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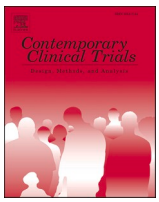

eHealth mindfulness-based music therapy for patients undergoing allogeneic hematopoietic stem cell transplantation: A pilot randomized controlled trial protocol

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ABSTRACT

Background: Allogeneic stem cell transplantation (allo-SCT) is the preferred therapy for patients with high-risk or relapsed hematologic malignancies, but may be complicated by psychological distress (e.g., depression, anxiety) and symptom burden (e.g., fatigue, pain). Mindfulness-based music therapy (MBMT), a relatively novel integrative medicine intervention that draws from mindfulness and music therapy principles, has shown promise in improving psychosocial outcomes and symptom burden in cancer patients. We outline an eHealth-based MBMT (eMBMT) intervention protocol examining: (1) feasibility, acceptability, and intended effects of eMBMT in improving HRQOL, symptom burden, and clinical markers of disease activity (e.g., infections), and (2) the extent to which eMBMT music therapy component-associated improvements in HRQOL, symptom burden, and disease activity are mediated by improvements in psychosocial and physiological (e.g., systemic inflammation, immune recovery) adaptation.

Methods: Participants (n = 60) with a hematologic malignancy undergoing allo-SCT will be randomized to receive eMBMT or an eHealth-based mindfulness meditation (eMM) intervention. eMBMT includes eight 60-min sessions facilitated by a music therapist focusing on mindfulness and music therapy. eMM includes eight 60-min self-led MM practices.

Results: Feasibility, acceptability, HRQOL, symptom burden, disease activity, and mediation effects of psychosocial and physiological adaptation will be assessed at baseline, pre-infusion, and post-engraftment with blood collection at baseline and post-engraftment.

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Conclusion: The current pilot RCT is the first eMBMT intervention to address the HRQOL and symptom burden of patients who are undergoing allo-SCT. Results will inform a fully powered RCT to establish preliminary efficacy of eMBMT on improvements in HRQOL, symptom burden, and disease activity.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is a potentially curative procedure for malignant hematologic diseases including high-risk or relapsed acute myeloid or lymphoblastic leukemia (AML, ALL), myelodysplastic syndrome (MDS) and high-risk lymphoma. An allo-SCT utilizes healthy blood stem cells from a donor to replace bone marrow cells that are not producing blood cells. Patients receiving an allo-SCT receive pre-transplant conditioning regimen (i.e., chemotherapy and/or radiation) prior to transplantation to suppress the immune system and reduce tumor burden [1]. These treatments can have a wide range of negative side effects (e.g., nausea, pain, fatigue, mood disturbance, risk of infections) [2]. Post-transplant complications (e.g., graft-versus-host disease [GVHD], infection) are not uncommon, and physical symptoms (e.g., fatigue, pain, nausea) and poor psychosocial functioning and emotional distress (e.g., anxiety, depression, social isolation) may persist well-beyond active treatment [3–6]. Psychological distress in allo-SCT has been associated with higher mortality rates and less favorable outcomes in the first-year post-treatment [5,7,8] including greater rates of GVHD and infection, longer hospitalization stays, and increased rates of readmission [9]. In contrast, better pre-treatment emotional well-being is associated with greater survival [10,11]. Therefore, programs that improve psychosocial symptoms and reduce symptom burden in allo-SCT may improve health-related quality of life (HRQOL), patient reported outcomes (PROs; patient's own report of the status of different domains of their health), and clinical outcomes (e.g., readmission, longer hospitalization).

Growing evidence indicates that mindfulness-based stress reduction (MBSR), mindfulness meditation (MM), and cognitive-behavioral stress management (CBSM) interventions have beneficial effects on psychosocial and physiological (e.g., inflammation, immunocompetence) adaptation and clinical outcomes in patients with cancer [12,13]. These and other integrative interventions (e.g., yoga) can provide multiple benefits [14] including reductions in fatigue, depression, anxiety, and sleep disturbance [15]. Mindfulness involves bringing attention to present moment experiences, including thoughts, feelings, and physical sensations, with acceptance and non-judgmental attitudes [16]. MBSR and MM have been effective in reducing cancer symptoms, cancer-related distress, depression, and improving self-efficacy, coping skills, and HRQOL in cancer [17,18] and other chronic conditions [19,20]. Despite these benefits, the inclusion of patients actively undergoing allo-SCT using integrative medicine interventions remains limited [15,21]. This limitation may be due to time-intensiveness (e.g., requiring 10 or more 90+ minute sessions) and physical and cognitive demands that can be challenging while undergoing acute allo-SCT treatment. Thus, there is a need to evaluate stress-reducing, low-demand, and comforting integrative approaches in allo-SCT.

