Pilot Study Evaluating Changes in Physical Function Measures in Stem Cell Transplant Patients at Risk for Steroid Myopathy

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I. BACKGROUND

Allogenic hematopoietic stem cell transplantation (HSCT) is used frequently for treating hematologic malignancies [1]. Graft-versus-host disease (GVHD) is one of the major complications of HSCT [2,3] and the main cause for transplant-related morbidity and mortality. GVHD has been divided into acute and chronic with distinct clinical manifestations. Manifestations of acute GVHD include maculopapular skin rash, nausea, vomiting, diarrhea and cholestatic jaundice.

The median occurrence for significant acute GVHD (grade II-IV) is about 40%. Moderate to severe acute GVHD occurs in up to 30% of patients despite receiving cells from a fully matched human leukocyte antigen (HLA) related or unrelated donor and immunosuppressive therapy [4,5,6]. Chronic GVHD is a common late challenge associated with HSCT. Roughly 50% of the patients experience some degree of chronic GVHD ranging from 30 to 80%. Chronic GVHD is a leading cause of late non-relapse related mortality

With such impact of GVHD on morbidity and mortality, effective prophylaxis of GVHD is quite important. A common approach for such prevention includes prophylactic use of a regimen with immunosuppressive agents given after HSCT. Corticosteroids (typically methylprednisolone or prednisone) are the standard therapy for patients with acute GVHD grade II-IV. The starting dose of steroids are generally 2mg/kg for all patients with grade II-IV acute GVHD except for isolated upper GI GVHD wherein 1mg/kg is commonly the starting dose. High dose corticosteroids are employed as a front line agent to treat this complication [5, 6, 7, 8]. High dose steroid therapy is associated with a variety of adverse side effects including avascular necrosis, cataracts, edema, gastritis, headaches, hyperglycemia, hypertension, hypokalemia, insomnia, infections, mood swings and steroid myopathy [9].

Steroid myopathy is the most significant complication of such corticosteroid therapy [8, 10]. Once patients become impaired with significant loss in functional status; outcomes are poor with marked increase risk of infections. Incidence rate of such myopathy has been estimated at least at 41% [10]. Although the presentation can be acute, most often it is insidious.

To date, research has been infrequent in this common complication of GVHD therapy. The only study to address this complication came from our institution [10] in the form of

a retrospective review of 180 patients. Seventy of these patients met inclusion criteria. Twenty nine of these patients were evaluated by physical therapists with manual muscle exam (MME) and for functional independence measure (FIM) scores. With MME data missing for 3 patients, 11 patients had scores of 3 out of 5 with MME (movement in full range of motion against gravity without resistance) in upper extremities. Thirteen patients had scores of 3 in lower extremities. These scores constituted myopathy from functional perspective. In 11 and 13 patients, scores of 4 out of 5 with MME (movement against moderate resistance) were noted with upper and lower extremities respectively. Patients with such strength may be able to ambulate and transfer independently but such independence is not guaranteed. The majority of the patients needed assistance with device(s). They also needed some degree of assistance when performing tasks including supine to sit transfer (17 out of 29), sit to stand transfer (18 out of 29), and walking (22 out of 29). This study was limited by being retrospective with likely only the severe cases referred for evaluation.

To date, despite being a common complication across many different diseases which necessitate high-dose steroid treatment, there is no formal definition or disease-severity index for patients with steroid myopathy. A major area of acute GVHD research is to develop therapies which minimize exposure to corticosteroids. These therapies may result in comparable GVHD response rates yet are ultimately preferable because of reduction in toxicity. Being able to quantify protection from steroid-myopathy is integral to interpreting these studies. The goal of this protocol is to perform a prospective pilot study to define steroid myopathy (definition, measures, incidence, severity) and impact on non-relapse mortality in a homogenous population of patients with newly diagnosed acute GVHD.

There are very limited studies and limited knowledge of the weakness and subsequent functional deficits that develop in patients with steroid myopathy. There are no formal tools used to identify or quantify impairments in patients suspected of having steroid myopathy. Steroid myopathy usually affects proximal musculature with preferential involvement of lower extremities, especially quadriceps [11]. With such weakness, significant functional sequelae include among others, inability to independently sit from supine position (only 31%) and stand from sitting position (28%) [10].

