored to the protracted needs of these caregivers while considering scalability and accessibility. We previously developed an evidence-based intervention for caregivers of patients undergoing HSCT that improved quality of life (QOL), caregiving burden and mood. We have since adapted this clinician-delivered intervention into a self-administered, digital health application (BMT-CARE app) and are currently evaluating the effect of this intervention on QOL in caregivers of patients receiving HSCT.

Methods and analysis The study design is a non-blinded randomised controlled trial of a digital health intervention for caregivers of patients undergoing HSCT at the Massachusetts General Hospital Cancer Center. We are enrolling and randomising 125 caregivers to receive the BMT-CARE app or usual care in a 1:1 assignment, stratifying by transplant type (autologous vs allogeneic). Caregivers assigned to the BMT-CARE app complete five self-guided modules designed to improve coping and stress management prior to and up to 60 days post-HSCT. The modules include interactive, gamified features and video vignettes to optimise engagement. Participants complete questionnaires at baseline and days 10, 60 and 100 post-HSCT. The primary outcome is comparison of QOL at day 60 post-HSCT. Secondary outcomes include caregiver burden, anxiety and depression symptoms, as well as post-traumatic stress symptoms. We are also exploring the usability of the BMT-CARE app to inform refinements prior to future testing.

Ethics and dissemination The study is funded by the Leukemia and Lymphoma Society and approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board (Protocol #22–634 v.1.5). The results of this study will be reported in accordance with the Consolidated Standards of Reporting Trials statement for non-pharmacological trials. Results will be disseminated at scientific meetings and in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The proposed study uses a non-blinded, randomised controlled trial design to compare the BMT-CARE app to a usual care control group in a sample of caregivers of patients receiving allogeneic or autologous haematopoietic stem cell transplantation (HSCT) (N=125).
⇒ The BMT-CARE app is based on the BMT-CARE clinician-delivered intervention, which was iteratively developed and refined using evidence-based methodology, was found to be feasible and acceptable and demonstrated preliminary efficacy for improving caregiver outcomes in a prior pilot randomised trial.
⇒ The BMT-CARE app is a self-administered digital health app that supports accessibility and scalability, reducing participant burden in a population with substantial demands and psychological distress.
⇒ The BMT-CARE app was designed to address the specific needs of caregivers before, during and after the HSCT process and uses several features to promote engagement and psychoeducation, including gamification strategies, videos of caregivers of HSCT survivors providing guidance and guided mindfulness exercises.
⇒ The non-blinded study design and the relatively homogeneous sociodemographic composition of our academic medical institution are potential limitations of the study.

Trial registration number NCT05709912; Pre-results.

INTRODUCTION

Caregivers of patients undergoing haematopoietic stem cell transplantation (HSCT) are essential members of the patient's care team and experience considerable psychological

distress and caregiver burden.[1 2] Our recent longitudinal study found that these caregivers report a substantial deterioration in their quality of life (QOL) and increased depressive symptoms *throughout* the HSCT process.[3] First, caregivers experience significant psychological distress as they prepare for the patient's HSCT hospitalisation at 3–4 weeks and cope with prognostic uncertainty.[3–10] During HSCT, caregivers' distress remains elevated as the patient receives high-dose chemotherapy associated with multiple toxicities, physical symptoms and prolonged hospitalisation.[4–8] Finally, in the first 3 months following HSCT, the caregiver helps the patient manage ongoing physical symptoms, frequent outpatient medical appointments and complex medication schedules, all while coping with the uncertainty of the illness.[9 10] As a result, caregivers have significant disruptions to their employment, home responsibilities and personal life, translating to immense psychological distress.[11–13]