Music-based interventions have shown promise in improving PROs in several chronic conditions [22–25]. One such intervention, music therapy (MT), delivered by a board-certified music therapist [24,26], has shown positive effects on several behavioral, physical, and psychological outcomes in clinical populations [27,28]. Music listening, songwriting, and instrument playing activate brain structures (e.g., mesocorticolimbic dopaminergic circuitry, amygdala, hippocampus [29,30]) involved in regulating autonomic, emotional, and cognitive functions, offering insights into MT's potential to improve mood, pain, anxiety, and depression [27,28]. In cancer, MT increases chemotherapy tolerance [31], adherence to medical treatments [32], engagement in healthy lifestyle programs [33], and pain management by impacting emotional well-being and buffering the stress response [34]. Activities such as music listening and singing have been shown to lower cortisol levels [35,36], enhance immune response (e.g., increase NK cell activity and immunoglobulin levels, reduce IL-6), and provide anti-inflammatory benefits [30,37,38]. MT has also been shown to reduce stress and blood pressure, and improve gait/balance, mood, memory, and cognitive functioning [39–43]. Positive outcomes are attributed to MT's ability to facilitate emotional processing and support, and developing therapeutic skills (e.g., relaxation) [44]. A recent Cochrane review emphasized the need for standardized, scalable protocols and RCTs to identify MT components positively impacting cancer patients' physical and psychological outcomes [45].

Mindfulness-based music therapy (MBMT) is founded on the principles of meditation practice and attitudes, cognitive neuroscience of music and mindfulness, and psychology (e.g., emotional regulation) [46]. MBMT blends MM's core elements with tailored MT to facilitate mindful listening to music and environmental sounds, enhancing attention, focus, and stress reduction. MBMT (a) facilitates the shift from physical and psychological suffering to soothing experiences via music; (b) offers a cathartic, safe space for emotional expression; (c) supports meaning-making and transcendence through music; and (d) strengthens social connections [47]. Emerging research indicates that MBMT improves anxiety, depression, pain, and quality of life in cancer patients [48–52], yet its effects in allo-SCT recipients remain unexplored.

Given the promising benefits of MBMT, we present a pilot RCT protocol, the first phase (R61) of a multi-phase (R61/R33) project, that evaluates the feasibility and acceptability of a newly developed eHealth-based MBMT (eMBMT) intervention tailored to adults receiving allo-SCT. We also evaluate the preliminary effect sizes of eMBMT compared to eHealth-based MM (eMM) on HRQOL, symptom burden (primary), disease activity, and psychosocial and physiological adaptation (secondary). Additionally, we will assess which eMBMT associated practice and skills uptake of MT components (e.g., music instrument playing, music listening, music engagement) and MM components (e.g., emotional regulation, mastery and ability, cognitive reorientation) are associated with improvements in HRQOL, symptom burden, and psychosocial and physiological adaptation. Our exploratory hypotheses include: (1) relative to eMM, participants receiving eMBMT will exhibit greater improvements in HRQOL, symptom burden, disease activity, and psychosocial and physiological adaptation from baseline to post-engraftment, (2) practice and skills uptake of specific MT components of MBMT from baseline to post-engraftment will be associated with the hypothesized improvements, and (3) improvements in HRQOL, symptom burden, and disease activity will exhibit mediational patterns through improvements in psychosocial and physiological adaptation from baseline to post-engraftment.

2. Material and methods

This project is funded by the National Cancer Institute (1R61CA263335-01A1), registered on ClinicalTrials.gov (NCT05968963), and approved by University's Institutional Review Board (eProst# 20230726).

