BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

A Phase III Randomized, Multicenter Trial Testing Whether Exercise or Stress Management Improves Functional Status and Symptoms of Autologous and Allogeneic Recipients

BMT CTN PROTOCOL 0902
Version 2.0

Study Chairpersons

Stephanie J. Lee, M.D., M.P.H.[1]
Paul B. Jacobsen, Ph.D.[2]

Smita Bhatia, M.D., M.P.H.[3]
Amrin Chowdhury[4]
Mary Horowitz, M.D., M.S.[5]
Heather Jim, Ph.D.[2]
Jennifer Le-Rademacher, PhD.[5]
Brent Logan, Ph.D.[5]
Navneet Majhail, M.D, M.S.[6]
J. Douglas Rizzo, M.D., M.S.[5]
Karen L. Syrjala, Ph.D.[1]
Galen Switzer, Ph.D.[7]
John R. Wingard, M.D.[8]
William Wood, M.D. [9]

Sponsored by the National Institutes of Health
National Heart, Lung, and Blood Institute
National Cancer Institute

[1] Fred Hutchinson Cancer Research Center
[2] H. Lee Moffitt Cancer Center
[3] City of Hope National Medical Center
[4] The EMMES Corporation
[5] CIBMTR, Medical College of Wisconsin
[6] University of Minnesota
[7] University of Pittsburgh
[8] University of Florida
[9] University of North Carolina

Core Study Participants:

Case Western Reserve University Consortium
- Ohio State University
- Oregon Health & Science University
- University Hospitals of Cleveland

City of Hope National Medical Center
Fred Hutchinson Cancer Research Center
Johns Hopkins University
University of Florida College of Medicine
University of Michigan Cancer Center
University of Minnesota
University of Nebraska Medical Center

Affiliate Study Participants:

Fox Chase/Temple University
H. Lee Moffitt Cancer Center
Karmanos Cancer Institute
Medical College of Wisconsin
Medical University of South Carolina
Rush University Medical Center

PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0902

A Phase III Randomized, Multicenter Trial Testing Whether Exercise or Stress Management Improves Functional Status and Symptoms of Autologous and Allogeneic Recipients

Principal Investigators: Stephanie J. Lee, M.D., M.P.H.
Paul Jacobsen, Ph.D.

Study Design: Phase III, randomized, unblinded, multicenter, prospective comparative study of exercise, stress management, the combination of exercise and stress management versus standard care to improve functional status and symptoms.

Patients complete baseline measures and are randomized to one of the four arms, stratified by center and type of transplant procedure (autologous/syngeneic, myeloablative allogeneic, reduced intensity/non-ablative allogeneic). The exercise and stress management interventions are designed to be self-administered after a brief, 10-15 minute training session.

Endpoint assessment will occur at 100 days +/- 14 days and 6 months +/- one month

Primary Objective: To determine whether exercise or stress management improves self-reported physical and mental functioning compared to standard care at 100 days using an intention to treat analysis

Secondary Objectives:

a) To determine whether exercise or stress management improves physical and mental functioning compared to standard care at 100 days, limiting the analysis to patients who survive and provide a Day 100 self-assessment (conditional analysis with main effects)

b) To compare physical and mental functioning among the 4 groups using pair-wise comparisons, limiting the analysis population to patients who provide a Day 100 self-assessment (pair-wise conditional analysis)

c) To compare symptoms (fatigue, pain, sleep, nausea, cancer and treatment distress) at 100 days among patients who provide a Day 100 self-assessment (conditional analysis)

d) To compare the number of hospital days within the first 100 days

e) To assess durability of effects by comparing functional status and symptoms at 6 months

f) To compare overall survival at 6 months

Eligibility:

Inclusions:

a) Age 18 years or older.

b) Able to speak and read English.

c) Able to exercise at low to moderate intensity - adequate cardiopulmonary reserve, as judged by self-reported ability to walk up one flight of stairs, no requirement for supplemental oxygen, and physician judgment.

d) Willing and able to provide informed consent.

e) Stated willingness to comply with study procedures and reporting requirements.

f) Planned autologous or allogeneic transplantation within 6 weeks.

Exclusions:

a) Orthopedic, neurologic or other problems which prevent safe ambulation and protocol adherence.

b) Participation in another clinical trial with quality of life or functional status as a primary endpoint.

c) Planned anti-cytotoxic therapies, other than TKI, Gleevac or Rituximab OR unless pre-approved by the protocol chair, within 100 days post-transplant.

d) Planned DLI within 100 days post-transplant.

e) Planned tandem transplant (autologous/autologous or autologous/allogeneic).

Treatment Description: **Exercise.** The goal is to have participants exercise by walking 3 to 5 times per week for at least 20 to 30 minutes at a maximum intensity of 50 to 75% of their estimated heart rate reserve.

Stress management. The goal is to have participants practice paced abdominal breathing, progressive muscle relaxation with guided imagery, and use of coping self-statements to decrease stress.

Standard care will follow institutional guidelines that reflect standard practices

All 4 groups will receive a general informational DVD about hematopoietic cell transplantation.

Accrual Objective: 700 subjects will be randomized approximately 1:1:1:1 across the four study arms.

Accrual Period: The estimated accrual period is 36 months.

Study Duration: Patients will be followed for 6 months after transplantation.

Statistical issues: The primary objectives of the study are to compare physical functioning and mental functioning between the groups who do or do not receive exercise training and between the groups who do or do not receive stress management training (factorial design). The sample size calculation is based upon having 85% power to detect differences of 0.5 STD in the primary endpoint between groups (exercise vs. no exercise or stress management vs. no stress management) after splitting the type I error rate across these 4 primary comparisons. This analysis controls for baseline assessment and clinical characteristics and accounts for cancelled transplants and missing data using an Intention-to-Treat analysis. Randomization will be stratified for balance based on center and type of transplant (autologous, myeloablative allogeneic, and non-myeloablative allogeneic groups).

TABLE OF CONTENTS

LIST OF APPENDICES

CHAPTER 1

1. BACKGROUND AND RATIONALE

The adverse effects of hematopoietic cell transplantation (HCT) on short and long term quality of life are well documented (reviewed in Pidala[1]). Patients experience numerous aversive symptoms (e.g., nausea, fatigue, and sleep disturbance) that are accompanied by declines in physical and mental well-being. Although most longitudinal studies show return to baseline functioning for the majority of patients, it may take 6 to 12 months or longer to reach this goal.[2,3]

Clinical trials have shown that training in stress management techniques and participation in formal exercise programs each offered in isolation are effective in improving quality of life in patients receiving standard-dose chemotherapy and HCT. Review of these studies suggests that stress management interventions primarily improve mental health outcomes and nausea. The impact of exercise training interventions is more variable; most studies report physical health benefits, with some studies also reporting mental health benefits. Small studies suggest that combining stress management training and exercise are feasible and well-tolerated, but whether the combination provides an additive or synergistic impact on quality of life outcomes has not been directly investigated.

The purpose of this study is to test whether exercise or stress management training delivered to autologous and allogeneic HCT patients prior to transplantation can improve functional status and the transplant experience.

1.1. Exercise

A 2008 review found 15 published studies of exercise in the context of HCT up through May 2007. A total of 609 patients were included in the review, with no study reporting any unexpected or negative effects.[4-19] Study size ranged from 12-100 participants with approximately half autologous and half allogeneic patients. Most involved isolated aerobic exercise programs such as walking, recumbent biking or treadmills and occurred during or after the transplantation process; strength training and combined strategies were evaluated less often. Significant benefits were reported for physical performance, quality of life, and fatigue.[20] A variety of biological, psychological, and social mechanisms have been proposed to account for the beneficial effects of exercise on quality of life in people with cancer.[21]

The University of Minnesota conducted a randomized trial of a structured walking regimen on a treadmill at a dosage of 15 minutes twice daily while in the hospital followed by 30 minutes of walking daily after discharge. Results in 122 patients showed a smaller decline in Karnofsky performance status in the exercise group compared to control patients which was not statistically significant in the whole group but was statistically significant in the subset of older and less fit patients receiving non-ablative conditioning ($p=0.04$). Compliance was excellent with 93% in the exercise arm exercising during hospitalization compared to 58% in the control arm. There were no differences in length of hospitalization or survival, but all trends favored the exercise group.[19]

Thus, self-administered exercise in the context of HCT, even during acute hospitalization, is feasible and small studies suggest significant benefits over standard care. Table 1.1 summarizes relevant studies.

TABLE 1.1 – SUMMARY OF EXERCISE TRIALS IN ADULT HCT

Author	Year	N	Study Characteristics	Intervention	Endpoints	Summary of Results
Cunningham BA, Morris G, Cheney CL, et al[1]	1986	30	RCT, allogeneic HCT	3 groups: Control, physical therapy 3x/week, physical therapy 5x/week	Muscle protein status measured by nitrogen balance, creatinine, 3 methylhistidine excretion	Results favored a muscle protein-sparing effect of exercise but patient heterogeneity problematic
Decker WA, Turner-McGlade J, Fehir KM[2]	1989	5	Single arm	Individualized endurance training/exercise prescription (30 min 3x/week)		Results not significant
Dimeo F, Bertz H, Finke J, et al[3]	1996	20	Single arm, 17 allogeneic and 3 autologous HCT, started 30 days post allogeneic HCT	Professionally administered rehab program, treadmill walking 5x/week for 6 weeks	Training speed, distance walked, maximal METs, heart rate, lactate concentration	Statistically significant ($p<0.001$) improvements in all measures pre-post in completers (n=14)
Dimeo FC, Tilmann MHM, Bertz H, et al. [4]	1997	36	Concurrent controls (n=18) and treated group (n=18) based on distance to hospital, autologous HCT	Professionally administered rehab program, treadmill walking 5x/week for 6 weeks	Maximal performance, maximum heart rates, hemoglobin, interviews at 7 weeks	Statistically significant improvement in maximum performance in the exercise group compared with controls ($p=0.04$), higher hemoglobin than controls ($p=0.04$), no difference in heart rates. Fatigue and limitations with usual daily activities reported by 25% of control patients, 0% of intervention patients in completers (n=36)

Author	Year	N	Study Characteristics	Intervention	Endpoints	Summary of Results
Dimeo F, Fetscher S, Lange W, et al[5]	1997	70	RCT, autologous HCT	Professionally administered exercise regimen of biking on a supine ergometer 30 min daily, goal to reach 50% of cardiac reserve, during hospitalization	Maximal speed on the treadmill test at discharge	Exercise group with less decrement in performance (p=0.05), higher maximal physical performance (p=0.04), shorter duration of neutropenia (p=0.01) and thrombocytopenia (p=0.06), severity of diarrhea (p=0.04), severity of pain (p=0.01) and duration of hospitalization (p=0.03) among completers (n=60). Similar results in multivariate regression
Dimeo FC, Stieglitz RD, Novelli-Fischer U, et al[6]	1999	59	RCT according to week recruited, autologous HCT	Professionally administered exercise regimen of biking on a supine ergometer 30 min daily, goal to reach 50% of cardiac reserve, during hospitalization	Patient-reported outcomes: POMS, SCL-90	Control group had increased fatigue and somatic complaints ($p<0.01$) and decreased vigor (p=0.05) but not in the exercise group. Exercise group had improvement in obsessive-compulsive traits, fear, interpersonal sensitivity, and phobic anxiety ($p<0.05$)
Dimeo F, Schwartz S, Fietz T, et al[7]	2003	66	Single arm, conventional chemo (n=45) or autologous HCT (n=21)	Professionally administered rehab program, treadmill walking 5x/week, during hospitalization	Walking speed, perceived effort at 80% maximum heart rate	No significant change over time, which was viewed as positive by the authors given the anticipated decline without exercise
Courneya KS, Keats MR, Turner AR. [8]	2000	25	Single arm, autologous HCT	Self-administered supine ergometer during hospitalization	Patient-reported outcomes: FACT-BMT, Bradburn Affect Balance Scale, SWLS (satisfaction with life scale), CES-D, STAI	40% reported no cycling at all, 24% reported no cycling or walking, mean combined cycling/walking was < 8 min/day. Exercise during hospitalization correlated with all Quality of Life (QOL) and PRO indices including depression, anxiety and days hospitalized except emotional and social well-being