Addressing HSCT caregivers' unmet psychosocial needs may buffer the negative effects of burden on caregivers' QOL and mood,[3 14] while also improving patient-reported QOL, symptom management and psychological distress.[9 10 15–22] Nevertheless, interventions targeting the unique needs of caregivers across each stage of the HSCT experience are lacking.[3 9 14 23] In two studies, investigators examined the effect of a problem-solving and a stress management intervention for caregivers only after HSCT hospitalisation,[23 24] neglecting the periods both before and during HSCT, times when caregivers often report the *highest* distress.[3] While other HSCT-caregiver interventions have shown promise, their effectiveness may be limited by factors such as small sample sizes,[23 25 26] vaguely defined interventions and lack of rigorous randomised trials, making it challenging to draw definitive conclusions from their findings.[9 22 23] More work is therefore needed to develop a population-specific, evidence-based and *accessible* intervention given the time-intensive demands of caring for a patient undergoing HSCT.[27]

We previously completed a pilot study of a cognitive behavioural therapy (CBT) based intervention to address the needs of caregivers of patients undergoing HSCT, known as BMT-CARE.[28] Participating caregivers attended six in-person sessions with a CBT-trained psychologist or social worker to address their concerns before, during and up to 60 days after HSCT. Specific intervention components included (1) psychoeducation about the HSCT process; (2) cognitive-behavioural strategies to facilitate effective coping with uncertainty, including cognitive restructuring, mindfulness and communication skills; and (3) behavioural strategies to promote caregiver mental and physical self-care.[28] The results from this trial indicated that BMT-CARE was feasible and led to statistically and clinically significant improvements in caregivers' QOL, caregiving burden and symptoms of depression and anxiety.[28] While results from the pilot trial demonstrated promise, several participants reported that attending in-person sessions was burdensome, and the study interventionists similarly found the frequency of visits to be a barrier to broad dissemination.[28] In addition, most caregivers of patients undergoing HSCT do not have access to CBT-trained clinicians in their transplant centres, limiting the scalability of this intervention. In an effort to address these barriers, we have adapted the clinician-delivered BMT-CARE into a digital health intervention (BMT-CARE app), which caregivers can self-administer, potentially optimising the intervention's accessibility and scalability.

The current report outlines the protocol of our randomised controlled trial (RCT) that began recruiting participants in February 2023, with recruitment expected to be complete by the end of 2024. The primary objective of the current study is to assess the efficacy of the BMT-CARE app versus usual care for improving caregiver QOL. We will also investigate the effect of the BMT-CARE app on other relevant psychosocial outcomes, including caregiver burden, symptoms of anxiety and depression, and post-traumatic stress symptoms. Finally, we will explore group differences in caregivers' coping and self-efficacy and examine the usability of the BMT-CARE app. The results of the present study will have important implications for how to best use innovative technology to widely disseminate evidence-based, population-specific, supportive care services to other highly distressed caregivers.

METHODS AND ANALYSIS

Study design

This is an RCT comparing a digital health intervention application, 'BMT-CARE app' versus usual care in 125 caregivers of patients receiving HSCT. Caregivers of patients with planned HSCT are recruited from the

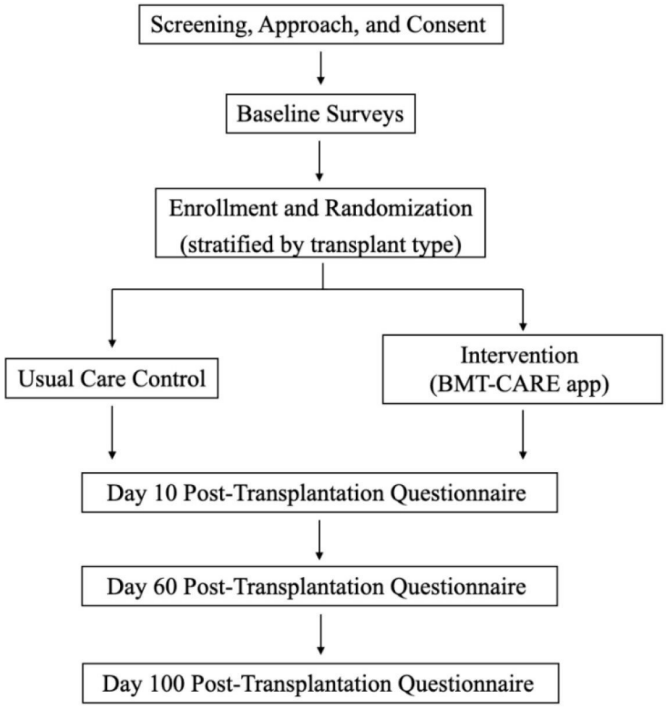


Figure 1 Study schema.