2.1. Design

We will recruit 60 adults diagnosed with a hematologic malignancy who are scheduled to receive an allo-SCT through Sylvester Comprehensive Cancer Center (SCCC) at University of Miami Health System. Participants will be randomized (1:1) to receive eMBMT ($n = 30$) or eMM ($n = 30$). eMBMT consists of eight sessions (five in-person and

three videoconferences) facilitated by a board-certified MT through an eHealth platform. eMM consists of eight self-led sessions conducted through an eHealth platform. Each session will last approximately 60 min. Assessments will include questionnaires at baseline (T1), pre-infusion (T2), and post-engraftment (T3), along with blood collection at T1 and T3. Select participants may also complete a final interview to discuss their experiences. Fig. 1 presents study and assessment timelines.

2.2. Setting

Recruitment, consent, and baseline will be conducted: (1) at SCCC's outpatient clinic prior to admission, or (2) in the SCT unit upon admission. While participants are admitted to the SCT unit, all activities (e.g., surveys, intervention sessions) will be conducted in person. After discharge, activities will be conducted: (1) at SCCC's outpatient clinic, or (1) via videoconference. SCCC's catchment area is largely urban, and the patient base is highly diverse regarding race, ethnicity, and country of origin (e.g., ~43% Hispanic; ~20% Black).

2.3. Participants and sample size

Eligible participants are adults (≥18 years old) diagnosed with a hematologic malignancy (e.g., MDS, AML, ALL),scheduled for allo-SCT, and fluent in English or Spanish. Exclusions include: a history of severe psychiatric illness (e.g., psychosis, active suicidality, inpatient treatment <12 months), severe cognitive impairment (per the Short Portable Mental Status Questionnaire (SPMSQ; [53]), hearing impairment, current alcohol/substance dependence, or recent participation (≤ 6 months) in music therapy/mindfulness programs. The SCCC SCT program performs approximately 150 allo-SCTs annually. Thus, with an 18% acceptance rate, we will recruit the proposed sample size ($n = 60$). We anticipate a 10% attrition rate ($n = 50$ at T3) which has been accounted for in the recruitment sample size.

2.4. Recruitment

Study staff will review electronic health records (EHR) and a consent-to-contact database of potentially eligible patients at SCCC. The team will contact potential participants for a screening interview, in-person or by phone, to verify eligibility. Recruitment flyers will be distributed through patient coordinators. Informed consent will be obtained following IRB-approved procedures.

2.5. Randomization

Participants will be randomized (1:1) via REDCap (a HIPPA compliant service for building and managing online surveys and databases) to either an eMBMT or eMM intervention following the baseline assessment.

2.6. Retention plan

Our goal is to achieve an 80% retention rate, supporting participants with regular phone calls or SMS text reminders for all sessions and assessments. Intervention participants will be informed about their right to request an online session if an in-person session is not feasible due to treatment side effects (e.g., nausea, weakness). Compensation is $50 per completed assessment (Total = up to $150), with an extra $50 for those chosen to complete a final interview.

2.7. Safety monitoring

Participants responding to questionnaires about sensitive topics may experience transient, mild anxiety. Extreme affective reactions (e.g., severe symptoms of depression, anxiety, and/or suicidality) will result in referrals to SCCC psychologists or psychiatrists. Venipuncture, used to obtain blood samples, has typically minor risks, including possible discomfort at the point of venipuncture.

2.8. Interventions

The eMBMT and eMM content were developed in collaboration with the study's board-certified MTs and study members with expertise in eHealth-based interventions, psycho-oncology, MBSR, integrative medicine, and allo-SCT interventions. *SmartManage: Tools for Health Living* [54] provides the platform for the eMBMT and eMM content. *SmartManage* is a patient-centered web application hosted by Bright-Outcome, Inc., a private company that develops applications to improve health. *SmartManage* is easy to use, editable by the study team, HIPPA compliant, and accessible via multiple platforms (e.g., tablets, smartphones). The refinement of the eMBMT and eMM platforms are described in detail in Fleszar-Pavlovic et al. (in preparation) [55]. Briefly, we conducted focus groups followed by usability and field testing of the newly developed eMBMT and eMM platforms with allo-SCT survivors. Data was gathered on survivors' opinions on the eMBMT and eMM prototypes, content detail, and platform features. Both platforms were iteratively refined based on focus group and