The diagnosis of steroid myopathy in HSCT patients was previously based on Manual Muscle Exam (MME) and Functional Independence Measure (FIM) [10]. However, manual muscle testing is examiner-dependent and can be non-specific. Tests such as the Peripheral Motor Deficits Scale (PMDS), Stepper test, and Ankle/Wrist index and Neuropathy Disability Score [12] have been used; however, these tools have not been validated and are rarely utilized in clinical or research settings. Laboratory and imaging tests cannot reliably diagnose steroid myopathy. Electromyography is an invasive test which cannot be used solely to make such a diagnosis as some of the findings may be non-specific. In addition, it may be too invasive in this setting of patients who have just received a stem cell transplant. The Adult Myopathy Assessment Tool (AMAT) has been used in patients with inflammatory myopathies, spinal and bulbar muscular atrophy [13], but has not been specifically utilized for steroid myopathy. This

assessment includes 7 timed functional tasks and 6 endurance tasks, has high inter-rater and intra-rater reliability and correlation with other physical assessments such gait speed, and the physical quality of life. The Brooke scale was developed to assess upper extremity functional performance in Duchenne Muscular Dystrophy patients and is easy to apply and interpret [14, 15]. It has also been applied in the rehabilitation setting for patients with spinal muscular atrophy [16] Again, none of these tests have been studied in patients with steroid myopathy.

No known therapy exists to prevent or to enhance recovery after the development of steroid induced myopathy, although rehabilitation measures may improve outcomes of these patients [17, 18]. Engaging in treatment for patients who develop steroid myopathy is not possible because the not much is known about the time course of the weakness that develops. There are no known tools to assess and measure the weakness; and thus, putting together a treatment regimen or even pursing a prospective study to implement an intervention becomes a challenge. A major objective of this research is to identify the best tools to capture steroid myopathy incidence and severity. An ideal tool should be: 1) easy to perform and measure by multiple disciplines, 2) easy to interpret the results, 3) be able to discern post-transplant disability from steroid myopathy, and 4) may be used with patients with varying severity of weakness.

Because there are limited diagnostic tools available to formulate a diagnosis of steroid myopathy, it is important to study the functional and physical changes that may occur if a patient develops steroid myopathy. It is important to use measures that are widely utilized in the literature such as the 6 minute walk test, 5 times sit-to-stand, and manual muscle testing, along as ones such as the AMAT and Brooke Scales, which have been used in other myopathy settings. Based on the patterns of physical and functional decline measured in this study, we can formulate surrogate markers that will be essential in conducting future prospective interventional studies in patients who have been diagnosed with or are at risk for developing steroid myopathy.

II. OBJECTIVES

Primary Objective:
1. To perform a pilot study to estimate the change in six physical and functional tests over time in patients with suspected acute graft-versus-host disease (GVHD) who have been initiated on treatment with corticosteroids.

Secondary Objectives:
1. To describe and potentially define steroid myopathy by following the patterns of the muscle loss and functional impairment in this population of patients.
2. To follow steroid myopathy and describe its incidence, its severity, and the impact on non-relapse mortality in a homogeneous population of patients with suspected acute graft-versus-host disease (GVHD) who have been initiated on treatment with corticosteroids at a quaternary institution in the inpatient and outpatient setting.

3. To estimate the adherence to an intermittently supervised exercise program in hematopoietic stem cell transplantation (HSCT) patients who are at risk of developing steroid myopathy.

Hypothesis – There will be a decline in muscle strength and functional measurements in patients with suspected graft versus host disease who have been started on corticosteroids which will be detected at the Day 28 follow up, and may be more robust at the Day 56 follow up. Steroid myopathy and steroid-myopathy severity is correlated with non-relapse mortality in patients with newly diagnosed acute GVHD.

III. STUDY ENDPOINTS:

Primary Endpoints:

- Physical and functional measurements and the changes in these measures over time.