Table 1 Eligibility criteria for the BMT-CARE app study

Inclusion criteria	Exclusion criteria
Adult caregivers (>18 years)	Caregivers of patients undergoing HSCT for benign haematological conditions
A relative or friend who lives with the patient or is a designated caregiver as indicated during the transplant process	Caregivers with acute or unstable psychiatric or cognitive conditions which the treating clinicians believe prohibit informed consent or compliance with study procedures
Caregiver of a patient receiving allogeneic or autologous HSCT for the treatment of cancer	
Ability to comprehend and speak English as the BMT-CARE app is presently only available in English	

HSCT, haematopoietic stem cell transplantation.

Massachusetts General Hospital (MGH) Cancer Center in Boston, Massachusetts. The study schema is depicted in figure 1. This study is approved by the Dana-Farber/Harvard Cancer Center (DF/HCC) Institutional Review Board (IRB; Protocol #22–634 v.1.5, first approval date 20 January 2023).

Participant selection

To be eligible, caregivers must be at least 18 years old, serve as the designated caregiver of a patient with an upcoming allogenic or autologous HSCT for the treatment of a haematological malignancy and be able to read and respond in English, since the BMT-CARE app is presently only available in English. Caregivers are not eligible if the patient is undergoing HSCT for a benign haematological condition. To optimise study adherence and retention, caregivers with acute or unstable psychiatric or cognitive conditions that prohibit informed consent or adherence to study procedures, as determined by the treating clinicians, are also ineligible. See table 1 for eligibility criteria.

Study procedures

Recruitment

A trained member of the study staff reviews the electronic health record (EHR) of patients scheduled for the transplant oncology clinic and/or the upcoming transplant log. Since these patients must have a designated caregiver ahead of the transplant hospitalisation, the study staff identifies potentially eligible caregivers of these patients with planned HSCT. After receiving written or verbal approval from the transplant clinicians (eg, physicians and advanced practice providers) to offer study participation, a trained member of the study staff approaches caregivers during a routine oncology visit or remotely over the telephone prior to the scheduled HSCT, explaining all study procedures and gauging the caregiver's interest in the study.

Enrolment and randomisation

Interested and eligible caregivers provide verbal informed consent either in-person or via telephone with trained study staff (form provided in the online supplemental material). Study participants complete baseline self-report assessments prior to HSCT (within 10 days of providing informed consent). If a caregiver provides consent but does not complete the baseline assessment, they are not registered on the study and do not count towards accrual numbers. Following completion of the baseline assessment, participants are randomised using a computer-generated randomisation scheme in a 1:1 fashion to either the BMT-CARE app or usual care, stratified by type of transplant (autologous vs allogeneic) due to known differences in caregiving burden.[3 29] We also obtain a Health Insurance Portability and Accountability Act (HIPAA) authorisation from patients in-person, electronically or by mail within 3 months of caregiver enrolment in order to collect information about their disease and transplant-related factors from the EHR.

Assessments

Enrolled caregivers in both study groups complete assessments at baseline (prior to HSCT), day 10 post-HSCT (±5 days), day 60 post-HSCT (±10 days) and day 100 post-HSCT (±10 days). These assessment points were selected given their clinical relevance in the HSCT population and are commonly used to capture the period before HSCT, during HSCT hospitalisation, the early post-hospitalisation recovery period and the post-acute recovery period.[3 30 31] Completion of study assessments occurs in-person (in a private space during inpatient or outpatient appointments), over the telephone or via Research Electronic Data Capture (REDCap),[32] a HIPAA-compliant online survey administration tool. The full assessment battery takes approximately 15 min to complete. See table 2 for more information on study assessments.