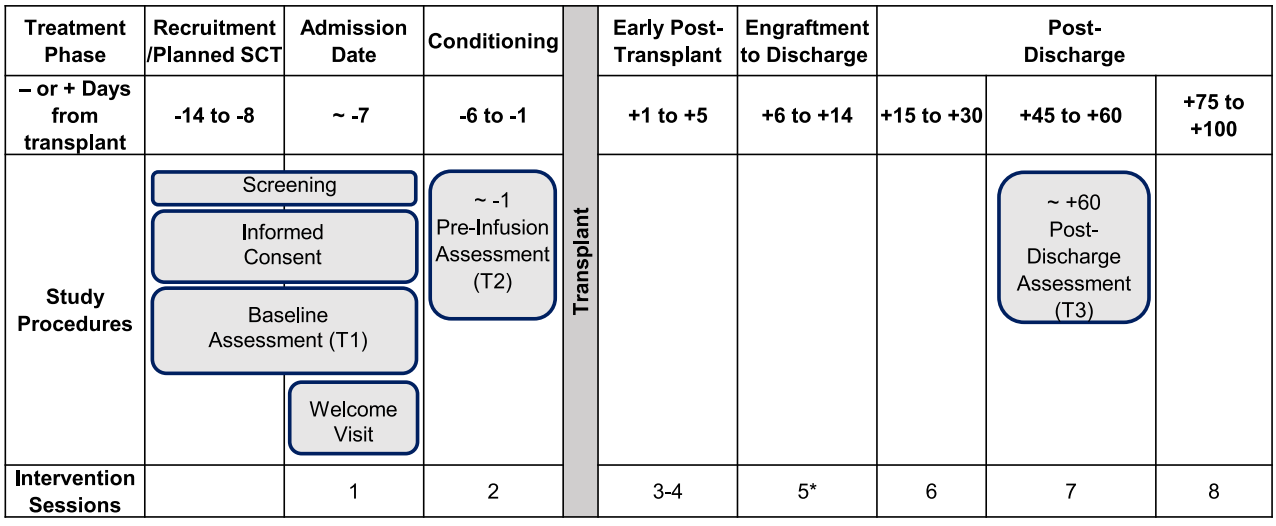

Fig. 1. Study Procedures and Intervention Schedule Across the Treatment Continuum.

usability/field-testing analyses for use in the pilot RCT.

2.8.1. eMBMT program

eMBMT participants will receive eight 60-min sessions facilitated by a board-certified MT and guided by the eMBMT *SmartManage* platform. The sessions will be delivered in-person or via videoconference. Sessions will focus on Jon Kabat-Zin's Attitudes of Mindfulness [56] (i.e., non-judging, patience, letting go, acceptance, trust, beginner's mind, non-striving). Each session will consist of a mindfulness attitude, building skills based on the attitude combined with components of MT, and in-session activities (e.g., music listening, playing an instrument, song writing, singing). Additionally, participants will be provided with supplementary resources (i.e., videos, audios, research articles) which expand on content learned as well as daily practices, which participants are encouraged to complete. Table 1 presents session topics and delivery timeline.

2.8.2. eMM program

Our comparison group consists of MM content that parallels eMBMT content, without MT components. Participants allocated to eMM will complete eight 60-min self-guided sessions facilitated by *SmartManage*. Each session focuses on MM based on UCLA's Mindful Awareness Practices [57] and Jon Kabat-Zinn's mindfulness meditation practices [56]. Each session will consist of a learning section, which provides background information and skills based on the specific topic and mindfulness attitude, and meditation practice tailored to SCT patients' experiences through audio meditations (See Table 1).

2.9. Study assessment schedule

Recruitment, assessments, and blood collection will occur throughout the participants' SCT treatment and recovery trajectory. Recruitment, baseline assessment, and first blood collection will be completed up to or on the date of admission (T1: $\sim \geq 7$ days before transplant). The pre-infusion assessment will occur during the conditioning phase (T2: ~1–6 days before transplant) and after completion of two eMBMT/eMM sessions. The post-engraftment assessment (T3) and second blood collection will be completed ~45 to 60 days post-transplant. In addition, eMBMT participants (n = 12–15) will be randomly selected for a final qualitative interview upon completion of the program. Fig. 1 presents assessments schedule.