Secondary Endpoints:

- Physical and occupational therapy is often prescribed for patients who develop steroid myopathy. It is unclear how many adhere to their exercise regimens. We will estimate the adherence to the study exercise program, tolerance for specific exercises and ability to advance exercises, and completion of study materials.
- We will also measure the percentage of patients who agree to participate in the study as this information will provide us with an estimate of the percentage of patients who may participate for future studies and measures.
- Patient self-reported outcomes in functional status and symptoms over time while being followed for GVHD.
- Overall status of disease and survival at day 180. This includes assessing the impact on non-relapse mortality at 6 months post-enrollment.
- We will assess other variables (age, gender, co-morbidities, type of graft, etc.) that may impact incidence of steroid myopathy in this group of patients.
- Changes in physical and functional measurements in comparison to their cumulative steroid dosing.
- Changes in physical and functional measurements in comparison to the severity of GVHD.

IV. ELIGIBILITY CRITERIA:

Inclusion:

1) Participants are willing and able to give written informed consent and to comply with all of the study visits and procedures.
2) Age ≥ 55years, or with a Sorror co-morbidity index of ≥ 3]
3) Post allogenic hematopoietic stem cell transplantation using bone marrow, peripheral blood or cord blood; or after pre planned donor lymphocyte infusion.

4) Presumptive diagnosis of acute GVHD necessitating high-dose corticosteroid treatment (with an approximate starting dose of methylprednisolone equivalent of 2mg/kg/day).
5) Within 5 days of receiving corticosteroid treatment
6) ECOG (Eastern Cooperative Oncology Group) performance status of 0, 1, or 2 or equivalent Karnofsky score of 60 or higher.
7) The patient is referred to the study by their stem cell transplant attending physician.

Exclusion:

1) Non-English speaking
2) Patients under 18 years of age
3) Underlying unstable cardiac or pulmonary disease in the opinion of the investigator that limits participant involvement in exercise.
4) Has a pre-transplant echocardiogram with ejection fraction <45%.
5) Requires supplemental oxygen to maintain O2 saturation >92%
6) Musculoskeletal injury that precludes participation in an exercise program
7) Inability to participate in a structured exercise program
8) Patients for whom the physician feels is unsafe for an exercise program
9) Platelets equal to or less than 10,000 or evidence of active bleeding
10) Patients who are unable to understand or follow through with the exercise program

V. STUDY PLAN

Given the pattern of weakness associated with steroid myopathy, we will measure the following:

a) Objective Functional/physical measures:
    - **a. Manual muscle testing**
        - i. Measure strength of shoulder abduction, elbow flexion, extension, hip flexion, and quadriceps bilaterally.
        - ii. Cumulative score out of 50 points total.
    - **b. Hip flexor and quadriceps strength via handheld dynamometer**
        - i. Reported as strength in pounds
    - **c. Six minute walk test**
        - i. Reported as meters
    - **d. 5x sit to stand**
        - i. Reported as total time in seconds
    - **e. Brooke Scale:**
        - i. Reported as numerically as 1-6.
            1. From arms at side, abduction of arms in full circle until touching overhead
            2. Can raise arms above head only flexing the elbow or using accessory muscles

3. Cannot raise hands above head, but can raise an 8 ounce glass of water to the mouth
4. Can raise hands to the mouth, but cannot raise an 8 ounce glass of water to the mouth
5. Cannot raise hands to the mouth, but can use hands to hold a pen or pick up pennies from the table
6. Cannot raise hands to the mouth and has no useful function of hands

f. **Adult Myopathy Assessment Tool (AMAT)** – Only portion of the test will be administered:
   i. Reported as summation of the tasks below (total 24 points).
      1. Arm raise (0-3)
      2. Sustained arm raise (0-4)
      3. Sit to stand (0-3)
      4. Sustained hip flexion (0-4)
      5. Sustained knee extension (0-4)

b) Subjective/Patient reported
   a. Self reported Improved (or PROMIS) Health Assessment Questionnaire
   b. PROMIS Short Form v1.0 – Physical Function 12a.
   c. MD Anderson Symptom Inventory (MDASI)
   d. FACIT-Fatigue Scale