BMT-CARE app

We developed the BMT-CARE app based on our conceptual framework, prior in-person intervention work and iterative stakeholder feedback in each application development stage.[28] Following a five-step process in accordance with the Framework for mHealth Intervention Development,[33] we (1) implemented a conceptual framework based on Van Houtven's model for caregiving interventions,[34] (2) developed a comprehensive intervention script in collaboration with a multidisciplinary team of oncologists and psychologists, (3) collaborated with a technical team of digital health application programmers (Zco Corporation) to translate the script into an interactive format to enhance caregiver engagement, (4) obtained stakeholder feedback on BMT-CARE app wireframes and (5) refined BMT-CARE app content through alpha and beta testing with stakeholders, including content experts in oncology and psychology (n=4) as well as patients (n=2) and caregivers (n=2). We designed the BMT-CARE app to be an educational and interactive

Table 2 Study instruments and data collection time points

Outcome/variable	Study measure	Baseline	10 days post-HSCT	60 days post-HSCT	100 days post-HSCT
Quality of life	CareGiver Oncology Quality of Life questionnaire	X	X	X	X
Caregiving burden	Caregiver Reaction Assessment	X	X	X	X
Anxiety symptoms	Hospital Anxiety and Depression Scale	X	X	X	X
Depression symptoms	Hospital Anxiety and Depression Scale	X	X	X	X
Symptoms of post-traumatic stress	Post-Traumatic Stress Disorder Checklist	X	X	X	X
Self-efficacy	Cancer Self-Efficacy Scale-transplant	X	X	X	X
Coping skills	Measure of Current Status Part A	X	X	X	X
Usability of the BMT-CARE app	System Usability Scale*			X	
Use of supportive care services	Self-reported utilisation of mental health services			X	

*This measure is administered only to participants randomised to the intervention arm.
HSCT, haematopoietic stem cell transplantation.

journey for caregivers as they face challenges associated with supporting a patient undergoing HSCT. See figure 2 for examples.

The BMT-CARE app includes five required modules. Caregivers participating in the intervention are asked to complete the modules starting from study enrolment prior to HSCT and up to 60 days post-HSCT. After completing each module, caregivers unlock additional features, incentivising them to complete the subsequent modules. The BMT-CARE app also provides reminders when participants are due for their next module. Participants access the BMT-CARE app using a study-issued iPad, where the app is already pre-downloaded. Should participants in the experimental arm have any technical difficulties while using the app, they may reach out to a trained member of the study team for support via phone or in-person at their next scheduled medical appointment. Each participant also receives two educational handouts that describe how to use an iPad (eg, home and volume controls) and orients them to the BMT-CARE app. We monitor adherence to the BMT-CARE app by electronically tracking the number of modules caregivers complete as well as time spent on each module. We expect that each module will take approximately 20 min on average to complete. Caregivers receive a reminder every other week until modules are completed.

Each of the five BMT-CARE app modules pairs clinical information with evidence-based mind-body strategies that help caregivers directly apply the information to improve daily self-management. Participants engage in didactics and exercises that guide them through coping and stress management content. While the core content mirrors that of the clinician-delivered intervention, the BMT-CARE app uses features in each module to help maintain engagement and reinforce new knowledge and skills, such as gamification strategies, videos of caregivers of HSCT-survivors and clinicians providing helpful tips, and guided mindfulness exercises. These multicomponent strategies are drawn from stress and coping theory,[35] cognitive behavioural therapies,[36] positive psychology[37] and mind-body medicine.[38 39] While the content of the BMT-CARE app maps onto the emotional needs of caregivers before, during and after HSCT, these evidence-based strategies may be beneficial in managing stress throughout the patient's entire cancer journey. The BMT-CARE app also includes an optional sixth module that provides helpful resources and review of the domains and skills covered in the first five modules. Participants in the intervention group continue to receive usual care in the form of any supportive care measures offered by the transplant team and self-report their use of these services at 60 days post-HSCT.