Author	Year	N	Study Characteristics	Intervention	Endpoints	Summary of Results
Mello M, Tanaka C, Dulley FL. [9]	2003	18	RCT, allogeneic HCT	Control vs. 6 week exercise program of active exercise, muscle stretching, treadmill walking for 40 min, 5x/week	Muscle strength	Control group had decreased strength, less change in exercise group; intergroup comparison not significant
Hayes SC, et al[10-13]	2003 2003 2004 2004	12	RCT and matching, autologous HCT	Professionally administered, control/stretching group vs. aerobic, treadmill, 3x/week 20-40 min at 70-90% of maximum heart rate and resistance exercise, 2x/week x 3 months	Lymphocyte number and function, total energy expenditure, body weight, body composition, patient-reported outcomes (CARES), peak aerobic capacity and muscular strength	No difference in immunologic parameters. Exercise group had gains in fat-free mass ($p<0.01$), decreased % body fat ($p<0.05$), improved QOL (global QOL, physical and psychosocial QOL, fewer and less severe problems), peak aerobic capacity ($p=0.05$) and upper and lower body strength ($p<0.01$) compared to controls
Coleman EA, Coon S, Hall-Barrow J et al. [14]	2003	24	RCT, autologous HCT	Control with encouragement to be active vs. Home-based exercise therapy with walking and strength resistance training with stretch bands	Fatigue, mood disturbance, sleep, lean body weight	Statistical improvement in lean body weight (8 completers)
Kim SD, Kim HS[15]	2006	35	RCT, allogeneic HCT	Control vs. bed exercise 30 min every day, relaxation breathing for 6 weeks	Lymphocyte count	Decrease in lymphocyte in the control group but not in the exercise group.

Author	Year	N	Study Characteristics	Intervention	Endpoints	Summary of Results
Wilson RW, Jacobsen PB, Fields KK[16]	2005	17	Single arm, > 6 months after either autologous (n=13) or allogeneic (n=4) HCT	Home based exercise, 20-40 min at 40-60% of predicted heart rate reserve, 3-5 x week for 12 weeks	Patient-reported outcomes: SF36, fatigue symptom inventory; ventilatory threshold (aerobic fitness)	Aerobic fitness, fatigue severity, physical well-being improved ($p<0.05$) (completers=13)
Carlson LE, Smith D, Russell J, et al[17]	2006	12	Single arm, > 6 months after allogeneic HCT	Individualized mild aerobic exercise program using ergometers, 15-30 minues, 3x week x 12 weeks	Patient reported outcomes: FACT-F, Brief Fatigue Inventory, CES-D, POMS; SCID; physiological measures (VT2, changes in stroke volume, heart rate, lactate level, perceived exertion)	Significant improvements in fatigue (BFI, FACT-F), vigor ($p<0.001$), VT2, stroke volume, and significant decrease in heart rate, lactate level and perceived exertion. The effect size for fatigue was 1.82 STD
DeFor TE, Burns LJ, Gold EMA, et al[18]	2007	100	RCT, allogeneic HCT	Control vs. structured walking program, treadmill walking 2x/day x 15 minutes while in hospital, 30 minutes daily as outpatients	Karnofsky performance status, self-reported well being, length of hospital stay, survival	Decline in KPS less in the exercise group than control group, but not statistically significant ($p=0.2$). In subset analyses, older and less fit patients receiving reduced intensity had less KPS decline than controls ($p=0.04$). Better physical well-being at hospital discharge in overall group ($p<0.01$) and better physical and emotional well being at discharge in non-myeloablative exercise group compared with control
Coleman EA, Coon SK, Kennedy RL et al[19]	2008	120	RCT, autologous HCT, myeloma	Control vs. Home-based individualized program, walking, stretching, strength resistance training 5x week	Number of RBC and platelet transfusions and total number of stem cell collection days	Exercise group had significantly fewer RBC transfusions and attempts at stem cell collection than controls; note that although randomized, exercise group had greater exercise capacity before HCT

Author	Year	N	Study Characteristics	Intervention	Endpoints	Summary of Results
Jarden M, Baadsgaard MT, Hovgaard DJ et al[20-22]	2007 2009 2009	42	RCT, allogeneic HCT	Control vs. Supervised, 1 hr 5x week of cycling, stretching, resistance training, progressive muscle relaxation and cognitive behavioral therapy	Aerobic capacity, muscle strength, functional performance, physical activity level, clinical outcomes, patient-reported outcomes (EORTC, FACT-An, HADS, Mimi Mac)	Intervention group had better physical capacity ($p<0.0001$), muscle strength, functional performance, less diarrhea ($p=0.01$), fewer days TPN ($p=0.02$). Longitudinal changes in QOL, fatigue and psychological well being showed a trend to better outcomes with intervention but not statistically significant. Separate paper reports less symptom intensity

[1] Cunningham BA, Morris G, Cheney CL, et al: Effects of resistive exercise on skeletal muscle in marrow transplant recipients receiving total parenteral nutrition. JPEN J Parenter Enteral Nutr 10:558-63, 1986
[2] Decker WA, Turner-McGlade J, Fehir KM: Psychosocial aspects and the physiological effects of a cardiopulmonary exercise program in patients undergoing bone marrow transplantation (BMT) for acute leukemia (AL). Transplant Proc 21:3068-9, 1989
[3] Dimeo F, Bertz H, Finke J, et al: An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. Bone Marrow Transplant 18:1157-60., 1996
[4] Dimeo FC, Tilmann MH, Bertz H, et al: Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. Cancer 79:1717-22, 1997
[5] Dimeo F, Fetscher S, Lange W, et al: Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. Blood 90:3390-4., 1997
[6] Dimeo FC, Stieglitz RD, Novelli-Fischer U, et al: Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer 85:2273-7, 1999
[7] Dimeo F, Schwartz S, Fietz T, et al: Effects of endurance training on the physical performance of patients with hematological malignancies during chemotherapy. Support Care Cancer 11:623-8, 2003
[8] Courneya KS, Keats MR, Turner AR: Physical exercise and quality of life in cancer patients following high dose chemotherapy and autologous bone marrow transplantation. Psychooncology 2000; 9:127-36
[9] Mello M, Tanaka C, Dulley FL: Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant 32:723-8, 2003
[10] Hayes S, Davies PS, Parker T, et al: Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme. Bone Marrow Transplant 31: 331-8, 2003
[11] Hayes SC, Rowbottom D, Davies PS, et al: Immunological changes after cancer treatment and participation in an exercise program. Med Sci Sports Exerc 35: 2-9, 2003.
[12] Hayes S, Davies PS, Parker T, et al: Quality of life changes following peripheral blood stem cell transplantation and participation in a mixed-type, moderate-intensity, exercise program. Bone Marrow Transplant 33:553-8, 2004
[13] Hayes SC, Davies PS, Parker TW, et al: Role of a mixed type, moderate intensity exercise programme after peripheral blood stem cell transplantation. Br J Sports Med 38:304-9; discussion 309, 2004
[14] Coleman EA, Coon S, Hall-Barrow J, et al: Feasibility of exercise during treatment for multiple myeloma. Cancer Nurs 26:410-9, 2003
[15] Kim SD, Kim HS: A series of bed exercises to improve lymphocyte count in allogeneic bone marrow transplantation patients. Eur J Cancer Care (Engl) 15:453-7, 2006
[16] Wilson RW, Jacobsen PB, Fields KK: Pilot study of a home-based aerobic exercise program for sedentary cancer survivors treated with hematopoietic stem cell transplantation. Bone Marrow Transplant 35:721-7, 2005
[17] Carlson LE, Smith D, Russell J, et al: Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study. Bone Marrow Transplant 37:945-54, 2006
[18] DeFor TE, Burns LJ, Gold EM, et al: A randomized trial of the effect of a walking regimen on the functional status of 100 adult allogeneic donor hematopoietic cell transplant patients. Biol Blood Marrow Transplant 13:948-55, 2007
[19] Coleman EA, Coon SK, Kennedy RL, et al: Effects of exercise in combination with epoetin alfa during high-dose chemotherapy and autologous peripheral blood stem cell transplantation for multiple myeloma. Oncology Nurs Forum 2008; 35: E53-E61

[20] Jarden M, Hovgaard D, Boesen E, et al: Pilot study of a multimodeal intervention: mixed-type exercise and psychoeducation in patients undergoing allogeneic stem cell transplantation. BMT 2007; 40: 793-800
[21] Jarden M, Baadsgaard MT, Hovgaard DJ, et al: A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. BMT 2009; 43: 725-737
[22] Jarden M, Nelausen K, Hovgaard D, et al: The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: a randomized controlled trial. J Pain Symptom Manage 2009; 38: 174-190.

1.2. Stress Management

Many studies suggest that professionally administered stress management training including progressive muscle relaxation training with guided imagery[22] and hypnosis[23] are effective in relieving nausea, vomiting and emotional distress in the period just before chemotherapy administration. A systematic review[24] identified two possible mechanisms for the effects of stress management: physiological relaxation and enhanced perceptions of self-efficacy and mastery. Both effects would seem highly beneficial to patients undergoing HCT. However, very few studies of stress management training have been performed in the HCT population.

Stress management does not have to be professionally directed. An important study compared professionally delivered stress management to self-administered training.[25] The training was similar to the proposed intervention in our trial, including instruction in three techniques (abdominal breathing, progressive muscle relaxation training with guided imagery, and coping self-statements) found to be effective in improving quality of life in a variety of clinical populations.[26-28] In the professionally administered form, training was provided during a 60-minute session conducted by a mental health professional. In the patient self-administered form, training was provided via materials distributed by a mental health professional. Only the self-administered form was superior to usual care in improving quality of life. Moreover, costs of this intervention were 68% less than average costs of other professionally administered stress management interventions for chemotherapy patients. Table 1.2 summarizes the relevant studies.

TABLE 1.2 – SUMMARY OF STRESS MANAGEMENT TRIALS IN ADULT HCT, PLUS SELECTED OTHER RELEVANT TRIALS

Author	Year	N	Sample Characteristics	Intervention	Endpoints	Summary of results
Syrjala KL, Cummings C, Donaldson GW, et al[1]	1992	67	RCT, allogeneic HCT	4 groups: hypnosis training, cognitive behavioral coping, therapist contact control, standard treatment. Two 90 minute sessions pre transplant, 10 in-hospital booster sessions	Pain, nausea, emesis, opioid use	Hypnosis training reduced pain. Nausea, emesis and opioid use did not differ among treatment groups

Author	Year	N	Sample Characteristics	Intervention	Endpoints	Summary of results
Syrjala KL, Donaldson GW, Davis MW, et al[2]	1995	94	RCT, allogeneic HCT	4 groups: Usual care; therapist support; relaxation and imagery training; and relaxation and imagery plus cognitive-behavioral coping skills. Pre-HCT training, seen twice a week for 20-40 min sessions.	Pain, nausea	Relaxation and imagery training decreased reported pain compared to standard care and therapist support; adding cognitive-behavioral training did not have an additive effect
Gaston-Johansson F, Fall-Dickson J, Nanda J, et al[3]	2000	110	RCT, auto HCT, breast cancer	2 groups: Comprehensive Coping Strategy Program (CCSP) of preparatory information, cognitive restructuring, relaxation with guided imagery; standard care. Training 2 weeks before HCT, audiotape provided. Reinforced 3 times during hospitalization.	Pain, fatigue, anxiety, depression, nausea	CCSP experienced decreased nausea and fatigue compared to controls. Anxiety was mild in the SSCP group and moderate in the controls.
Jacobsen PB, Meade CD, Stein KD, et al[4]	2002	411	RCT, outpatients receiving chemotherapy	3 groups: Usual psychosocial care; Professionally administered form of stress management training (60 minutes); or patient self-administered form of stress management training (10 minutes) prior to chemotherapy.	Functional status (SF36), depression, anxiety	Compared with patients who received usual care only, patients receiving the self-administered intervention reported significantly better physical functioning, greater vitality, fewer role limitations because of emotional problems, and better mental health. No difference in QOL between the control group and the Professionally administered training group. The cost of the self-administered training was 68% less than the professionally administered training.