c) Baseline demographics
   a. Pre-transplant comorbidity index (Sorror)
   b. Underlying disease requiring transplantation
   c. Disease stage at the time of transplant
   d. Donor type
   e. Graft Source

d) GVHD-associated measurements at baseline and after initiation of corticosteroids at Day 14(+/-5), 28 (+/-5), and 56 (+/-5)
   a. Organ Stage and Grade of GVHD (see Table 1)
   b. Corticosteroid dose at that time and cumulative corticosteroid dose through day 56.
      i. Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25. Prednisone doses for each subject will be converted to mg/kg. The cumulative and average corticosteroid doses will be calculated over time.
   c. GVHD Response (at days 14, 28, 56)
   d. Body mass index (BMI), albumin, prealbumin levels. Albumin and possibly prealbumin levels are collected by the stem cell transplant team whether

the patient is on study or not (standard of care) and are not research-specific procedures. Prealbumin levels will be recorded if they are obtained by the medical team.

e) During the Day 180 post-transplant follow up:
    a. Acute and chronic GVHD assessment, if patient is returning to MDACC
        i. Grade of GVHD, GVHD response
    b. Body mass index (BMI), albumin levels, will be collected from the medical record if available.
    c. Non-Relapse Mortality: non-relapse mortality due to any cause other than the underlying malignancy, will be assessed at Day 180
    d. Overall survival: Overall survival will be computed up to Day 180

With the exception of the baseline demographic information, physical/functional measures, patient reported questionnaires, and GVHD-associated measurements will be recorded at the following time points:

a. Baseline (at the time of screening, consent and enrollment into the study)
b. Day 14 (+/-5)
c. Day 28 (+/-5)
d. Day 56 (+/-5)

It will take approximately 15 minutes to perform the physical function tests and it will take approximately 20 minutes to complete the patient questionnaires during each patient evaluation session.

If a participant remains hospitalized as an inpatient, he or she will continue to participate in the exercise program allocated to them and the above measures will be recorded at the appropriate time intervals. The medical indication for hospitalization, discharge diagnoses and length of hospital stay will be recorded.

Table 1: Overall Acute GVHD Response
Participants will be graded according to the modified Keystone Grading Schema displayed in the table below.

Modified Keystone Grading Schema

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No Rash	Rash <25% BSA	25-50% BSA	>50% BSA	Bullae and desquamation
Lower GI Tract	<500 ml/day stool volume	500-1000 ml/day stool volume OR Severe	1001-1500 ml/day stool volume	>1500 ml/ day stool volume	Severe abdominal pain +/- ileus, frank blood or melena

		nausea and vomiting			
Liver	Bilirubin ≤2 mg/dl	2.1-3 mg/dl	3.1-6 mg/dl	6.1-15 mg/dl	>15 mg/dl

Abbreviations: BSA = body surface area; GI = gastrointestinal (1)

1. **Acute GI GVHD Response Criteria:** Proportion of subjects with CR, PR, MR, NR and Progression will be determined over time. Scoring of CR, PR, MR, Progression and NR will be in comparison to the participant's acute GI GVHD Stage (see lower GI tract row of above table). Response will be based on the following response definitions:
   - **Complete Response (CR)**: a Stage of 0 for the GVHD grading in the lower GI tract with no additional intervening therapy for their GVHD.
   - **Partial Response (PR**): improvement by at least 1 Stage in GI GVHD symptoms without progression in others with no additional intervening therapy for their GVHD.
   - **Mixed Response (MR)**: improvement in lower GI tract with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
   - **Progression:** deterioration in lower GI tract.
   - **No Response (NR):** absence of any improvement or progression as defined above. Subjects receiving secondary therapy (including need to re-escalate steroid dose to ≥2.5 mg/kg/day of prednisone; or methylprednisolone equivalent of 2 mg/kg/day) will be classified as non-responders.
2. **Response for All Organs Involved with Acute GVHD:** Proportion of subjects with CR, PR, MR, Progression and NR for all organs involved with acute GVHD will be determined over time. Scoring of CR, PR, MR, Progression and NR will be in comparison to the participant's acute GVHD Stage (see table of Modified Keystone Grading Schema above). Response will be based on the following response definitions:
   - **Complete Response (CR)**: a Stage of 0 for the GVHD grading in all evaluable organs with no additional intervening therapy for their GVHD.
   - **Partial response (PR**): improvement by at least 1 Stage in 1 or more organs involved with GVHD symptoms without progression in others with no additional intervening therapy.
   - **Mixed response (MR)**: improvement in 1 or more organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
   - **Progression:** deterioration in at least 1 organ without any improvement in others.
   - **No response (NR):** absence of any improvement or progression as defined. Subjects receiving secondary therapy (including need to re-escalate corticosteroid dose to ≥2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) will be classified as non-responders.