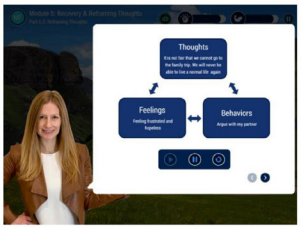
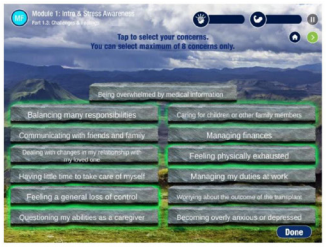
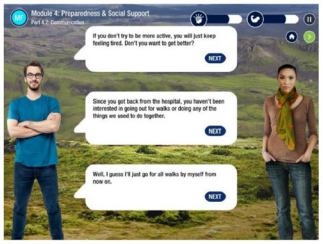
Control group

Caregivers randomised to the control group receive usual care, which entails caregivers meeting with a transplant social worker alongside the patient prior to HSCT. While the social worker may offer coping skills, this single visit is typically not long enough to offer in-depth CBT or ongoing formal support, and many caregivers continue to have unmet psychosocial needs over the HSCT process.[3] Caregivers in both the usual care and BMT-CARE app groups are able to access social work, psychiatry, psychology and other supportive care services as needed by contacting a member of the patient's medical team. Given the possible heterogeneity in participants' use of supportive care services, we ask caregivers in both study groups to self-report their use of services in the past 3 months at 60 days post-HSCT in order to track and control for potential differences.

Participant and public involvement

Both the BMT-CARE intervention and app were created with direct involvement of stakeholders and their explicit feedback, including feedback from transplant physicians, oncology clinicians, psychologists, social workers, HSCT caregivers and patients, and trained behavioural interventionists. First, this digital health intervention is based on our team's BMT-CARE psychosocial intervention,[28] which was developed using (1) a multidisciplinary team

Name of digital health app: The Caregiver App	
Interactive journey: The BMT-CARE app is designed as an interactive journey for caregivers of HSCT recipients to navigate the HSCT continuum from admission to recovery	
Educational resources: The BMT-CARE app includes medical information and practical guidance on navigating the HSCT process	

Evidence-based content: The BMT-CARE app leverages an evidence-based CBT framework to address the needs of caregivers based on our experience with the in-person intervention	
Personalization: Participants choose concerns that are relevant to them and their situation	
Communication: Communication exercises are included to enhance patients' self-efficacy when communicating with patients and the health care team	

Gamification: Games and gamification strategies are incorporated throughout the BMT-CARE app to reinforce learning and promote engagement	
Mindfulness Exercises: The BMT-CARE app includes mindfulness exercises such as guided meditation and relaxation exercises	

Figure 2 Screenshots from the BMT-CARE app. Screenshots from the BMT-CARE app, Cancer Outcomes Research and Education Program (CORE/Massachusetts General Hospital Cancer Center), created in partnership with Zco Corporation, JMJ and AE-J. All individuals depicted in the images have provided informed consent for their photographs to be used in this publication and are aware that these images are being included in the article. HSCT, haematopoietic stem cell transplantation.

of oncologists and psychologists; (2) findings from our previous longitudinal analysis of caregiver distress before, during and after HSCT;[3] (3) evidence-based treatment components previously tested in cancer settings;[40] and (4) a thorough review of the literature.[10 41] The ensuing BMT-CARE manual then underwent continued, iterative, evidence-based development, in which the content and structure were refined using qualitative feedback from an open pilot study of six caregivers. We incorporated this feedback for intervention refinement and tested BMT-CARE in a subsequent randomised controlled pilot trial of 100 caregivers.[28] The BMT-CARE clinician-delivered intervention was found to be feasible, acceptable and led to statistically and clinically meaningful improvements in caregivers' QOL, caregiving burden, coping ability, caregiving self-efficacy and anxiety and depressive

symptoms.[28] These promising findings encouraged us to adapt clinician-delivered BMT-CARE into a digital health intervention (BMT-CARE app) in order to evaluate the efficacy of a more scalable form of the intervention.[28] In developing the BMT-CARE app, we first incorporated caregivers' qualitative feedback following their completion of the clinician-delivered intervention into the script for the BMT-CARE app translation. As discussed previously, the BMT-CARE app creation and modifications also used stakeholder feedback to improve the original wireframes and incorporate alpha and beta user feedback from caregivers, patients and oncology clinicians ahead of finalising the BMT-CARE app.