2.10. Primary outcomes

Primary outcomes of interest are feasibility, acceptability, and the preliminary effect sizes for HRQOL and symptom burden. We will follow Bowen's [58] recommendations to establish feasibility through acceptability and demand. Acceptability will be assessed with bi-weekly phone calls to evaluate acceptance and confidence in using information presented in eMBMT and eMM [58]. Demand will be measured through recruitment, retention, and attendance rates. A 60% recruitment rate, and 80% retention and attendance are deemed acceptable per prior oncology studies [59,60]. We will also collect *SmartManage* usage data based on the frequency, intensity, time, and type (FITT) principle [61] which includes number of logins per participant, modules viewed (i.e., total number; % completed), time spent on the website, and number of completed exercises per session. HRQOL will be measured with the Functional Assessment of Cancer Therapy - Bone Marrow Transplant (FACT-BMT) [62]. The FACT-BMT captures multiple domains of HRQOL including physical, functional, social, and emotional well-being, as well as allo-SCT concerns. Pain and fatigue will be assessed with the PROMIS® Pain and Fatigue-Short Forms [63–65]. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will assess cognitive function [66]. The Pittsburgh Sleep Quality Index (PSQI) will assess sleep quality [67].

2.11. Secondary outcomes

Disease activity will be extracted from the EHR and assessed by the number of days to engraftment, number of days of hospitalization, readmissions, readmission days, and the presence of chronic GVHD and grade, Cytomegalovirus (CMV) activation, treatment-related and other complications (e.g., infections).

2.12. Mechanisms of action across eMBMT and eMM

The 15-item Short Form of the Five Facet Mindfulness Questionnaire (FFMQ-SF) will assess the five facets of mindfulness (i.e., observing, describing, acting with awareness, non-judging, and non-reactivity to inner experience) [68]. MT skills will be assessed with an adapted version of the Music Use (MUSE) Questionnaire to capture music mastery specific to: (a) music instrument playing to assess the intensity of practice, measured by duration and frequency, as well as regularity of instrument playing, (b) music listening to assess intensity of music listening, and (c) music engagement style [69]. eMBMT mindfulness and MT skills will be assessed with an adapted 24-item version of the MUSE to evaluate mindfulness-based music therapeutic components for (a) emotional regulation, (b) mastery and ability, (c) mood enhancement, and (d) cognitive reorientation [69].

2.13. Mediators

This study assesses preliminary evidence of how specific MT mechanisms impact the primary and secondary outcomes via eMBMT

Table 1
eMBMT and eMM Session Topics, Delivery Timeline, and Delivery Mode.

Sesson	Timepoint	eMBMT			eMM	
		Mindfulness	Music Therapy	Delivery	Mindfulness	Delivery
1	Admission	Program Orientation	Music Listening & Breathing to Music	In-person	Program Orientation & Mindfulness	eHealth
2	Conditioning	Non-Judging	Mindfulness-based Music Listening & Writing	In-person	Mindful Attitudes	eHealth
3	Early Post-Transplant	Patience	Focused Music & Environmental Sound Listening	In-person	Mindbody Wisdom & Healing	eHealth
4	Early Post-Transplant	Letting Go	Music-assisted Relaxation	In-person	Trust & Balance	eHealth
5	Engraftment to Discharge	Acceptance	Music-assisted relaxation with body scan	In-person	Mindful Coping	eHealth
6	Post-Discharge	Trust	Vocal Toning Exercises	eHealth	Strategies of Heart & Mind	eHealth
7	Post-Discharge	Beginners Mind	Novel Instruments & Music Listening	eHealth	Deepening & Expanding	eHealth
8	Post-Discharge	Non-Striving	Instrumental Improvisation & Creative Expression to Music	eHealth	Moving into the World	eHealth

improvements in psychosocial and physiological adaptation. Psychosocial adaptation as a potential mediator will be assessed on a basis of: (a) depression measured by the 9-item Patient Health Questionnaire (PHQ-9) [70], (b) anxiety measured by the 7-item Generalized Anxiety Disorder (GAD-7) questionnaire [71], and (c) cancer-specific distress measured by the 22-item Impact of Events Scale-Revised (IES-R) [72]. Physiological adaptation as a potential mediator will be assessed by: (a) systemic inflammation measured by serum cortisol and pro- and anti-inflammatory cytokines (i.e., GM-CSF, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and TNF-α) [73], (b) thymic function by quantifying T cell receptor excision circles (TREC) [74], and (c) regulatory T cells, T cell differentiation, and recovery (i.e., CD3, CD4, CD8, CD45RA, CD27 [to define naïve/memory subsets]; CD25, CD127 and intracellular foxP3 staining [to define T_{reg}], CD16 and CD56 [to define NK cells], and CD19 [to define B cells]. Medications required for the allo-SCT procedure (e.g., immunosuppressives, steroids) may impact inflammatory and immune markers; therefore, we will collect and code the timing and dosage of immunosuppressive agents, steroids, and other medications, and assess any confounding effects.