Patient Recruitment

Eligible patients with newly diagnosed GVHD will be recruited from the MDACC outpatient stem cell transplant clinic and the MDACC inpatient stem cell transplant primary service. The stem cell transplant attending physician will be the primary recruiter to the study. Patients will be referred to our research team within 5 days of initiating corticosteroids for the presumptive diagnosis of GVHD. In the event that a patient's biopsy results in no GVHD, but the patient has been on high-dose corticosteroids for four or more days, they will still remain on study as they may still be at risk for steroid myopathy. The following screening tests will be performed after receiving verbal consent from the patient. Patients will complete the Physical Activity Readiness Questionnaire (PAR-Q). Furthermore, they will undergo baseline physical

functioning tests (walk 10 meters, 5x sit-to-stand test). Thus, their potential to participate in a home-based exercise program will be screened based on subjective reports and objective demonstration. Based on their responses, they will be enrolled onto the study or they will be triaged to the study principal investigators for further review. For instance, if they are having on-going cardiopulmonary symptoms, they will be re-evaluated by their primary stem cell physician for medical clearance for an exercise regimen and if they have musculoskeletal concerns, they will be referred to physical medicine and rehabilitation for further evaluation.

For the PAR-Q screening questions:

- If the patient has any "Yes" responses to questions 1-4, they will be referred back to the Stem Cell Transplant attending physician, who will decide to clear the patient for exercise, or if they require a cardiology consultation prior to initiating exercise.
- If they respond "Yes" to questions 5 and 7, they will be triaged to one of the Physical Medicine and Rehabilitation faculty who is over-seeing the study. They can potentially evaluate the patient face-to-face during the screening period, or will speak with the patient to determine their eligibility to participate in the study.
- In the event that the patient is excluded from the study based on the PAR-Q, the patient will either be referred to Physical Medicine and Rehabilitation for a clinical consultation to address their impairments or referred to outpatient physical and occupational therapy (where they may receive a supervised therapy program).

Participants from both inpatient and outpatient who are recruited for this study will receive a strengthening and walking program.
We plan to approach approximately 70 patients to invite them to participate in this study with an accrual of 3 new participants per month with an anticipated accrual period of approximately 24 months.

When the stem cell transplant team initiates a patient on corticosteroids for newly-diagnosed GVHD, they will contact our study staff. Our study staff will meet with the patient face-to-face at the stem cell transplant clinic or the Ambulatory Transfusion Clinic (ATC). Follow up visits will also be conducted in the stem cell transplant clinic or ATC, as this is where the patients will attend their routinely scheduled clinic appointments. They will be asked a series of questions about their exercise tolerance and to screen for any adverse events (script included). During the follow up face-to-face visits (Day 14, 28, 56, and 180), we will obtain repeat measures (questionnaires and functional measures).

Exercise Regimen
The American College of Sports Medicine exercise guidelines for cancer survivors encourage a combination of 150 minutes of moderate-intensity aerobic activity and two to three weekly sessions of strength training, but caution that exercise programs should

be adapted to the needs of each cancer survivor [21]. There are currently no guidelines for exercise in patients undergoing treatment for cancer. Studies show that exercise prior to and immediately after HSCT show significant differences strength, endurance, functional performance, and quality of life. [22, 23]. There is also evidence that isokinetic strength training can reverse corticosteroid-induced muscle wasting [24]. As muscle weakness and deconditioning are frequently seen sequelae after HSCT and as steroid myopathy develops, patients are often referred to physical and occupational therapy to address the weakness. Thus, it is important to employ an exercise and endurance regimen to preserve strength and to circumvent further functional decline.