Outcomes

Table 2 lists the study assessments and the time points at which they are administered.

Demographic and clinical characteristics

During the baseline assessment, caregivers self-report their age, race, ethnicity, gender identity, marital status, religion, education, income, relationship to the patient, living situation in relation to the patient, employment status, extent of isolation (measured on a 5-point Likert scale; 1=*Never*to 5=*Always*) and perceived confidence with technology across two items (measured on a 4-point Likert scale; 1=*Very Comfortable* to 4=*Very Uncomfortable*). In addition, trained study staff extract information about the patient's disease and transplant-related characteristics from the EHR, including patients' type of transplant, underlying disease and HSCT hospitalisation length-of-stay.

Primary outcome

The primary aim of this study is to evaluate the efficacy of the BMT-CARE app compared with usual care for caregiver QOL at day +60 post-HSCT. The current study measures QOL using the CareGiver Oncology Quality of Life (CarGOQOL) questionnaire.[42] The CarGOQOL is a 29-item scale, previously validated in caregivers of patients with haematological malignancies, that produces 10 different subscales (eg, psychological well-being, physical well-being, relationship with healthcare) of caregiver QOL as well as a composite score. Higher scores reflect greater QOL.[43]

Secondary outcomes

In addition, the current study examines the effects of the intervention on other psychosocial outcomes (caregiver burden, anxiety and depression symptoms and post-traumatic stress symptoms) at day +60 post-HSCT and longitudinally. We use the Caregiver Reaction Assessment (CRA) to measure caregiving burden, a 24-item scale that assesses burden across five domains.[44] Anxiety and depression symptoms are measured with the Hospital Anxiety and Depression Scale (HADS), a 14-item scale with two separate subscales to evaluate symptoms of both anxiety and depression.[45] To assess caregivers' symptoms of post-traumatic stress from the patient's diagnosis, we use the 20-item Post-Traumatic Stress Disorder (PTSD) Checklist.[46]

Exploratory outcomes

Finally, we measure caregiver coping and self-efficacy to explore both potential intervention mechanisms and effects of the intervention both at day +60 post-HSCT and longitudinally. To achieve this, we use the Measure of Current Status Part A (MOCS-A)[47] to assess caregivers' self-perceived status on several coping skills (eg, relaxation, cognitive restructuring and assertive communication) and the Cancer Self-Efficacy Scale-transplant (CASE-t)[23 48] to measure caregivers' confidence in managing the impact of HSCT. Finally, we will continue to monitor feasibility (ie, enrolment rates, retention rates, iPad return rates, completion/adherence to the intervention modules) and acceptability metrics. We are specifically exploring the usability of the BMT-CARE app using the System Usability Scale[49] at day +60 post-HSCT, which is administered solely to those assigned to the BMT-CARE app. The System Usability Scale includes 10 Likert-scale items and 2 open-ended questions regarding what participants found to be most useful and important.

