BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs FOR BMT CTN PROTOCOL #0902

Study Question and Study Population

1. Why is this an important study?

There are strong preliminary data that the exercise and stress management interventions being tested are beneficial when used by patients undergoing hematopoietic cell transplantation. However, transplant centers do not currently have the resources to provide training and reinforcement for patients. Only a large, multi-center study will provide compelling evidence to make such training standard of care. The 2007 Michigan BMT CTN State of the Science Symposium identified such a randomized trial as a high priority study.

2. Aren't centers already encouraging exercise and stress reduction?

Although most centers do encourage exercise and avoiding stress, a survey of Core centers showed that few to none had formal exercise programs or stress management training available. The interventions to be tested are more intensive than casual exercise and stress reduction. For example, the exercise arms are encouraged to exercise by walking 3-5 times per week for 20-30 minutes at a maximum intensity of 50-75% of estimated heart rate reserve. The stress management arms will use paced abdominal breathing, progressive muscle relaxation with guided imagery, and use of coping self-statements to decrease stress.

3. Why does this need to be done in BMT CTN?

Smaller single institution studies have reported strong effects of exercise and stress reduction programs, but these were generally resource intensive programs. The proposed BMT CTN study will test whether a self-administered, easily disseminable form of training improves symptoms, functional status and quality of life. These are the data and materials necessary to provide all transplant patients with access to these interventions.

4. Why include all graft sources, GVHD prophylaxis regimens etc? Should the population be more homogeneous?

All graft sources and GVHD prophylaxis regimens are included in order to maximize accrual and so that study results may be representative of the entire spectrum of patients undergoing transplantation. It is anticipated that randomization with stratification by center and conditioning intensity should result in even distribution of transplant-related characteristics.

5. **Why do you allow patients who are already exercising or using stress reduction to participate in the study?**

   The exercise intervention provides an exercise prescription (target heart rate and duration) and reinforcement during transplantation. This intervention is likely different than what most patients think of as "exercise." There are several approaches to stress reduction, and it is unlikely that patients have received training in the same three used in the intervention arm.

6. **The study is too large and expensive. Can't you target a specific population (autologous patients, reduced intensity conditioning recipients, myeloablative recipients)?**

   There are preliminary data in all populations for benefit from these interventions. Conducting the trial using wide eligibility criteria will improve accrual, speed completion of the trial and ensure results are generalizable to general transplant practices today.

7. **Can patients enrolled on this study participate in other BMT CTN, cooperative or institutional research studies?**

   One of the exclusion criteria is participation in another clinical study with quality-of-life or functional status as a primary endpoint. However, we would allow patients to be on other clinical trials and in fact would encourage co-enrollment. We do not anticipate the interventions we are testing and the outcomes we are measuring will interfere with other studies, nor will participation in other studies interfere with our research questions. Several therapeutic studies have quality of life or functional status as secondary endpoints. Co-enrollment will be allowed as long as the Principal Investigators of both studies agree.

<u>Choice of Study Interventions</u>

8. **Shouldn't the exercise intervention be more intensive?**

   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.

9. **Shouldn't the interventions be supervised by trained professionals?**

   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 is not feasible within current center resources. Second, two randomized studies, one testing an exercise intervention and one evaluating stress management training, found greater effects with the self-administered interventions than supervised programs.

10. Are exercise and use of stress management techniques feasible in transplant patients within the first 3 months?

Yes, these exercise and stress management techniques have been shown to be feasible in cancer patients, including patients undergoing HCT, so we already know they can be effective and safe. What this study will test is whether an easily disseminated intervention can provide the benefits observed in smaller, single institution studies.

11. Wouldn't delaying use of the exercise or stress reduction intervention until after the patients recover from the acute toxicity of transplant improve their ability to participate and increase the likelihood of a positive study?

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.

12. What will transplant centers tell study participants about exercise and stress management if they are not randomized to that arm?

Transplant centers should continue to provide their standard of care regarding exercise and stress management to all patients, whether they are participating in the CTN study or not. This may include counseling, training or other means to support patient recovery. Almost all centers do encourage patients to exercise, but we know from our center survey that very few provide formal exercise plans or stress management training as part of standard of care.