Table 2 presents measures and delivery timepoints.

2.14. Covariate adjustment

Initial analyses will check statistical assumptions and group differences in sociodemographic (e.g., sex, age, education, employment, race/ethnicity), medical variables (e.g., conditioning therapy [radiation; intensive vs. reduced-intensity chemotherapy], cancer type, donor type [matched vs. haploidentical; related vs. unrelated]), and music background via music listening, music instrument playing, and music training subscales of the Music Use Questionnaire (MUSE) [69]. Since intervention allocation is random, variable distribution should be balanced; however, further adjustments will be made for baseline values for outcome measures accordingly.

2.15. Quality control

2.15.1. Intervention fidelity

eMBMT fidelity will be maintained through: (a) utilizing board-certified MTs experienced in manualized interventions for oncology patients, (b) employing an eMBMT facilitator manual developed to accompany *SmartManage*, (c) user metrics captured via *SmartManage* (i.e., logins, module completion, session duration), and (d) documenting the eMBMT content delivery via a session-specific fidelity checklist. Fidelity checklist satisfactory performance will be defined as ≥80% on the fidelity rating scale (e.g., adherence to content, effectiveness in presenting content, and participant skill acquisition). eMM fidelity will be maintained through reminder calls and user metrics via *SmartManage*.

2.15.2. Data management

After randomization, participants will receive a unique study ID. Data entry will occur in REDCap, and documents using study IDs (not containing PHI) will be password-protected and stored on a UM firewalled server accessible only to team members. Biospecimens will be processed and stored in a UM laboratory under de-identified record IDs. Bio-sample data will be stored in a secure UM firewalled and password-protected private network and only linked to participants via their unique record ID.

2.16. Statistical analysis

Demographic variables will be summarized using descriptive statistics for the overall sample and by subgroups (e.g., Spanish speaking vs. non-Spanish speaking, type of hematological malignancy). Counts and percentages will be used to summarize the distribution of categorical variables (e.g., race, ethnicity). Median, range, mean, and standard deviation will be used for continuous variables (e.g., age). Association between categorical variables will be tested using either chi-square or if needed with Fisher's exact test. Continuous variables will be tested using Student's *t*-test and/or Mann-Whitney *U* test. For correlation coefficients, Pearson's correlation coefficients and Spearman's correlation coefficients will be estimated along with corresponding 95% confidence intervals. We will also compute internal consistency for all scales, and if reliability is <0.70, we will delete items as needed [75]. Type-1 error will be set to 5% ($\alpha = 0.05$) for calculating confidence intervals and performing hypothesis testing and all tests will be two-sided. If needed, Bonferroni correction will be used to keep familywise error rate to 5%. Standard statistical goodness-of-fit measures will be used to assess any of the model fittings. Missing values will be handled with appropriate statistical methods. First, we will examine the proportion of missing values among our outcome variables. Then, we will explore missing data mechanisms (i.e., missing completely at random [MCAR], missing at

Table 2
Study measures and assessment timepoints.