Safety and adverse events

Adverse events (AEs) are discussed at the weekly meetings and reported to the DF/HCC IRB. For example, participants may find some items in the assessment battery to be upsetting, or they may experience fatigue from the length of the assessment battery. Moreover, because this study targets symptoms that interfere with QOL, it is possible that some participants experience depressive symptoms. The PI (principal investigator) will be notified should a patient endorse severe psychological distress and/or suicidal ideation at any point during the study. The PI or a trained member of the study team will immediately contact the participant to conduct a safety risk assessment and make appropriate referrals as necessary. We do not anticipate that any research participants will be withdrawn from the study without their consent. If a participant requests withdrawal from the study, we will ask them if they are comfortable sharing their reason for withdrawal to ensure that there are no AEs to report to the IRB. Lastly, we do not anticipate any study-related events meeting the Food and Drug Administration's definition of a serious adverse event (SAE), and, therefore, SAEs will not be reported to the IRB, unless they are potentially related to the study procedures. The study will be stopped immediately if the DF/HCC IRB determines that the risks outweigh the benefits.

Data collection and management

The PI of the study oversees all aspects of data collection and management and meets with the study team weekly to ensure adherence to the study protocol. We collect and store participant data using REDCap and scan and save any physical documentation with protected health information (eg, paper consent forms) to a secure drive

within the encrypted MGH network before destroying. We maintain a separate list of patient names and study IDs, which we save in password-protected files. On study forms, we use the case number only to protect confidentiality. We only use identifiers such as patient names during the initial data retrieval process; these will be destroyed once we have obtained all data records and completed data analysis. At the completion of the study, the MGH research team members will download limited data files from REDCap. Participants' responses to survey questions will remain confidential.

Statistical analysis

We conducted a power analysis using the Stata statistical software package.[50] Based on our previous work with this population,[28] a sample size of 125 will allow>85% power to detect at least a 7.9-point difference (medium effect size) in caregiver QOL between groups at 60 days post-HSCT based on an equal-variance t-test with a two-sided 0.05 significance level, assuming a 15% missing data rate and a SD of 13.

In accordance with the intention-to-treat principle, each participant will be included in their randomly assigned group for all primary analyses. To examine our primary endpoint, we will use Analysis of Covariance (ANCOVA) to compare caregiver QOL (CarGOQOL) at day +60 post-HSCT between the study groups while controlling for baseline values and demographic and clinical factors (including use of supportive care services) as necessary for any substantial imbalances in baseline variables. To analyse our secondary endpoints, we will use ANCOVA to compare caregiver burden (CRA), anxiety symptoms (HADS-Anxiety), depression symptoms (HADS-Depression) and post-traumatic stress symptoms (PTSD Checklist) between the study groups at day +60 post-HSCT, controlling for baseline values and demographic and clinical factors as necessary. A multiplicity correction will be used to interpret secondary outcome results. We will calculate standardised effect sizes (eg, Cohen's d) to compare the magnitude of the intervention effect across caregiver-reported outcomes. Additionally, we will use linear mixed models of the longitudinal data, allowing us to account for dependency among means over time and control for demographic and clinical factors when examining change between groups (BMT-CARE app vs usual care) in each caregiver-reported outcome (ie, QOL, caregiving burden, anxiety, depression and post-traumatic stress symptoms), across multiple time points (baseline and days 10, 60 and 100 post-HSCT).[40 41] These models will include fixed effects for time since HSCT, group and time-by-group interaction to allow comparison of the outcome trajectories between groups, as well as random effects for participant and time (ie, random intercepts and slopes).

The current study will also compare exploratory endpoints including coping skills (MOCS-A) and caregiver self-efficacy in managing the impact of HSCT (CASE-t) between the study groups at day +60 post-HSCT using the same approaches described above. We will also explore coping and self-efficacy as potential interventional mechanisms using mediation. Lastly, we will descriptively report the usability of the BMT-CARE app in those assigned to the intervention group for future app refinement.

Primary analyses will include available data without imputation of missing data. The characteristics of caregivers who complete versus do not complete the day +60 post-HSCT survey will be compared descriptively. We will conduct sensitivity analyses to explore how various assumptions about missing data and differences between completers and non-completers affect the estimated outcomes. Sensitivity analyses may include multiple imputation, pattern mixture modelling or joint modelling approaches to account for missing data.