Author	Year	N	Sample Characteristics	Intervention	Endpoints	Summary of results
Wilson RW, Taliaferro LA, Jacobsen PB[5]	2006	39	Pilot feasibility study, outpatients receiving chemotherapy	5-10 minute training, goal to exercise 20-40 min at 50-75% estimated heart rate reserve 3-5 times/wk and stress management techniques, reinforced before each chemotherapy cycle	Functional status (SF36)	24 completed the study (10 became ineligible due to death, chemotherapy stopped etc; 5 chose not to complete the study). Paired t tests showed improvements since baseline in bodily pain and mental health

1. Syrjala KL, Cummings C, Donaldson GW. Hypnosis or cognititve behavioral training for the reduction of pain and nausea during cancer treatment: a controlled clinical trial. Pain 1992; 48: 137-146.
2. Syrjala KL, Donaldson GW, Davis MW, et al: Relaxation and imagery and cognitive-behavioral training reduce pain during cancer treatment: a controlled clinical trial. Pain 63:189-98., 1995
3. Gaston-Johansson F, Fall-Dickson J, Nanda J et al. The effectiveness of the Comprehensive Coping Strategy Program on clincal outcomes in breast cancer autologous bone marrow transplantation. Cancer Nurs 2000; 23: 277-285.
4. Jacobsen PB, Meade CD, Stein KD, et al: Efficacy and costs of two forms of stress management training for cancer patients undergoing chemotherapy. J Clin Oncol 20:2851-62, 2002
5. Wilson RW, Taliaferro LA, Jacobsen PB. Pilot study of a self-administered stress management and exercise intervention during chemotherapy for cancer. Support Care Cancer 2006; 14: 928-935.

1.3. Rationale for Combined Exercise and Stress Management

This trial includes a group that receives training in both stress management and exercise training, based on the hypothesis that the combined intervention may yield greater improvements in a broader array of quality of life outcomes than either form of training alone. That is, it may be possible to combine the anticipated mental health benefits with stress management training with the physical health benefits hypothesized with exercise training to achieve synergistic results. Most studies suggest that there are some mental health benefits attainable with exercise and conversely, some physical and symptom benefits associated with stress management. There is no evidence to suggest that exercise has negative mental health benefits or that stress management has negative physical benefits. The protocol team acknowledges the theoretical negative interaction between the interventions based on overwhelming patients with too many instructions and expectations however the balance of the evidence suggests that assuming additive effects is reasonable.

Exercise research suggests several ways in which exercise training might increase the potency of stress management training. First, exercise training may serve as an effective distractor during periods of acute stress. Second, cardiorespiratory benefits of exercise training may enhance physiologic responses to progressive muscle relaxation and deep breathing. Third, engaging in exercise training may improve mood[29,30] and enhance perceptions of self-efficacy and mastery. Similarly, research on stress management training[31,32] suggests at least two ways in which stress management training might increase the potency of exercise training. First, by promoting active problem solving, stress management training may reduce barriers to engaging in exercise training. Second, by reducing physiologic reactions to stress, stress management training may increase capacity to engage in exercise training.

Potential synergy between the stress management and exercise training is an important secondary analysis that will use pairwise analytic techniques.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

Phase III, randomized, unblinded, multicenter, prospective comparative study of exercise or stress management versus standard care to improve functional status and symptoms.

2.2. Hypothesis and Study Objectives

The primary hypothesis of this trial is that use of self-administered exercise or stress management techniques by hematopoietic cell transplant recipients will improve their transplant experience and post-transplant functioning. Specifically, we hypothesize that the exercise intervention will primarily improve physical functioning, and the stress management intervention will primarily improve mental functioning. Secondary analyses will test whether the combination of both interventions will have additive or synergistic effects on these endpoints. Symptoms may be improved and days of hospitalization may be decreased by the interventions.

2.2.1. Primary Objective

To determine whether exercise or stress management improves self-reported physical and mental functioning compared to standard care at 100 days after transplantation.

2.2.2. Secondary Objectives

To compare several secondary measures of an improved transplant experience. Specifically, secondary analyses will determine whether physical and mental functioning differs among the groups in patients surviving 100 days and providing self-reported data. We will also explore whether the combination of both interventions has an additive or synergistic effect on these endpoints. Secondary analyses will also test whether symptoms (fatigue, pain, sleep, nausea, cancer and treatment distress) are less at 100 days and number of hospital days within the first 100 days is decreased by the interventions. We will also test whether benefits are durable by comparing functional status and symptoms at six months between the intervention groups and the control arm. Survival at 6 months will be compared.

2.3. Patient Eligibility for Randomization

2.3.1. Patient Inclusion Criteria

Patients may be included in this trial if they meet all of the following criteria:

1. Age 18 years or older – the interventions and assessment tools have not been validated for children.
2. Able to speak and read English – interaction with the interventionist trainer and endpoint measurement must occur in English. If the interventions are proven effective, then additional studies to create and validate a culturally appropriate intervention will be required.
3. Able to exercise at low to moderate intensity – current participation in a supervised or unsupervised exercise program is allowed.
4. Adequate cardiopulmonary reserve, as judged by self-reported ability to walk up one flight of stairs, no need for supplemental oxygen, and physician judgment.
5. Willing and able to provide informed consent.
6. Stated willingness to comply with study procedures and reporting requirements.
7. Planned autologous or allogeneic transplantation within 6 weeks.

2.3.2. Patient Exclusion Criteria

Patients will be excluded from this trial if they meet any of the following criteria:

1. Orthopedic, neurologic or other problems which prevent safe ambulation and protocol adherence.
2. Participation in another clinical trial with quality of life or functional status as a primary endpoint.
3. Planned anti-cytotoxic therapies, other than TKI, Gleevac or Rituximab OR unless pre-approved by the Protocol Chair, within 100 days post-transplant.
4. Planned DLI within 100 days post-transplant.
5. Planned tandem transplant (autologous/autologous or autologous/allogeneic).

2.4. Interventions

All intervention groups require that participants have access to a DVD player to watch the video materials. For those few patients without such access, we will ensure that they are able to view the DVD in the clinic. The stress management group requires a CD player. Almost all participants are expected to own such equipment or have ready access to it. Descriptions of the interventions are in section 2.4.1-2.4.4 below. Additional details are found in section 4.3. All "Day +X" refer to "days post transplant," for example, "Day 30 +/- 7 days" refers to 30 +/- 7 days after graft infusion.

2.4.1. Exercise

Participants assigned to the Exercise arm will receive a packet of materials from the study interventionist, along with a brief (10 minute) personalized introduction to the home-based exercise intervention. The packet of materials will consist of a videotape (or DVD if preferred), a brochure, a workbook, and an electronic step counter (Digi-Walker Model #SW-651-04). Participants will be instructed to view the 15 minute videotape and directions in the brochure for exercise training before admission for transplantation. The videotape and brochure discuss the rationale and potential benefits of engaging in regular exercise. The emphasis is on walking, as previous research has demonstrated relatively high rates of adherence and quality of life benefits with such programs,[33] and most transplant units can accommodate this form of exercise. The videotape and brochure provide information about the importance and practice of warming up and cooling down, pulse monitoring during exercise, proper attire and footwear, recommendations regarding hydration, suggestions about when and where to exercise, precautions and advice about when not to exercise, cautions regarding overtraining, advice on addressing perceived barriers to exercise, and instructions on how to operate the electronic step counter. Interspersed throughout the videotape and brochure are testimonials provided by patients about the benefits of exercise training. The goal is to have participants exercise at least 3 to 5 times per week for at least 20 to 30 minutes at a maximum intensity of 50 to 75% of their estimated heart rate reserve. This goal is consistent with guidelines for exercise in cancer patients developed by Courneya et al. and published by the ACSM.[34] Although the exercise instructions are not tailored to the level of prior exercise, the exercise goal is based on target heart rate. Because attained heart rate with any particular level of exercise varies according to prior physical conditioning and current health status, the use of the target heart rate automatically adjusts for past and current strength and conditioning. This intervention is expected to exert beneficial effects on quality of life by improving cardiorespiratory fitness[35] and perceived control of the symptom experience. Participants will be provided with log forms that they can use to record their exercise schedules. However, these logs are for their use and will not be analyzed for research purposes.

On Day 30 +/- 7 days participants will meet briefly with the same interventionist whenever possible. The purpose of this meeting is to answer any questions about the intervention and promote adherence to exercise recommendations. This meeting will also be used to monitor for contraindications to continuation of moderate intensity exercise. To minimize contamination across intervention conditions, participants randomized to Exercise will be provided with only general advice regarding stress management (i.e., to continue using any techniques they currently use to manage stress). The interventionist will meet with the patient again in person or by phone at approximately 60 +/- 7 days post transplant. Whenever possible, this should be the same interventionist who previously met with the patient.

2.4.2. Stress Management

The Stress Management intervention to be used is the same intervention used in prior studies of patients receiving chemotherapy.[25] Participants will receive a packet of materials from the study interventionist, along with a brief (10 minute) standardized introduction to the self-administered

intervention. The packet of materials will consist of a videotape (or DVD if preferred), audiotape (or CD if preferred), brochure, and workbook. Participants will be instructed to first view the 15 minute videotape and then follow brochure directions about further training, practice, and use of stress management techniques. The videotape and brochure discuss sources and manifestations of stress during treatment and potential benefits of using stress management techniques. They also provide brief instruction in paced abdominal breathing, progressive muscle relaxation with guided imagery, and use of coping self-statements, as well as recommendations for practicing these techniques. Testimonials about the benefits of stress management training provided by patients are interspersed throughout the videotape and brochure. The paced breathing exercise follows a format similar to that developed by Turk et al.[36] The relaxation and guided imagery exercise uses a format similar to that developed by Burish et al.[22] The use of coping self-statements is adapted from Meichenbaum's stress inoculation training.[37] Selection of these intervention components was guided by a cognitive-behavioral model of symptom management.[36] Consistent with this model, this intervention is expected to exert beneficial effects by reducing appraisals of stress, increasing perceived self-efficacy in managing stress, and increasing perceived control of the symptom experience. Participants will be provided with log forms with which to record practice of the three stress management techniques. However, these logs are for their use and will not be analyzed for research purposes.

On Day 30 +/- 7 days the same interventionist will meet with the participant briefly to answer any questions about the intervention, encourage the continued use of stress management techniques as recommended, and monitor for any adverse reactions to use of the techniques. To minimize contamination across intervention conditions, participants randomized to Stress Management will be provided with only general feedback about fitness testing and only general advice about exercise during transplant (i.e., to maintain any usual patterns of exercise to the extent possible). The interventionist will meet with the patient again in person or by phone at approximately 60 +/- 7 days post transplant. Whenever possible, the interventionist meeting with the patient at 30 and 60 days should be the same interventionist who previously met with the patient.