13. What about newer approaches to exercise such as "functional" exercises or even Web-based systems that allow people to track their progress? Would these approaches be more effective than the current intervention?

The goal of the exercise intervention is to get patients to exercise for 3-5 times per week for 20-30 minutes achieving their target heart rate. Walking is usually the most convenient and favored way of achieving this heart rate goal, but any other form of exercise is allowed. "Functional" exercises, or incorporating exercise into movements used in routine daily activities, also can accomplish the exercise goal as long as the effort is sustained for long enough. However, these types of exercises have not been tested in HCT patients and no preliminary data about their effectiveness and safety exist for this population. Web-based or other systems are not formally part of the intervention to be tested, but patients may be informed about their availability if they wish to use them.

Choice of Study Design

14. Why the complicated 4 arm randomization? Couldn't you just compare the combined intervention vs. standard care?

The Protocol Team carefully considered this suggestion but felt after much debate that it was important to retain the 4-arm randomization. If differences are seen between the intervention and control groups, then it will be important to understand the components of the intervention contributing to those differences. It may also be that training patients in both exercise and stress management actually increases burden and decreases adherence to use of either intervention so the Protocol Team did not want that to be the only intervention tested. Similarly designed trials in patients receiving cyclic chemotherapy have been feasible.

15. Shouldn't you try to measure whether patients are using the interventions?

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. 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. We will collect self-reported use of exercise and stress management in all arms.

16. Shouldn't objective measures of functional status be used rather than self-reported 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 test, but this would add burden to the participants and sites, and may not be feasible in busy clinical areas.

17. What was the reason for primary endpoint assessment at 100 days post transplant?

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. Primary endpoint assessment at 100 days was felt to best balance these considerations.

18. Should there be more explicit criteria to ensure patients are safe to continue using the interventions?

We did not include specific medical criteria for continued participation in exercise or stress management because we anticipate that close monitoring by clinical staff as part of standard care is the most effective way to judge whether patients should continue to exercise or use stress management techniques.

19. How will "toxicities" associated with the interventions be handled?

We do not anticipate major toxicities attributable to study participation. Medical risks of study participation are expected to be low but could conceivably be due to exercise participation. 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. Please note that none of the instruments used to collect patient-reported outcomes is intended to detect anxiety, depression, or suicidal or homicidal ideation.

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.

20. Why are you using an intent-to-treat analysis?

The protocol team, including statisticians from CTN, NHLBI and EMMES, debated the analytic plan extensively including use of an intention-to-treat design versus a conditional analysis (of all surviving patients or only those providing Day 100 assessment). After considerable discussion, we have designated the intention-to-treat approach as the primary analysis, using all randomized patients regardless of whether they undergo transplantation, use the assigned intervention, survive to Day 100, or provide Day 100 self-assessments. Please note that in order to be randomized, patients must first complete baseline assessments, so we will have complete baseline data for the randomized population.

Use of an intention-to-treat design is the gold standard for randomized clinical trials. It protects against bias from the intervention affecting survival or ability to collect primary endpoint data, and it answers the question of whether the entire enrolled population benefits from the interventions. There will be missing data from patients who are randomized but not transplanted, those who die before Day 100, and survivors who do not provide Day 100 assessments. Assumptions will have to be made for these missing data (see question below)

A very important secondary analysis will be a conditional analysis of surviving patients who complete Day 100 assessments. This analysis excludes patients who are not transplanted, die before Day 100, or survive but do not provide Day 100 assessments. This analysis answers the question of whether the intervention is beneficial to survivors who complete the assigned intervention.

The protocol team wishes to stress that in a behavioral trial of this type, the secondary endpoints are of considerable interest and will be evaluated regardless of whether the trial achieves its primary endpoint. Power calculations show that sufficient survivors will be available to address the secondary endpoints using pairwise comparisons between the four intervention groups.

21. How will you assign functional status scores to the patients who do not undergo transplantation, die before Day 100, or are alive at Day 100 but do not provide self-reported assessments?

A variety of methods are available to handle missing patient self-reported data. For the primary analysis, we have opted to assign the following scores for Day 100: score lower than the lowest reported score for patients who are not transplanted or who die; score higher than patients who die but lower than the lowest reported score for patients who do not provide Day 100 data. Please note that we do not expect the study interventions to affect ability to undergo transplantation, survival or likelihood of collecting Day 100 data so we anticipate similar percentages in each group.