Limitations

This study is not without limitations. First, the patient population at MGH is homogenous, such that many are white, non-Hispanic and of higher socioeconomic status and educational backgrounds compared with the greater Boston area. Future trials will incorporate a multisite design in order to increase sample diversity and generalisability of findings. The use of a digital health application also has the potential to bias the sample to be younger or more resourced; however, we provide devices and training for interested and eligible caregivers without access to such technology. Next, it is not possible for a digital health intervention such as the BMT-CARE app to be blinded, further increasing the risk of bias. The usual care group may also be a limitation, given it does not specifically provide an attention-matched control. However, participants in the usual care group have the opportunity to use supportive care resources and self-report their use of these services at 60 days post-HSCT. Next, we chose to move straight to an efficacy trial given the established feasibility, acceptability and promising efficacy of our in-person BMT-CARE intervention and strong feasibility from our group's prior digital health studies.[28 51 52] Our next step will be to conduct a larger scale efficacy trial at multiple cancer centres in order to establish efficacy across a more representative sociodemographic and geographically representative sample. Future work may also: (1) compare the clinician-delivered intervention to the app in a three-arm comparative effectiveness trial; (2) enrol more than one caregiver for any given patient as there are often multiple people that contribute to the patient's wellness throughout the HSCT process; and/or (3) examine the impact of the BMT-CARE app on patient-reported outcomes.

ETHICS AND DISSEMINATION

The study is funded by the Leukemia and Lymphoma Society and is approved by the Dana Farber/Harvard Cancer Center Institutional Review Board (DF/HCC IRB; Protocol #22–634 v.1.5). Any modifications to the protocol

are submitted as a formal IRB amendment. Approved changes are communicated to all participants and study staff, and if deemed necessary by the IRB, enrolled participants are reconsented to the amended study protocol. We obtain informed consent from all study participants. The consent includes all study procedures, information about potential risks and benefits of participation and information regarding whom the participant can contact for further questions. It also states that participation is voluntary, they can refuse to answer any question or withdraw from the study at any time, and that study participation is in no way related to the patient's medical care. All participant information and study source documents will remain confidential and will be scanned and stored on secure institutional computers and in REDCap in accordance with HIPAA. In addition, all study staff have undergone extensive training on study procedures, data management and human subjects' protection to ensure data security, patient confidentiality and responsible conduct of research.

The BMT-CARE app is a digital health intervention with minimal risk for physical harm; however, it is possible that participants may experience increased psychological distress as a result of intervention content. Should a participant exhibit or express distress while completing the study questionnaires, they will be reassured that they need not answer any questions they find upsetting and may withdraw at any time. If participants remain distressed, both the PI and the primary oncology clinician will be notified. Should several participants express distress over an individual survey item, the research team will review the questionnaire and contact the IRB to consider removing it from the study. If a participant reports severe psychological distress or suicidal ideation during the study, the PI will determine the need to involve mental health services and take further action as necessary. A data monitoring committee is not indicated in this low-risk study; instead, the MGH research team reviews all data pertaining to safety during their weekly investigative team meeting. These weekly reports include AEs but also other data that may reflect differences in safety such as treatment retention rates and reasons for dropout.

The study is registered on ClinicalTrials.gov (NCT05709912). Results of the study, including an unanticipated early termination of the trial, will be posted to the ClinicalTrials.gov database at the conclusion of the study. In the event that the study is terminated early, the posting of these results will be completed within 30 days of completion of data analysis. We anticipate that a significant proportion of the patients undergoing HSCT will die during or within months of completing the study; therefore, we will not proactively contact participants at the conclusion of this study but will encourage them to contact us if they would like to receive updates and information on the research findings. Data will only be accessible by MGH study staff and may only become available to others on reasonable request and an IRB-approved data use agreement. Primary, secondary and exploratory findings of the current study will be published in peer-reviewed journals and disseminated at academic conference proceedings. All authors listed on any resulting publications or presentations will have made substantial contributions to the study design, data collection, data analysis and/or manuscript draft.

Current trial status

Recruitment of participants started on 6 February 2023, and as of 20 December 2024, 125 caregivers have enrolled.

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