	Construct	Instrument/Variables	Timepoints		
			T1	T2	T3
Sample Characteristics & Potential Confounders	Sociodemographic	Age, Education, Employment, Relationship Status, Race/Ethnicity, Acculturation (Short Acculturation Scale for Hispanics [74])	X		
	Medical Measures	Blood cancer type; cell counts (e.g., neutrophils, platelets); Acute or Chronic GVHD; Infection; Donor Type (i.e., matched vs. haploidentical; related vs. unrelated); Conditioning Therapy (i.e., radiation; intensive vs. reduced-intensity chemotherapy)	X	X	X
	Music Background	The Music USE Questionnaire (MUSE)—Music Background Subscale [58]	X		X
MT Mechanisms	eMM Mindfulness Skills	The Five Facet Mindfulness Questionnaire—Short Form (FFMQ-15) [57]	X		X
MBMT Mechanisms	eMBMT Music Therapy Skills	MUSE—Instrument Playing, Music Listening, & Music Engagement Subscales [58]	X		X
	eMBMT Music & Mindfulness Skills	MUSE—Cognitive & Emotional Regulation Subscale [58]	X		X
Psychosocial Adaptation	Depression	Patient Health Questionnaire (PHQ-9) [59]	X	X	X
	Anxiety	Generalized Anxiety Disorder (GAD-7) [60]	X	X	X
	Cancer-Specific Distress	The Impact of Events Scale-Revised (IES-R) [61]	X	X	X
Physiological Adaptation	Inflammation	Serum Cortisol; IL 1β, IL6, TNF-α, IL-8, IL-10	X		X
	Immune Reconstitution	Regulatory T-Cells; Thymic Function	X		X
Quality of Life & Symptom Burden	HRQOL	Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) [51]	X	X	X
	Pain, Fatigue, & Sleep	PROMIS Pain [52]; Fatigue-Short Forms [53]; Pittsburgh Sleep Quality Index (PSQI) [56]	X	X	X
	Cognitive Function	The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [55]	X		X
	Hospital days & Readmission	Number of days; Readmissions; Readmission days			X
Disease Activity	Chronic GVHD, CMV Activation, & Infections	Chronic GVHD, CMV Activation, Infections			X

T1: ≥ 7 days before transplant; T2: 6 to 1 days before transplant; T3: 45–60 days post-transplant; CMV: Cytomegalovirus; GVHD: graft-versus-host disease.

random [MAR], and missing not at random [MNAR]) as well as missing data patterns (i.e., monotone vs. non-monotone). Depending on the amount of missingness, full informational maximum likelihood (FIML) and multiple imputation might be considered.

2.16.1. Qualitative analyses

Bi-weekly phone calls assessing participants' acceptance and confidence using eMBMT and eMM and the final qualitative interviews assessing overall experience using the programs will be analyzed with a Rapid Qualitative Analysis (RQA) approach [76]. RQA is a pragmatic method which is crucial for guiding the refinement of digital interventions. Study staff will develop a coding matrix, individually code the transcripts, and meet to complete a comprehensive final matrix summarizing data to facilitate the identification of themes.

2.16.2. Quantitative analyses

For the study to be considered feasible, the following benchmarks will be used: 60% enrollment of eligible patients, 80% of participants retained throughout the study (from T1 to T3 assessment), and 80% completion all intervention sessions [60,77]. We will assess effects of MT components of the eMBMT and mindfulness components of both the eMBMT and eMM on HRQOL, symptom burden, disease activity, intervention targets/mechanisms, and measures of psychosocial and physiological adaptation while controlling for relevant sociodemographic and clinical measures. Trends ($p < .10$) and changes in means in the expected direction will provide evidence of preliminary effects of the intervention conditions and its components [78]. Effect sizes of the intervention components will be computed as the ratio of the difference in the change means of the study conditions (eMBMT vs. eMM) divided by the standard deviation of the outcome. Descriptives will characterize the sample and ensure values are within ranges [79]. For non-normality, log transformations or non-parametric statistics will be utilized. Sociodemographic and medical variables will be considered as covariates if correlated with outcomes ($p < .10$). We utilize an intent-to-treat approach and retain all participants. Our main analyses will use 95% confidence intervals for all estimates. Retention rates (expected 80%), can be estimated to be within ~12% of the true value in each condition with 95% confidence. We use *t*-tests and Chi-square or Fisher's exact tests to examine differences in feasibility (e.g., retention) and acceptability ratings (e.g., attendance) across patient characteristics (e.g., AML vs. CML) [78].

Our mediation analyses will fit multivariate trajectory models for both psychological and physiological adaption, and secondary outcomes, and examine the role of the potential mean changes of psychological and physiological adaption on the potential mean changes of secondary outcomes. We will use the "product of coefficients" test, which is based on the distribution of the indirect effect of the intervention through the mediator [80]. This procedure tests whether the product of the coefficients from the intervention to the mediator and from the mediator to the outcome is significantly different from zero. Specifically, we will estimate paths between the intervention condition and mediators (a path), and between mediators and outcomes (b path). Effect sizes will be calculated as the ratio of the mediation effect to the total effect. We will also test each MT and mindfulness components' preliminary effects on the mediators and study outcomes to identify potential mechanisms of change.