2.4.3. Combination Exercise and Stress Management

The combined Exercise and Stress Management intervention will combine the major elements of the interventions described above. Participants will receive a packet of materials from the study interventionist, along with a brief (15 minute) personalized introduction to the interventions. The packet of materials will consist of a videotape (or DVD if preferred), an audiotape (or CD if preferred) of progressive muscle relaxation and guided imagery, a brochure about exercise and stress management, and an electronic step counter. Instructions and information regarding stress management and exercise will be identical to those included in the other videotapes. The videotape will include footage not appearing in the other two videotapes explaining the benefits of engaging in both stress management and exercise during treatment and is approximately 25 minutes in length. Selected patient testimonials from the other videotapes will also be included. A brochure combining the major elements of the other two brochures will also be produced. The introduction to the combination intervention provided by the study interventionist will combine the elements described above for the Exercise and Stress Management interventions.

Participants in this intervention condition will be provided with log forms to record practice of stress management techniques and completion of recommended exercise training. However, these logs are for their use and will not be analyzed for research purposes.

On Day 30 +/- 7 days the same interventionist will meet with the participant briefly to answer any questions about the interventions, encourage the continued use of the interventions as recommended, and monitor for any adverse reactions. The interventionist will meet with the patient again in person or by phone at approximately 60 +/- 7 days post transplant. Whenever possible, the interventionist meeting with the patient at 30 and 60 days should be the same interventionist who previously met with the patient.

2.4.4. Standard Care Only (informational DVD)

Patients randomized to standard care only will receive usual psychosocial care and a general transplant DVD produced by the National Marrow Donor Program entitled, "Words of Experience. Stories of Hope" which covers a variety of pre and post-transplant topics. The DVD is approximately 45 minutes long organized into a series of chapters, is appropriate for both autologous and allogeneic patients, and does not provide any instruction in exercise or stress management techniques.

Patients randomized to standard care only will be informed of their assigned condition and receive the DVD. The interventionist will briefly discuss the topics of the DVD and elicit questions. To minimize contamination across intervention conditions, participants randomized to the control group will be provided with only general advice about exercise and stress management during treatment (i.e., to maintain any usual patterns of exercise to the extent possible and to continue using any techniques they currently use to manage stress).

All groups (exercise, stress management, combined exercise and stress management, and control) will receive the same general transplant DVD.

2.4.5. Training of Interventionist

It is anticipated that designated interventionists will be research personnel trained as physicians, nurses or nurse practitioners, physician assistants, social workers, research assistants, data managers or other persons familiar with HCT. A center must designate two individuals who will be trained to provide instructions about the intervention to study participants. The requirement for two trained interventionists per center is to ensure availability throughout the enrollment period, and also to allow one interventionist to deliver the patient training and the other to collect outcome measures if necessary. Ideally, each center will designate a third person, uninvolved with intervention delivery, to collect patient-reported outcomes.

Prior to enrollment of the first participant, the interventionists will undergo extensive training under the supervision of Protocol Team members that includes instruction in how to implement protocols for introducing each intervention, explaining intervention materials, identifying a recommended duration and intensity of exercise, and answering questions during the initial contact. Training will also include review of protocols for telephone contacts and follow-up

contacts with participants. A key element of the training will be instruction in how to avoid contamination among the intervention conditions. Interventionists will only be recorded with subjects enrolled in the study.

2.4.6. Quality Control of Intervention Delivery

Some intervention sessions will be audio taped during the study for quality control to verify the intervention is delivered properly. Sites will be informed of the selection process for selecting the interventions to audio tape. The Protocol Team Member, who will evaluate the interventions, will provide feedback to the interventionists at sites. Interventionists at participating centers should adhere to the "BMT CTN 0902 Evaluation of Intervention Delivery SOP" for guidelines regarding selection process of the interventions to be taped and feedback from the evaluator. In addition, the two trained interventionists at each center should use the Fidelity Checklists to ensure all the requirements of an intervention are met, as explained in the SOP.

2.5. Stem Cell Transplantation

Patients may receive any type of transplant conditioning, any type of stem cell source and donors may be HLA-matched or mismatched. Prior transplantation is allowed. Syngeneic donors are allowed and will be included in the stratum of autologous procedures. Graft-versus-host disease prophylaxis, graft engineering, monitoring for and treatment of complications and supportive care will be per institutional standards. Definitions of myeloablative and reduced intensity/nonmyeloablative conditioning regimens for the purposes of stratification and randomization will be per Center for International Blood and Marrow Transplant Research definitions.

2.6. Design Rationale

In planning the current study, several alternative methodological approaches were considered but not adopted.

- **Dose intensity of the exercise intervention:** The most successful exercise interventions generally involve a more intensive exercise program including personal trainers, personal exercise equipment, strength plus aerobic training and increased contact with boosters. However, these approaches are not currently feasible within the personnel and financial constraints of transplant centers, so the intervention could not be widely disseminated. We envision the current study as a test of dissemination. Despite the strong preliminary evidence that formal exercise programs are beneficial and the fact that most centers encourage their patients to exercise during HCT, almost none provide formal exercise training or use home-based exercise programs.
- **Delivery of the intervention:** The Protocol Team opted for interventions that are self-administered after a brief training session based on two considerations. First, as noted above for exercise, an intensive delivery system in not feasible within current center resources. Second, two randomized studies, one testing an exercise intervention[33] and one evaluating stress management training,[25] found greater effects with the self-administered interventions than supervised programs.

- **Delay of intervention delivery:** Many quality of life intervention programs target a period later after transplantation, both for practical as well as scientific reasons. Favoring delayed study is the fact that the period of greatest toxicity is likely to be immediately post-transplant, interfering with participants' ability to use the interventions effectively. Acute toxicity and early mortality may make it difficult to discern any intervention benefits. Differences in early mortality and complication rates among patient subpopulations may add unwanted noise. Arguments for early delivery include that other exercise and stress management studies have detected benefits of interventions applied early during the transplant process. From a practical perspective, it is easier to enroll patients prior to transplant and train them in use of the interventions. It is also possible that use of the intervention prior to admission could increase the efficacy of the intervention once transplant commences.
- **Objective measures of intervention use:** The use of objective measures of intervention use rather than subjective self-report use of interventions was considered. Although wrist-worn actigraphs which measure actual activity could be used for this purpose, we were concerned about the feasibility and expense of outfitting study participants with this equipment. Previous studies of cancer patients employing actigraphs have been characterized by relatively small sample sizes.[38,39] Daily patient diaries were considered but deemed too burdensome in this population. As this is primarily an effectiveness trial of dissemination based on solid preliminary studies, we felt that the extra costs and logistical difficulties did not justify the information to be learned.
- **Objective endpoint measures:** The use of objective measures of physical and mental functioning was considered. Physiologic testing through exercise stress tests require special equipment and personnel, and are time consuming and costly. We considered measurement of a 2 or 6 minute walk[40,41] test, but this would add burden to the participants and sites, and may not be feasible in busy clinical areas.
- **Timing of endpoint assessment:** The primary endpoint could be assessed earlier or later than 100 days. An earlier assessment time might increase the number of evaluable participants but would increase the heterogeneity of symptoms due to different conditioning agents and intensity. A later assessment time might dilute the effect of the intervention due to treatment-related mortality, relapse, loss to follow up and other events.
- **Analytic design:** An intention-to-treat analysis which assigns functional scores to patients who either die before endpoint assessment or who fail to provide 100 day self-reported data was selected as the primary analysis in order to provide the most conservative estimate of the interventions' effectiveness. Because of the large number of anticipated deaths and missing Day 100 data severely inflates the target sample size, the primary analysis will exploit the factorial design and collapse groups according to the intervention being tested (stress management vs. no stress management, exercise vs. no exercise). A critical secondary analysis will address the clinical question of whether one or more of the intervention arms improve functional status and symptoms among patients who survive using pairwise comparisons.
- **Exclusion of children:** We designed the study for adults since the interventions and many of the instruments are only validated in adults. It is possible, perhaps likely, that

adolescents may need a different approach to stress management and exercise than these self-directed interventions, and we were reluctant to extrapolate from adult to adolescents without appropriate validation studies.

2.7. Study Risks

Medical risks of study participation are expected to be low but could conceivably be due to exercise participation such as an exercise-related musculoskeletal injury. Adverse events due to exercise participation will be reported. There is a very low risk that the patient-reported measures or practice of stress management techniques might actually increase patient distress. If a member of the study team becomes aware of psychosocial distress, they will notify the patient's clinical provider who will assess the patient and make appropriate referrals according to standard institutional practice. Increased psychosocial distress due to study participation will be considered a severe adverse event and will be reportable; distress incidentally noted will not be reported to research entities. For example, a participant reporting distress but not attributing it to study participation will be considered "incidentally noted distress." If distress is attributed to study participation by the patient, then it will be considered a severe adverse event.

We do not expect the biobehavioral interventions under study to be related to engraftment, graft-vs-host disease, infections, relapse or organ complications such as pulmonary, hepatic, neurologic etc. These complications are seen after allogeneic and autologous HCT and are very unlikely to be biologically associated with study participation. These types of transplant-related complications will be considered expected events for the purposes of this study. In addition, exercise or stress management complications, as described above such as musculoskeletal injury or increased awareness of stress, are considered expected.

Unexpected severe adverse events are events related to participation in exercise or stress management that are plausibly related to study participation. For example, development of an arrhythmia during exercise or falling and breaking a hip during exercise are considered unexpected severe adverse events.

2.8. Study Benefits

It is unknown whether study participants will experience any benefits. We hope that functional status will be improved and symptoms will be lessened by these interventions.

2.9. Study Withdrawal

Subjects may be withdrawn from study participation if the treating physician believes it is in the patient's best interest to cease collection of patient-reported outcomes. Temporary or permanent discontinuation of exercise or stress management techniques is NOT a reason for subject withdrawal, since the analysis is on an intent-to-treat basis and patients are evaluable even if they never use any of the techniques.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Primary Endpoint

3.1.1. Functional Status

The Physical Component Score (PCS) and Mental Component Score (MCS) of the SF-36 will be the primary endpoint measures of functional status.

The Acute (past week) Version of the MOS 36-Item Short Form (SF-36), a widely used self-report measure designed to assess perceived health and functioning, contains eight scales: Physical Functioning (PF), Role-Physical (R-P); Bodily Pain (BP); General Health (GH); Vitality (VT); Social Functioning (SF); Mental Health (MH); and Role-Emotional (R-E).[42,43] Scales are comprised of different numbers of items and use a variety of rating formats. Raw scores are converted to a standard metric (0-100), with higher scores being indicative of a better health state. The SF-36 also yields two summary scores reflecting the underlying two-dimensional factor structure: Physical Component Summary (PCS) scale and Mental Component Summary (MCS) scale. These summary scores are derived by multiplying the z-score for each scale by its respective physical or mental factor score coefficient and summing the products. Resulting scores are then transformed into T-scores (mean=50; standard deviation=10). Factor analysis has shown that the PF, R-P, and BP scales have stronger loadings on the "physical" component than the "mental" component, with the reverse being true for the MH, R-E, and SF scales.[42] The GH and VT scales have noteworthy loadings on both the physical and mental components. The validity and reliability of the SF-36 has been established in a number of clinical populations, including cancer patients[43] The SF-36 has been used in several BMT CTN trials including BMT CTN 0102 (Auto/Auto vs. Auto/Allo HCT for Multiple Myeloma) and BMT CTN 0202 (Autologous vs. Allogeneic HCT for follicular lymphoma).