Other approaches using baseline assessments, single item scores collected at Day 30 and Day 60 and clinical characteristics to impute scores for missing patients will also be carried out as a secondary analysis.

22. Accrual estimates – See separate summary of Accrual Estimates.

23. What are the recruitment strategies if applicable, and proposed plans for monitoring study accrual?

Core Clinical Centers and non-Core Centers will participate. Transplant centers will follow their local institutional practices for recruiting patients on research studies.

Patient information and educational materials explaining this study will be prepared by the NMDP Office of Patient Advocacy and made available to centers in paper form and on the Web.

Monthly accrual reports will be provided to the NIH. Additionally, recruitment reports based on the CIBMTR database will be provided every six months. The screening reports will summarize reasons for non-enrollment and reasons for ineligibility.

24. What are the proposed plans for data acquisition, transfer, management and analysis?

A web-based data entry platform will be used for all BMT CTN supplemental forms. Data are transmitted encrypted using secure socket layer (SSL) technology. SSL is the standard used by banks in their electronic transactions. This platform includes online missing forms reports as well as other reports as deemed useful by the transplant centers. A User's Guide and Data Management Handbook will be developed for reference and training of clinical research associates (CRAs).

Data collected on CIBMTR data forms will be transferred electronically from the CIBMTR to EMMES on a regular basis. Any data relevant to real-time monitoring of safety or efficacy endpoints will be collected on BMT CTN supplemental forms, e.g. deaths.

Missing forms reports are updated daily. Queries will be developed to check for missing and inconsistent data. Queries will be distributed to the centers at least monthly.

Analysis files will be prepared prior to each Data and Safety Monitoring Board (DSMB) meeting. Most analyses will be conducted using SAS and following the statistical analysis plans outlined in each protocol.

25. What is the monitoring and overall coordination of protocol management (e.g., Brief summary of plans to run the study – initiation, coordination, data collection, and monitoring)?

A protocol coordinator is assigned to each BMT CTN protocol. The protocol coordinator is responsible for the daily operational needs of the study and of the participating transplant centers. The protocol coordinator oversees enrollment and data collection issues and is in regular communication with CRAs at participating transplant centers. The protocol coordinator also works closely with the protocol officer with respect to adverse event reporting and to medically related protocol questions.

A form submission schedule is developed for each BMT CTN protocol and is included in these materials. A visit schedule will be provided to the transplant centers for every enrolled patient. This schedule will detail the dates of all expected visits and list of forms and/or samples required at each visit.

Initiation site visits will be conducted for all participating centers. These visits will either be in-person visits to the centers or be held via conference call with all transplant center personnel involved with this protocol.

DCC staff, including at a minimum the protocol coordinator, will conduct periodic monitoring visits to the participating clinical centers and laboratories. The primary purpose of these visits is to conduct data audits. Other activities include those required to enhance data quality, ensure study integrity, satisfy regulatory requirements, and evaluate site performance. Site visits will occur at variable frequency throughout the course of the studies, depending primarily upon the stage of the study, site performance, and sponsoring agency requirements.

Unexpected serious adverse experiences will be reported according to BMT CTN guidelines. The protocol officer will review all unexpected serious adverse experiences. Expected transplant-related toxicities will be collected on each patient using the calendar-driven reporting system that has been previously reviewed and approved by the DSMB. There is an interim statistical monitoring plan for efficacy and safety endpoints. The protocol statistician or other DCC statistical staff will ensure that programs are in place to conduct the interim monitoring in accordance with the statistical analysis plans in each protocol.

26. Are there any specific study training plans necessary to accomplish the research goals (eg. Workshops, study certification)?

CRAs will be certified for data submission by the DCC after participating in an in-person meeting or in a training session conference call with the protocol coordinator.

Each study site will have two research personnel trained to deliver the interventions. The Protocol Team will be responsible for training and certification of interventionists through prepared materials, conference calls, role playing, and review of practice audiotapes. In addition, in-person training sessions will be held at the annual Tandem meeting to provide additional training opportunities.