3. Discussion

Patients receiving allo-SCT experience a reduced HRQOL and significant symptom burden along with poor psychosocial adaptation including anxiety, depression, and social isolation that can persist long after the completion of treatment [3–8]. Therefore, the development of programs that reduce negative psychosocial and physiological factors and symptom burden in allo-SCT to improve HRQOL, PROs, and clinical outcomes are necessary. Emerging literature indicates that MBMT significantly reduces pain, anxiety, negative mood, and fatigue and improves sleep in cancer populations [49,50]. However, the impacts of MBMT on patients undergoing an allo-SCT remains largely unknown. Taken together, these findings establish the foundation for the current research. The current study is the first to develop a protocol that assesses the feasibility and acceptability and the preliminary effect sizes of eMBMT compared with eMM on increasing HRQOL and reducing symptom burden and disease activity in hematologic cancer patients undergoing an allo-SCT.

3.1. Innovative features

The eMBMT intervention is innovative in several ways. First, we refine and evaluate a complex, novel integrative medicine intervention, developed by our team, which draws from evidence-based programs across several disease populations. Second, rather than collapsing MT components into traditional categories of active vs. passive therapy we evaluate specific components of MT (i.e., music listening, music writing, instrument playing, singing, improvisation, vocal toning, soothing sounds, music assisted relaxation) and their unique contribution to study outcomes and psychosocial and physiological mediators. This addresses a significant gap in the literature by improving understanding of what components of MT favorably impact health outcomes. Third, the delivery of eMBMT is aligned with key clinical pivotal points across the inpatient continuum. Finally, the inclusion of biological measures such as T-cell receptor excision circle (TREC) assays and inflammatory cytokines adds clinical significance to this study.

3.2. Limitations

We acknowledge several limitations of the proposed work. First, eMBMT requires in-person sessions, which may be challenging for patients experiencing treatment side effects (e.g., fatigue), potentially leading to incomplete sessions. Second, unlike the self-led eMM, eMBMT is facilitated by a MT which may enhance participant engagement and personalization, resulting in higher satisfaction or perceived benefit. Thus, delivery mode differences may make it challenging to attribute observed effects solely to the MT components. Third, there are inherent challenges of comparing two novel interventions in a previously untested patient population (e.g., isolating effects, population variability); however, comparing eMBMT versus eMM and measuring skills and practice of music therapy allows us to isolate mechanisms of action (i.e., music instrument playing, music listening, music engagement) via which MBMT impacts HRQOL and symptom burden. Lastly, the current R61 phase has a small sample size, limiting statistical power. The next phase (R33) will include a fully powered RCT to examine the intervention's preliminary efficacy.

4. Conclusions

This pilot RCT develops a low-demand, stress-reducing, integrative approach for allo-SCT patients to improve HRQOL and reduce symptom burden and disease activity. eMBMT meets the demand for manualized and scalable interventions to establish specific MT components that impact physical and psychological outcomes in cancer.

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CRediT authorship contribution statement

Sara E. Fleszar-Pavlovic: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Blanca Noriega Esquives:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Arianna E. Brito:** Writing – review & editing, Writing – original draft, Methodology. **Ann Marie Sia:** Writing – review & editing, Writing – original draft. **Mary Adelyn Kauffman:** Writing – review & editing, Conceptualization. **Maria Lopes:** Writing – review & editing, Writing – original draft. **Patricia I. Moreno:** Writing – review & editing, Conceptualization. **Tulay Koru-Sengul:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis. **Rui Gong:** Writing – review & editing. **Trent Wang:** Writing – review & editing, Investigation, Conceptualization. **Eric D. Wieder:** Writing – review & editing, Resources, Methodology, Funding acquisition, Conceptualization. **Maria Rueda-Lara:** Writing – review & editing, Investigation, Conceptualization. **Michael Antoni:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Krishna Komanduri:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Teresa Lesiuk:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Frank J. Penedo:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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