3.2. Secondary Endpoints

3.2.1. Symptoms

The SF-36 provides measures of pain and fatigue. Two questions using a similar format as the SF-36 will be added to measure nausea. Cancer and treatment distress will be measured by the acute version of the Cancer and Treatment Distress (CTXD) scale, a 27 item validated measure of distress with domains of Uncertainty, Health Burden, Family Strain, Identity and Managing the Medical System used extensively in HCT studies.[3,44] Sleep. The Pittsburgh Sleep Quality Index (PSQI)[45] is a widely used seven item self-report measure of sleep patterns and difficulties. A modified version will be used to obtain self-reports of the following for the past week: sleep quality, sleep latency, sleep efficiency, and use of sleeping medications.[46] The reliability and validity of the PSQI has been demonstrated in a variety of clinical populations, including cancer patients.[45,47]

3.2.2. Days of Hospitalization

The number of hospital days within the first 100 days after graft infusion will be collected for patients surviving at least 100 days.

3.2.3. Late Outcomes (6 months)

The SF-36, CTXD and Pittsburgh Sleep Quality Index will be collected from participants at six months.

3.2.4. Survival (6 months)

Overall survival is defined as the interval between transplantation and death or last follow-up. Patients alive when the study closes or lost to follow up are censored at the date of last contact. Both survival at 6 months and overall survival at last follow-up will be reported.

3.3. Additional Clinical Factors

3.3.1. Demographic, Clinical and Transplant Characteristics

As in our previous research,[25] we will assess the following via chart review or self-report: age, race/ethnicity, marital status, education, occupation, employment status, income, co-morbid medical conditions.[48-51] In addition, we will collect information on use of prescription and nonprescription medications, alcohol, tobacco. Height and weight will be used to calculate body mass (wt[kg]/ht[m^2]). Standard patient and transplant factors will be collected such as disease type, disease stage, prior chemotherapy treatment, conditioning regimen, graft source, graft-versus-host disease prophylaxis, transplant complications, relapse and survival.

3.3.2. Intervention Credibility

Intervention credibility will be assessed using self-report measures adapted from our previous research.[25] The use of three identical items across intervention conditions will allow for personnel collecting these forms to remain blinded to intervention assignment. Participants will be asked to rate the following on 7-point scales (0=not at all to 6=extremely) after meeting with the interventionist: anticipated effectiveness of the assigned intervention in improving quality of life, skill and competency of the interventionist, and perceived importance of making the assigned intervention available to other patients. These data will be used to confirm the equivalence of the three intervention conditions with regard to credibility.

3.3.3. Exercise Activity

Exercise activity will be assessed using the Leisure Score Index (LSI) of the Godin Leisure-Time Exercise Questionnaire[52] and a one item version of the Stages of Change Form for Exercise (SOC-E).[53] The LSI consists of 18 questions that assess the average frequency of mild, moderate, and strenuous exercise in a typical week. As in our current research, the LSI will be modified to include assessment of average duration of exercise and perceived exertion.[54] We

will rely on standard scoring to compute a total score.[52] The reliability and validity of the LSI has been found to compare favorably with other self-report measures of exercise in terms of test-retest scores and correlations with objective activity monitors and objective fitness indices.[55] The LSI will be collected at baseline, 30 days, 60 days, 100 days and 6 months. The SOC-E consists of a 5-choice response format that can be used to classify respondents' stages of change for adoption of regular exercise (i.e., precontemplation, contemplation, preparation, action, or maintenance). The typical 6-month anchoring has been modified to three months for the current study to reflect the interval between assessments. Information will be used to confirm expected differences in exercise between participants randomized to the different groups. In addition, these data will be used to explore "dose-response" relationships between amount of exercise and magnitude of changes in quality of life outcomes.

3.3.4. Stress Reduction Activity

Stress reduction activity will be assessed in all participants using the 5-item Stress Reduction Checklist (SRC).[25] The methods assessed are those that comprise the Stress Management intervention. Each method is listed by the term used to describe it in the intervention as well as by an operational definition. Thus, participants can complete it regardless of whether they received instruction in stress management. All assessments (baseline, 30 days, 60 days, 100 days, and 6 months) will be keyed to the past week. In previous research, we found that SRC scores documented expected differences in use of stress management techniques between subjects who did and did not receive instruction in stress management.[25] SRC data will be used to confirm expected differences in use of stress management techniques between participants randomized to different groups and explore possible differences in use of stress management techniques between participants randomized to Stress Management along versus Combined Exercise and Stress Management.

TABLE 3.3: PATIENT-REPORTED MEASURES

	# Items	Enroll-ment	30 days +/- 7 days	60 days +/- 7 days	100 days +/- 14 days	6 months +/- 1 month
Primary and Secondary Endpoints						
• SF-36 (SF-36) + 2 nausea items	38	X	Ψ	Ψ	X	X
• BMT Distress Scale (CTX-D)	27	X			X	X
• Pittsburgh Sleep Quality Index (PSQI)	7	X			X	X
Exercise Measures						
• Leisure Score Index (LSI)	18	X	X	X	X	X
• Stages of Change for Exercise (SOC-E)	1	X	X	X	X	X
Stress Management Measures						
• Stress Reduction Checklist (SRC)	5	X	X	X	X	X
Sociodemographic, Habits and Beliefs						
• Age, Sex, Race, Ethnicity, Education, Marital Status	9	X				
• Smoking, Alcohol	6	X				
• Intervention Credibility	3	X*				
Total # of Items (Estimated Time)	114	114 (20 min)	25 (5 min)	25 (5 min)	88 (15 min)	88 (15 min)

* after meeting with the interventionist

Ψ Single item general health question from the SF-36 1 (SF-1)

CHAPTER 4

4. PATIENT REGISTRATION, ENROLLMENT AND RANDOMIZATION

4.1. Approaching Patients, Eligibility Screening and Obtaining Consent

Subjects may be approached for enrollment on this protocol once they are scheduled for transplantation as long as the planned transplant date is within six weeks. Transplant physicians or other center staff will evaluate patient eligibility for enrollment onto this protocol. Eligibility criteria will be verified and ineligible patients will proceed off study and no further study procedures will be conducted. Eligible patients willing to potentially participate in the trial will have a thorough discussion about the protocol with an investigator, a sub-investigator, clinical research nurse, or research coordinator. If necessary, this discussion may take place by telephone. During the discussion, the purpose of the study and study procedures will be presented as objectively as possible, and the potential benefits and risks of participation will be explained. The patient will be given a copy of the entire signed consent document to keep. The last page of the consent document must be signed by the patient and by the clinician who discussed the protocol. Transplant center personnel will record the documentation of patient consent in EMMES AdvantageEDC^{SM} (Electronic Data Capture, an Internet-based data entry system) and patients will be registered through AdvantageEDC.

4.2. Study Registration and Randomization

Once the subject is deemed eligible, has given written informed consent, completed the baseline assessment, and the transplant center has confirmed patient eligibility and necessary stratification variables, randomization occurs. A subject may be randomized on to one of four arms: exercise, stress management, combined exercise and stress management, or standard care. If a patient consents but discontinues trial participation prior to randomization, they will be replaced.

4.3. Training and Reinforcement in Intervention Use

Once a patient is randomized, the intervention must be delivered before the day of graft infusion (Day 0). Thus, subjects will meet with the interventionist for 10-15 minutes to receive their self-administered materials and brief training. Subjects randomized to standard care will meet with the interventionist to discuss the information in the pamphlet.

If transplantation occurs more than two weeks after the training session, the interventionist will briefly contact the patient within seven days of graft infusion (Day 0 +/- 7 days) to reinforce use of the intervention. In addition, the interventionist will meet with patients from all four groups at Day 30 +/- 7 days in person or by phone, to briefly reinforce use of the assigned intervention if applicable and to remind the patient about endpoint assessment at Day 100 and six months. A similar contact will occur at approximately Day 60 +/- 7 days for all groups.

4.4. Patient Assessment

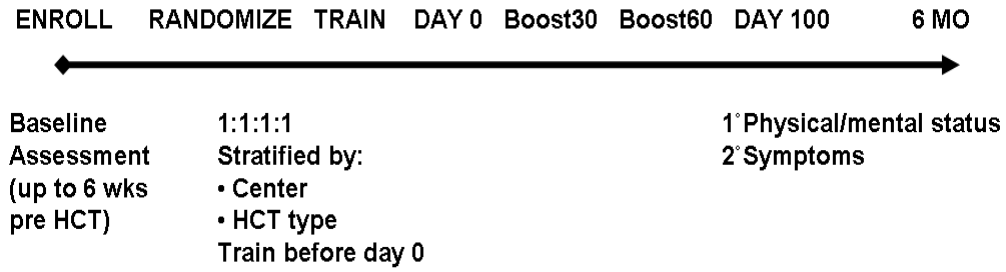
4.4.1. Endpoint Assessment

Patient self-reported information relevant to endpoint assessment will be collected at baseline (before randomization), at 100 days +/- 14 days, and at six months +/- one month. Patients may complete these assessments on paper forms or by responding to questions read verbatim by the assessor. The optimal method of self-reported data collection is via self-administered paper surveys. Study staff will carefully review all self-completed paper forms for ambiguous responses and missing data, and clarify these with the participant. Reasons for inability to complete the assessments will be recorded. If a patient is not able to complete self-administered instruments or prefers interviewer-administered assessments, data will be collected via this mechanism, either in person or over the phone. The method of data collection will be recorded.

4.4.2. Use of Intervention

At the time of the Day 30 and Day 60 reinforcements and again at the Day 100 and six month assessments, self-reported use of the interventions and one item about general health will be recorded. In order to decrease social desirability bias, these forms will be given to the patient to complete later and return via self-addressed, stamped envelope. If the information must be collected by interview, the other interventionist or other study personnel will contact the patient.

See Table 3.3 for a summary of patient assessments.



4.5. Study Monitoring

As the primary concerns about trial participation will be distress with the self-assessments and injuries related to exercise, monitoring will be focused on these issues. Patients will be monitored clinically with laboratory assessments, physical exams, restaging studies and other testing deemed to be standard practice and appropriate by the treating physician and the transplant center.

4.5.1. Case Report Forms

A description of the forms, the procedures required for forms completion and timeliness of submission can be found in the Data Management Handbook and User's Guide. Forms that are not received within the specified time are considered delinquent. Transplant centers can view submitted past due, and expected forms via AdvantageEDC. A missing form will continue to be requested either until the form is reported, or until an exception is granted.

4.5.2. Reporting Patient Deaths

Death of subject information must be reported to the BMT CTN Data Coordinating Center (DCC) within one business day of the event notification to the transplant center. If the cause of death is unknown, it need not be recorded at the time of the initial reporting. However, once the cause of death is known, the form must be updated.

4.5.3. Reporting Serious Adverse Events

4.5.3.1. Patient SAEs

Reporting of patient serious adverse events (SAE) will be consistent with standard BMT CTN procedures but be limited to events which are possibly, probably or definitely associated with participation in this study since this protocol does not involve any pharmacologic treatment or invasive procedures. Unexpected, grades 3-5 adverse events (AEs) will be reported through an expedited AE reporting system via the web-based electronic data capture system, AdvantageEDC. Unexpected, grades 4-5 AEs must be reported within 24 hours of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Other SAEs will be tracked periodically as defined in the Form Submission Schedule, staged according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The Data and Safety Monitoring Board will receive summary reports of all adverse experiences on at least an annual basis. Please see section 2.7 for definitions and examples of expected and unexpected SAEs.

4.5.4. CIBMTR Data Reporting

Centers participating in BMT CTN trials must register and provide transplant outcome data on all consecutive hematopoietic stem cell transplants done at their institution during their time of BMT CTN participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedure and forms developed by CIBMTR for the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allogenic transplant recipients.)

Patients enrolled in this trial will remain on pre selected form submission track (Transplant Essential Data track also known as "TED" track or Comprehensive Report From track also known as "CRF" track) that was originally assigned by the CIBMTR algorithm. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

4.6. Quality Control

Because of this protocol relies on patient-reported outcomes for the primary analyses, collection of these data are critical. We anticipate up to a 15% inability to collect Day 100 data from surviving patients based on logistic problems and patient refusal. However, center compliance will be monitored every three months. If a center falls below 75% for its cumulative compliance with Day 100 data collection, procedures will be instituted to evaluate whether continued participation in the trial is warranted. This evaluation will result in either corrective actions or suspension of participation.

At least two interventionists at each participating center must complete interventionist training and be certified by a protocol team member before the center can begin enrollment on the trial, similar to other studies in which a center personnel needs to demonstrate competence in investigational cell processing techniques before they can enroll protocol patients. Centers should adhere to guidelines outlined in the BMT CTN 0902 SOP.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design

The protocol is designed as a factorial trial with two interventions, exercise and stress management, which results in four treatment arms: standard care, exercise only, stress management only and the combination of exercise and stress management. The primary objective of this randomized phase III trial is to test the ability of exercise training or stress management training to improve physical and mental functioning at Day 100.

5.1.1. Accrual

It is estimated that three years of accrual will be necessary to enroll the targeted sample size of 700 patients, based on a survey sent to centers. Both Core and Affiliate Centers will enroll patients on this study. Accrual will be reported by race, ethnicity, and sex.

5.1.2. Randomization

All patients will be randomized in a 1:1:1:1 ratio using random block sizes for the four arms. Randomization will be stratified by transplant center and type of transplant procedure (autologous/syngeneic, myeloablative allogeneic, or reduced intensity/non-myeloablative allogeneic).

5.1.3. Primary Endpoint

The co-primary endpoints are physical functioning and mental functioning at Day 100 as measured by the SF-36, which will be scored according to the instructions of the developer. The primary analysis will be performed using the intent-to-treat principle so that all randomized patients will be included in the analysis, classified according to their randomized treatment assignment. Patients who have missing data due to death will be scored as the lowest value, and patients who are alive but are missing the Day 100 outcome will be scored as the next lowest value. In the primary analysis, the effect of an intervention (exercise or stress management) on an outcome (PCS or MCS) will be determined by collapsing arms with the intervention into the treatment group and arms without the intervention into the control group then comparing the outcome between control vs. treatment groups. For example, the effect of exercise on physical functioning will be determined by comparing the PCS scores between two groups, one comprised of standard care and stress management only arms vs. the other comprised of exercise only and combination arms. These comparisons will be done using the Mann-Whitney test. Detailed analysis plan including imputation of incomplete data is given in Section 5.5.

5.2. Sample Size and Power Calculations

5.2.1. Power Calculation for Primary Intention-to-Treat Analysis

The primary objective of this study is to determine if training patients to practice exercise or stress management during transplantation improves the patient's experience, as measured by physical and mental functioning. Because of the co-primary endpoints, the allowable Type I error rate $\alpha = 0.05$ is divided in half so that the significance level to be used is $0.05/2 = 0.025$ for each end point.

To account for the missing data in an intent-to-treat analysis, the sample sizes shown in Table 5.2 were calculated by Monte Carlo simulations with 10,000 replications based on the following assumptions. First, it is assumed that the functional status scores (MCS or PCS) are normally distributed and the detectable difference between two groups is δ SD; values of δ at 0.4 and 0.5 were considered. Furthermore, it is assumed that there is no difference in survival and no difference in incomplete data collection at Day 100 for surviving patients between groups. All deaths occurring prior to Day 100 regardless of treatment were assigned a functional status score which is lower than the lowest observed functional status scores. All surviving patients missing the Day 100 assessment irrespective of treatment were given a functional status score higher than deaths and lower than the lowest observed function status.

The completed functional status scores including observed and imputed values were compared between groups using a nonparametric Mann-Whitney test. The power to detect a δ SD difference using the ITT analysis with the target sample size of 700 patients is given in Table 5.2 for various plausible rates for Day 100 mortality and missing data among survivors. In particular, assuming Day 100 mortality rate of 15% in both groups and incomplete assessment in 15% of the surviving patients, the target sample size of 700 patients will have 85% power to detect a 0.5 SD difference in functional status scores between groups. Other plausible rates for mortality and missing data are also included.

TABLE 5.2: POWER TO DETECT VARIOUS EFFECT SIZES IN THE PRIMARY ITT ANALYSIS

Effect size δ, in SD	**Day 100 Mortality**	**Proportion of Survivors Missing Day 100 Forms**	
		15%	**10%**
0.4	**15%**	67%	77%
	10%	77%	87%
0.5	**15%**	85%	93%
	10%	92%	97%

5.2.2. Power Calculation for Key Secondary Analysis of Main Effects in Survivors who Complete Day 100 Assessments

The effect of exercise or stress reduction on mental and physical functioning in survivors who completed Day 100 assessments will be determined in a series of secondary analyses. The power calculations for these secondary analyses are based on the same assumptions as in 5.2.1, namely 15% mortality by day 100 and 15% missing data among survivors at the 100 day follow-up visit. PCS and MCS scores will be compared between exercise vs. no exercise groups and stress management vs. no stress management groups by collapsing arms as described in the primary analysis. Because of the co-primary endpoints, the allowable Type I error rate is divided in half. A sample size of 700 gives 87% power to detect an effect size of 0.3 SD between groups on any of the two endpoints using the evaluable patients. With the same sample size, this analysis provides the power to detect a much smaller effect size than in the primary ITT analysis.

5.2.3. Power Calculation for Key Secondary Analysis Comparing all Four Treatment Combinations in Survivors who Complete Day 100 Assessments

In another key secondary analysis, PCS and MCS scores will be compared between all pairs of treatment combinations. There are six pair-wise comparisons between four treatment arms. To adjust for multiple comparison, the Type I error rate is divided in six. The Type I error rate is further divided in half due to the co-primary endpoints so that the significance level to be used is 0.05/12=0.0042. A sample size of 700 gives 86% power to detect an effect size of 0.5 SD between any pair of treatments on any of the two endpoints, using the evaluable patients and under the same assumptions about mortality and missing data as in Sections 5.2.1 and 5.2.2.

5.3. Interim Analysis Plan

5.3.1. Interim Analysis for Efficacy

No interim analysis for efficacy will be performed for several reasons. First, because of the short anticipated accrual period (3 years) and primary endpoints assessment at 100 days, we will almost have completed enrollment before the results of the interim analysis are known. Second, physical risks to participants are likely to be minimal so the risks are low of exposing participants to an inferior treatment arm or alternatively, denying participants or other patients access to effective interventions. Third, the use of co-primary endpoints would require that both be found significant at an interim analysis in order to stop; otherwise the power to detect differences in the other endpoint would be impacted. This makes it less likely that an interim analysis would result in a closure of an arm. Finally, stopping enrollment to one of the intervention arms at an interim analysis would impact the ability to investigate interactions and synergism between the two interventions, which is an important secondary analysis.

5.3.2. Interim Analysis for Futility

No interim analysis for futility will be performed. All intervention arms are considered minimal risk to participants. Dropping one arm at the interim analysis will compromise the ability to evaluate secondary endpoints, which are also of considerable interest. Finally, dropping of either

the exercise alone arm or stress management arm alone will compromise the ability to evaluate the added impact of the combination arm. For all these reasons, no interim analysis for futility will be performed.

5.4. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all patients. Characteristics to be examined are: patient characteristics (age, sex, race/ethnicity, performance status, disease and disease risk, CMV status, and psychosocial and functional factors); donor characteristics (donor type, HLA-match, age, sex, CMV status); graft characteristics (type, CD34+ or total nucleated count per kg); and transplant characteristics (type, conditioning, GVHD prophylaxis). Between groups comparisons will be performed for continuous variables via a Kruskal-Wallis test and for categorical variables, via the chi-square test.

Before conducting the secondary analyses described below, the distributional properties of study variables will be examined to determine if variance stabilizing or normalizing transformations should be applied. Participants who complete the study and are alive at Day 100 will be compared to participants who drop out before Day 100 in order to identify predictors of attrition. Although participants will be randomly assigned to intervention conditions, significant differences may be present among the conditions on demographic, disease, or treatment variables. To identify these potential confounding variables, intervention and control conditions will be compared on all baseline demographic and disease variables and on all treatment variables measured during the course of study participation.

5.5. Analysis Plan

5.5.1. Analysis of Primary Endpoints

The analysis of primary endpoints will include all randomized subjects, classified according to their randomized treatment allocation, irrespective of treatment actually received. Two comparisons will be considered in the primary analysis, comparing exercise vs. no exercise groups and comparing stress management vs. no stress management groups. The effect of exercise training will be estimated by collapsing arms with exercise versus arms without exercise and the effect of stress reduction will be analyzed by collapsing arms with stress reduction vs. arms without stress reduction. The effect of each intervention will be analyzed on both mental and functional outcomes. In this analysis, all patients who die within 100 days post transplant will be given MCS and PCS scores lower than the lowest observed scores and all survivors missing Day 100 assessment will be given scores higher than patients who died but lower than the lowest observed scores. The completed functional status scores will be compared using a Mann-Whitney test with a two-sided significance level of 0.025.

5.5.2. Analysis of Secondary Endpoints

1. **Conditional analysis of functional status in survivors with Day 100 assessments:** This analysis is limited to the population of survivors who provide Day 100 self-reports. The main effect of exercise training will be estimated by collapsing arms with exercise versus

arms without exercise and the effect of stress reduction will be analyzed by collapsing arms with stress reduction vs. arms with stress reduction. The effect of each intervention will be analyzed on both mental and functional outcomes. MCS and PCS scores will be compared at a two-sided significance level of 0.025.

2. **Pair-wise conditional analysis of functional status in survivors with Day 100 assessments:** This analysis is limited to the population of survivors who provide Day 100 self-reports. MCS and PCS scores will be compared between each pair of treatment arms in this analysis. Four treatment arms result in six pair-wise comparisons. The two-sided significance level to be used in this analysis is 0.0042. We will also test for an interaction between the two interventions, exercise and stress management. The direction of a statistically significant interaction will allow for determination of a synergistic effect, where the combined effect is greater than what is expected from the combination of the two single interventions vs. an interaction where the combined effect is lower than what would be expected from combining the two interventions.
3. **Overall survival:** This analysis will include all randomized subjects. The event is death from any cause. The time to this event is the time from randomization to death, loss to follow-up or the end of study, whichever comes first. Patients alive at the time of last follow-up are considered censored. Survival curves will be estimated separately for each treatment groups using the Kaplan Meier product limit estimator. Overall survival will be compared between groups using a log-rank test.
4. **Assessment of missing data:** Graphical presentations and logistic regression analysis will be performed to understand the missing data mechanism as well as to identify factors associated with incomplete data for survivors. Plots of change in functional status scores from baseline to 100 days and 6 months stratified by time of drop-out will be generated separately for each group to determine pattern of missingness. Logistic regression will be used to identify baseline and clinical characteristics associated with missing data. All demographics and baseline characteristics listed in Section 5.4 along with the single item SF-1 general health information collected at Day 30 and 60 and the baseline functional scores measured at enrollment will be included in the logistic model.
5. **Functional status scores with multiple imputation:** In this analysis, incomplete data for surviving patients will be replaced by values resulting from multiple imputations where the missing values will be estimated by regression models which will include the baseline functional scores, the SF-1 measurement at Day 30 and 60 and various combinations of factors significantly associated with missing data. We will then analyze these alternate imputation schemes using a Mann-Whitney test on all patients in an ITT analysis (where patients who die are scored at the bottom), or using linear mixed models including only patients who are alive at Day 100.
6. **Symptoms:** Domain and summary scores will be calculated for each instrument according to the recommendations of the developers. These will be compared between groups using the Kruskal-Wallis test, adjusting for baseline scores for patients survive to Day 100.

7. **Days of hospitalization:** The total number of hospital days within the first 100 days, adjusted for the duration of follow-up will be compared between groups using the Kruskal-Wallis test for all randomized patients.
8. **Functional status and symptoms at 6 months:** The analytic design will be similar to the 100 day approach.

5.5.3. Analysis of Additional Clinical Factors

1. **Intervention Credibility:** Intervention credibility scores will be compared between intervention conditions using the Kruskal-Wallis test.
2. **Exercise Activity:** LSI scores (at 30 days, 60 days, 100 days, 3 months and 6 months) will be compared between groups using the Kruskal-Wallis test, adjusting for baseline scores.
3. **Stress Reduction Activity:** SRC scores (at 30 days, 60 days, 100 days, 3 months and 6 months) will be compared between groups using the Kruskal-Wallis test, adjusting for baseline scores.

5.6. Safety Analysis

The reporting of serious adverse events will be consistent with standard BMT CTN procedures. The type and severity of adverse events will be described and compared between the four arms.

APPENDIX A

HUMAN SUBJECTS

Subject consent: Candidates for the study will be identified as described in Chapter 4 of the protocol. The Principal Investigator or his/her designee at each transplant center will contact the candidates and enroll them onto the study. The study coordinator at each center will provide the patient with information about the purpose of the study and obtain consent. The Network will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local Internal Review Board (IRB). The DCC will verify the adequacy of the consent forms. Each center must provide evidence of IRB approval.

Confidentiality: Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

Participation of women, children, minorities and other populations: Women and ethnic minorities will be included in this study. Children will not be included.

Accrual will be monitored within each center with the expectation that the enrolled patient population is representative of the transplanted patient population at each center. Representation will be examined by comparing gender, race, ethnicity and age distributions. Accrual of minority patients will be expected to be in proportion to the number of minority patients transplanted at each center. The DCC and NHLBI will discuss enrollment anomalies with the centers.

APPENDIX B

INFORMED CONSENTS
AND
EDUCATIONAL MATERIAL

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

Informed Consent to Participate in Research

Your Name: _____

Study Title: A Phase III Randomized, Multi-center Trial Testing Whether Exercise or Stress Management Improves Functional Status and Symptoms of Autologous and Allogeneic Recipients.

Protocol: 0902

Co-Investigator: Stephanie J. Lee, M.D., M.P.H
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North
Mailstop D5-290
Seattle, WA 98109-1024
Phone: 206-288- 7222

Co-Investigator: Paul B. Jacobsen, Ph.D.
H. Lee Moffitt Cancer Center & Research Institute
12902 Magnolia Drive
Tampa, FL 33612
Phone: 813-745-3862

Transplant Center

Investigator: _____

Sponsor: The National Institutes of Health (NIH), the National Heart, Lung, and Blood Institute, and the National Cancer Institute gave financial support for this research study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Introduction

You are invited to join a research study. The main goal of this study is to learn whether patients who participate in an exercise program, a stress management program, or both programs will feel better after transplant compared to patients who do not participate in either program. We also want to know what areas of your physical and emotional health might improve after transplant and how long any improvement may last.

Your participation in the study will last 6 months. Seven hundred people will participate. You will have an equal chance of being placed in one 1 of 4 different groups. Each group will receive a different program. We will explain the 4 groups in this Consent Form. All of the clinics in this study will report their results, so we can compare all of the groups at the end of the study.

Group 1	Group 2	Group 3	Group 4
General Information	Exercise	Stress Management	Exercise and Stress Management

This Consent Form will tell you about the purpose of the research, its possible risks and benefits, other options available to you, and your rights as a participant in the study. Please take your time to read and understand the information in this form before you make your decision.

Everyone who takes part in research at [insert facility name] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can leave the study at any time.
- If you decide to leave the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You may wish to discuss other alternatives with your doctor.

1. Background

This research study is sponsored by The National Institutes of Health (NIH), the National Heart, Lung, and Blood Institute (NHLBI), and the National Cancer Institute (NCI) through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Previous studies suggest that patients who exercise or use stress management methods after transplant may experience better physical and emotional health than patients who do not exercise or use stress management techniques after transplant. Although previous studies suggest benefits, we don't know if you will get any benefits by taking part in this study. That is why we are doing this research study. What we learn may help to improve the quality of life of other patients after transplant.

2. Purpose

The main goal of this study is to learn whether patients who participate in an exercise program, stress management program, or a combination of an exercise and stress management program will feel better after transplant compared to patients who do not participate in either program. We also want to know what parts of your physical and emotional health improve after transplant and how long any improvement lasts.

3. The Right to Ask Questions and/or Leave the Study

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[Insert contact info]

Being in this study is voluntary. You can choose not to be in this study, or leave this study at any time.

If you choose to not join or you decide to leave this study, your regular medical care will not be affected in any way. If you decide to not join this study, you will still receive the usual physical and emotional care given to transplant patients.

Even if you leave the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

Your study doctor and study staff will be available to answer any questions that you may have about joining or leaving this study.

4. Procedures

If you decide to join this study, you will need to sign this Consent Form. We will give you a copy of the signed form to keep.

You will continue to have regular physical exams, laboratory tests, and other evaluations that are standard care by your doctor and transplant center.

Once you agree to join, we will randomly assign you to 1 of 4 groups before you have your transplant.

Group 1 will get general information about transplantation and how to take care of themselves after their transplant.

Group 2 will get information about exercise and be asked to exercise regularly after their transplant.

Group 3 will get information about stress management and be asked to use stress management methods after their transplant.

Group 4 will get information about exercise and stress management and be asked to exercise regularly and use stress management methods after their transplant.

A member of the research team will meet with you to explain details about your group and the materials you will use for the study. You will need to review some of the materials at home. We think it will take you about one hour to go through the packet of materials. If you do not have a DVD or CD player, equipment will be available in the clinic or hospital that you can use to review the materials.

Details About the Study Groups

- **Group 1 - General Information**
  If you are assigned to this group, you will get a DVD about transplantation and how you can take care of yourself after transplant. The DVD is about 45 minutes in length and covers topics such as preparing for transplant, engraftment, early recovery and long-term recovery.
- **Group 2 - Exercise**
  If you are assigned to this group, in addition to the general information DVD you will get a packet of materials along with a short (10 minute) introduction to exercising at home. Your packet of materials will include a DVD, a booklet that shows you how to exercise after your transplant and a log to help you keep track of your activity. We will also give you an electronic step counter to help you track how much you walk for exercise.

  As part of the study, we may ask you to walk for exercise at a time and location of your choice as often as 3 to 5 times a week for up to 20-30 minutes each time.
- **Group 3 - Stress Management**
  If you are assigned to the stress management group, in addition to the general information DVD you will get a packet of materials along with a short (10 minute) introduction to stress management. Your packet will include a DVD, compact disc (CD), a booklet

which shows you different ways to better manage stress after your transplant, and a log to help you track the methods you use.

As part of the study, we may ask you to use stress management techniques such as paced abdominal breathing, progressive muscle relaxation with guided imagery, and use of coping self-statements to decrease stress.

- **Group 4 - Exercise and Stress Management**
  If you are assigned to the group that combines exercise and stress management, in addition to the general information DVD you will get a packet of materials along with a short (15 minute) introduction to exercise and stress management. Your packet will include a DVD, and compact disc (CD), a booklet about exercise and stress management, a log to help you track your exercise and stress management activities, and an electronic step counter.

  As part of the study, we may ask you to walk for exercise at a time and location of your choice as often as 3 to 5 times a week for up to 20-30 minutes each time.

  We may also ask you to use stress management techniques such as paced abdominal breathing, progressive muscle relaxation with guided imagery, and use of coping self-statements to decrease stress.

Scheduled Study Visits or Phone Contacts

A study visit or telephone contact is a meeting that you have with the person in charge of the study or another member of the research team. You will need to have five (5) study visits or contacts over six months. Your enrollment visit will be done in person. The remaining follow-up visits for this study may be done in person or by phone.

Study Visits or Contacts

1. Enrollment, any time between 6 weeks and one day before transplant – up to 40 minutes (if you enrolled more than two weeks before your transplant, you will also get an extra reminder call before your transplant). At the enrollment visit you will complete baseline questionnaires (approximately 20 minutes), receive your materials, and may receive training based on your group assignment (approximately 10-20 minutes)
2. One (1) month after transplant - 10 minutes. You will talk with a member of the study team and complete questionnaires (5 minutes).
3. Two (2) months - 10 minutes. You will talk with a member of the study team and complete questionnaires (5 minutes).
4. Three (3) months (100 days) - 15 minutes. You will complete questionnaires (15 minutes).
5. Six (6) months - 15 minutes. You will complete questionnaires (15 minutes).

Your total length of study participation will last 6 months.

Study Evaluations

Your study enrollment session and every follow-up visit will include several surveys for you to complete that may be on paper or asked by the study staff. The surveys will help us evaluate the different activities of each group at the end of the study. All of the in-person visits will happen during your regularly scheduled appointments.

The surveys for this study will ask questions about:

- Your physical and emotional health
- How often and how long you have exercised between visits and contacts
- The number of times you may have used certain methods to manage stress between visits and contacts

Additional Evaluations and Procedures

During the study, some of the research staff's contacts with participants will be recorded on audio tape. The purpose of this recording is to make sure that the research team members continue to carry out the research procedures correctly. You will be asked for permission before any audio recording of your contact with research staff.

5. Alternative Treatments

If you choose to not join or you decide to leave this study, your regular medical care will not be affected in any way. Whether or not you join this study, you will receive the usual physical and emotional care given to transplant patients at your transplant center.

Physical and emotional care choices may include:

- Meeting with a nurse or social worker.
- Attending patient support groups to help you with the stress and side effects of your treatment.

Please talk with your doctor about other options. Every treatment option has benefits and risks. Your study doctor will discuss these options with you. If you decide not to participate in this research study, your medical care will not be affected in any way.

6. Risks and Discomforts

Small but possible risks for this current study are primarily related to exercise. The chances that these things might happen to you are considered to be small because you will be screened for any existing health conditions (for example, heart or lung disease) as part of your evaluation prior to transplantation that would make it unsafe for you to exercise.

Possible risks from exercise include:

- Shortness of breath (dyspnea)
- Muscle or joint sprains (musculoskeletal injury)
- Foot pain or blisters
- Heat-related injury (dehydration) that might result from exercise training

Muscle tensing as part of active relaxation and deep breathing for stress management may feel uncomfortable to some people. You should not practice any stress management methods that feel painful or uncomfortable.

If you do decide to participate, we will take extra measures to limit the chances of you getting hurt. These measures include exercise plans that are a good fit for your physical condition and suggesting ways to prevent possible muscle strain and soreness as well as dehydration.

If you have any of the problems due to exercising or using the stress management methods that we have described, tell the person in charge of this study or study staff at your next visit. If these problems bother or worry you or if you have other problems, call the person in charge of this study at *[telephone number]*

New risks might appear at any time during the study that are different from the risks listed in this Consent Form. We will promptly tell you of any new information that might affect your decision to participate.

7. Possible Benefits

Taking part in this study may or may not make your health better.

Earlier studies suggest that patients who exercise or use stress management methods after transplant may experience better physical and mental well-being than patients who do not exercise or use stress management methods after transplant. Although earlier studies suggest benefits, we don't know if you will get any benefits by taking part in this study. That is why we are doing this research study. What we learn may help to improve the quality of life of other patients after transplant.

8. New Information Available During the Study

During this research study, new information about exercise or stress management methods or the risks and benefits of the study may become known to the study doctors. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and you will be offered all available care to suit your needs and medical condition.

9. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy.

Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Your study number is not related to your name, social security number or medical record number at [insert facility name].

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
- Other authorized study organizations
- We will not identify you by name in any publications or reports that come from these organizations or groups.

10. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment. If you are asked to leave the study, the reasons will be discussed with you.

Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You cannot keep appointments.
- The study is stopped for any reason.

11. Physical Injury as a Result of Participation

It is important that you tell the doctor responsible for this study if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

12. Compensation or Payment

You will not be paid for your participation in the research study. You will not get compensation or reimbursement for any extra expenses (travel, meals, etc.) you may have through your participation on this trial.

13. Costs & Reimbursements

You and/or your health plan/insurance company will need to pay for all of the costs of treating your cancer. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. However, participation in this study does not require any additional medical tests, evaluations or procedures so we do not anticipate that participation in this study will cost more than routine care.

All costs of your care will need to be paid by you and/or your health plan/insurance company.

The companies that make the materials used in this study did not plan or design this clinical trial. They will also not have a part in analyzing the results of this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask for your free copy.

14. Ethical Review

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

15. Further Information

If you need any information about this study, or if you have any problems while you are participating in this study you can contact the study doctor or his/her staff. They may be contacted at the telephone numbers listed here.

[Insert name and contact details]

16. Independent Contact

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[Insert appropriate contact details]

Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose individual health information for research purposes

A. Purpose

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Phase III Randomized, Multi-center Trial Testing Whether Exercise or Stress Management Improves Functional Status and Symptoms of Autologous and Allogeneic Recipients.

B. Individual Health Information to be Used or Disclosed

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight).
- Medical history (for example: diagnosis, complications with prior treatment).
- Findings from physical exams.
- Laboratory test results obtained at the time of work up and after treatment (for example: blood tests, biopsy results).

C. Parties Who May Disclose My Individual Health Information

The researcher and the researcher's staff may collect my individual health information from:

(List hospitals, clinics or providers from which health care information can be requested).

D. Parties Who May Receive or Use My Individual Health Information

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigators
  - Stephanie J. Lee, M.D., M.P.H, Co-Investigator
  - Paul B. Jacobsen, Ph.D., Co-Investigator
- Members of the BMT CTN Data and Coordinating Center and 0902 Protocol Team
- The Center for International Blood and Marrow Transplant Research (CIBMTR) and the National Marrow Donor Program (NMDP)
- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

- Other:_____

_____

E. Right to Refuse to Sign this Authorization

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study. My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. Right to Revoke

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. Potential for Re-disclosure

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. This authorization does not have an expiration date.

TITLE:
A Phase III Randomized, Multi-center Trial Testing Whether Exercise or Stress Management Improves Functional Status and Symptoms of Autologous and Allogeneic Recipients.

PROTOCOL NUMBER:
0902

INVESTIGATORS:
Stephanie J. Lee, M.D., M.P.H, Co-Investigator
Paul B. Jacobsen, Ph.D., Co-Investigator

Participant Name	Date
Signature	Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

Signature	Date
Signature of Counseling Physician	Date

APPENDIX C

REFERENCES

1. Pidala J, Anasetti C, Jim H: Quality of life after allogeneic hematopoietic cell transplantation. Blood 114:7-19, 2009
2. Lee SJ, Fairclough D, Parsons SK, et al: Recovery after stem-cell transplantation for hematologic diseases. J Clin Oncol 19:242-52., 2001
3. Syrjala KL, Langer SL, Abrams JR, et al: Recovery and long-term function after hematopoietic cell transplantation for leukemia or lymphoma. Jama 291:2335-43, 2004
4. Cunningham BA, Morris G, Cheney CL, et al: Effects of resistive exercise on skeletal muscle in marrow transplant recipients receiving total parenteral nutrition. JPEN J Parenter Enteral Nutr 10:558-63, 1986
5. Decker WA, Turner-McGlade J, Fehir KM: Psychosocial aspects and the physiological effects of a cardiopulmonary exercise program in patients undergoing bone marrow transplantation (BMT) for acute leukemia (AL). Transplant Proc 21:3068-9, 1989
6. Dimeo F, Bertz H, Finke J, et al: An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. Bone Marrow Transplant 18:1157-60., 1996
7. Dimeo F, Fetscher S, Lange W, et al: Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. Blood 90:3390-4., 1997
8. Dimeo FC, Tilmann MH, Bertz H, et al: Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. Cancer 79:1717-22, 1997
9. Dimeo FC, Stieglitz RD, Novelli-Fischer U, et al: Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer 85:2273-7., 1999
10. Courneya KS, Keats MR, Turner AR: Physical exercise and quality of life in cancer patients following high dose chemotherapy and autologous bone marrow transplantation. Psychooncology 9:127-36, 2000
11. Dimeo F, Schwartz S, Fietz T, et al: Effects of endurance training on the physical performance of patients with hematological malignancies during chemotherapy. Support Care Cancer 11:623-8, 2003
12. Coleman EA, Coon S, Hall-Barrow J, et al: Feasibility of exercise during treatment for multiple myeloma. Cancer Nurs 26:410-9, 2003
13. Mello M, Tanaka C, Dulley FL: Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant 32:723-8, 2003

14. Hayes S, Davies PS, Parker T, et al: Quality of life changes following peripheral blood stem cell transplantation and participation in a mixed-type, moderate-intensity, exercise program. Bone Marrow Transplant 33:553-8, 2004

15. Hayes SC, Davies PS, Parker TW, et al: Role of a mixed type, moderate intensity exercise programme after peripheral blood stem cell transplantation. Br J Sports Med 38:304-9; discussion 309, 2004

16. Wilson RW, Jacobsen PB, Fields KK: Pilot study of a home-based aerobic exercise program for sedentary cancer survivors treated with hematopoietic stem cell transplantation. Bone Marrow Transplant 35:721-7, 2005

17. Kim SD, Kim HS: A series of bed exercises to improve lymphocyte count in allogeneic bone marrow transplantation patients. Eur J Cancer Care (Engl) 15:453-7, 2006

18. Carlson LE, Smith D, Russell J, et al: Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study. Bone Marrow Transplant 37:945-54, 2006

19. DeFor TE, Burns LJ, Gold EM, et al: A randomized trial of the effect of a walking regimen on the functional status of 100 adult allogeneic donor hematopoietic cell transplant patients. Biol Blood Marrow Transplant 13:948-55, 2007

20. Wiskemann J, Huber G: Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. Bone Marrow Transplant 41:321-9, 2008

21. Courneya KS: Exercise interventions during cancer treatment: biopsychosocial outcomes. Exerc Sport Sci Rev 29:60-4, 2001

22. Burish TG, Snyder SL, Jenkins RA: Preparing patients for cancer chemotherapy: effect of coping preparation and relaxation interventions. J Consult Clin Psychol 59:518-25, 1991

23. Syrjala KL, Donaldson GW, Davis MW, et al: Relaxation and imagery and cognitive-behavioral training reduce pain during cancer treatment: a controlled clinical trial. Pain 63:189-98., 1995

24. Carey MP, Burish TG: Etiology and treatment of the psychological side effects associated with cancer chemotherapy: a critical review and discussion. Psychol Bull 104:307-25, 1988

25. Jacobsen PB, Meade CD, Stein KD, et al: Efficacy and costs of two forms of stress management training for cancer patients undergoing chemotherapy. J Clin Oncol 20:2851-62, 2002

26. Meichenbaum D, Novaco R: Stress inoculation: a preventative approach. Issues Ment Health Nurs 7:419-35, 1985

27. Carlson CR, Hoyle RH: Efficacy of abbreviated progressive muscle relaxation training: a quantitative review of behavioral medicine research. J Consult Clin Psychol 61:1059-1067, 1993

28. Fried R: Breathing as a clinical tool, in Mostofsky DI, Barlow DH (eds): The management of stress and anxiety during medical disorders. Needham Heights, Allyn & Bacon, 2000

29. Dunn AL, Trivedi MH, O'Neal HA: Physical activity dose-response effects on outcomes of depression and anxiety. Med Sci Sports Exerc 33:S587-97; discussion 609-10, 2001

30. Scully D, Kremer J, Meade MM, et al: Physical exercise and psychological well being: a critical review. Br J Sports Med 32:111-20, 1998

31. Blumenthal JA, Jiang W, Babyak MA, et al: Stress management and exercise training in cardiac patients with myocardial ischemia. Effects on prognosis and evaluation of mechanisms. Arch Intern Med 157:2213-23, 1997

32. Dusseldorp E, van Elderen T, Maes S, et al: A meta-analysis of psychoeduational programs for coronary heart disease patients. Health Psychol 18:506-19, 1999

33. Segal R, Evans W, Johnson D, et al: Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. J Clin Oncol 19:657-65, 2001

34. Courneya KS, Mackey JR, Quinney HA: Neoplasms, in Myers J, Herbert W, Humphrey R (eds): American College of Sports Medicine's resources for clinical exercise physiology: musculoskeletal, neuromuscular, neoplastic, immunologic and hematologic conditions. New York, Lippincott, 2002

35. Courneya KS, Mackey JR, Bell GJ, et al: Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 21:1660-8, 2003

36. Turk DC, Meichenbaum D, Genest M: Pain and behavioral medicine: A cognitive-behavioral perspective. New York, Guilford Press, 1983

37. Meichenbaum D: Stress inoculation training. New York, Pergamon Press, 1985

38. Schwartz AL: Daily fatigue patterns and effect of exercise in women with breast cancer. Cancer Pract 8:16-24, 2000

39. Schwartz AL, Mori M, Gao R, et al: Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. Med Sci Sports Exerc 33:718-23, 2001

40. Du H, Newton PJ, Salamonson Y, et al: A review of the six-minute walk test: Its implication as a self-administered assessment tool. Eur J Cardiovasc Nurs, 2008

41. Rostagno C, Gensini GF: Six minute walk test: a simple and useful test to evaluate functional capacity in patients with heart failure. Intern Emerg Med 3:205-12, 2008

42. Ware JE, Kosinski M, Keller SD: SF-36 physical and mental health summary scales: a user's manual. Boston, The Health Institute, New England Medical Center, 1994

43. Ware JE, Snow KK, Kosinski M, et al: SF-36 Health Survey: a manual and interpretation guide. Boston, The Health Institute, New England Medical Center, 1993

44. Syrjala KL, Abrams J: Scoring Manual for the Cancer and Treatment Distress (CTXD) scale, 2005

45. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193-213, 1989

46. Broeckel JA, Jacobsen PB, Horton J, et al: Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol 16:1689-96, 1998

47. Carpenter JS, Andrykowski MA: Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res 45:5-13, 1998

48. Katz JN, Chang LC, Sangha O, et al: Can comorbidity be measured by questionnaire rather than medical record review? Med Care 34:73-84, 1996

49. Sorror M, Storer B, Sandmaier BM, et al: Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. Cancer 112:1992-2001, 2008

50. Sorror ML, Maris MB, Storb R, et al: Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106:2912-9, 2005

51. Sorror ML, Sandmaier BM, Storer BE, et al: Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol 25:4246-54, 2007

52. Godin G, Jobin J, Bouillon J: Assessment of leisure time exercise behavior by self-report: a concurrent validity study. Can J Public Health 77:359-62, 1986

53. Marcus BH, Selby VC, Niaura RS, et al: Self-efficacy and the stages of exercise behavior change. Res Q Exerc Sport 63:60-6, 1992

54. Borg G: The perception of physical performance, in Shephard RJ (ed): Frontiers of Fitness. Springfield, IL, Charles C. Thomas, 1971

55. Jacobs DR, Jr., Ainsworth BE, Hartman TJ, et al: A simultaneous evaluation of 10 commonly used physical activity questionnaires. Med Sci Sports Exerc 25:81-91, 1993