The exercise regimen will include an 8-week, home-based strengthening walking program.

- MDACC physical medicine and rehabilitation (PM&R) physicians will supervise the conduct of the exercise intervention.

- Research staff trained by the PM&R faculty will implement the exercise intervention.

- Furthermore, many of these patients receive outpatient physical therapy as standard of care. If the participant is receiving outpatient physical therapy, the skilled therapy team will incorporate this exercise regimen in their outpatient program and the participant will be encouraged to continue with our exercise regimen as their home program.

- The inpatient and outpatient groups will be given the same set of exercises (strengthening and walking), instructions for adherence, and follow up measurements will be conducted at the standard time intervals as outlined in in Section V:
    - Baseline (at the time of screening, consent and enrollment into the study)
    - Day 14 (+/-5)
    - Day 28 (+/-5)
    - Day 56 (+/-5)
    - Day 180 post transplant (+/- 30 days)

a) Resistance/strengthening

All participants will be instructed to perform resistance/strengthening exercises for a 30 minutes period three times a week. The resistance exercises used in this study are designed to engage multiple upper body muscles and lower limb muscles.

The exercises consist of seated and standing weight-bearing exercises. The patients will start with body-weight based exercises and will graduate to ones requiring resistance with the use of exercise bands. The upper body exercises will strength deltoids, scapular stabilizers, triceps and rotator cuff musculature. These exercises will include the use of elastic exercise bands. The lower limb

exercises will strengthen the hip flexors, gluteus musculature, quadriceps, and gastrocnemius-soleus complex. These exercises will include (but are not limited to) leg lifts, hip abductions, and calf presses.

The participants will be instructed to perform the upper and lower body exercises prescribed for a duration of 30 minutes 3 times per week. Participants will perform 1-3 sets of 12 repetitions of each exercise. Most of the exercises will require the use of exercise bands. Once they are able to perform 3 sets of 12 repetitions of an exercise, they will graduate to the next level of increasing resistance. The participants will be given a set of three bands which determine the level of resistance: easy, moderate, and hard. They will record the date, the color of elastic exercise band used, the number of repetitions and sets, and their perceived intensity of the exercise based on the Borg Rating of Perceived Exertion (RPE) scale (the scale will be included in the participants' activity log).

The participants in the strengthening program will be encouraged to complete an additional 5 minutes of stretching daily. They will be provided with a handout demonstrating upper and lower body stretches to help alleviate the onset of delayed muscle soreness.

All participants will be encouraged to perform stretches before and after their strengthening exercises. We will provide them with diagrams of sample stretches they may perform.

b) Walking program

All participants will be instructed to initiate a walking program. The walking program will consist of walking at a comfortable pace for 20 to 30 minutes during each walking session. They will walk at least three times a week. The goal is to achieve a fairly light intensity of exercise (Borg RPE of 8-10) and progress a moderate intensity (Borg RPE of 11-12). Each participant will be provided a pedometer and will be instructed to record the number of steps taken each day.

Each participant will meet face-to-face with a member of the research staff. The participant will receive a patient exercise booklet that includes information on exercise, research staff contact info, exercise precautions, diagrams on the exercises, and the exercise and activity log. They will also receive a pedometer and exercise bands. Each participant will watch the exercise video clips on a computer or have the exercises demonstrated to them. The patient will have the opportunity to perform the exercise or request for the exercise to be demonstrated again for them. Thus, every participant receives the same education on the exercise regimen. We can also email them a link for the exercise clips to review from home. Furthermore, they will be instructed on the use of the pedometer and for filling out their exercise logs during the initial visit.

Each participant will be issued an exercise activity log book to record their daily activity: record their walking activity (time, intensity, number of steps) and to record the number of exercises they are able to complete during each exercise session (time, intensity, types of exercises, repetitions). They will also include if they performed exercises or activities not outlined in our study.

These activity log books will be used to monitor the patients' activity adherence.

If participants have internet access and choose to enter their exercise activity online, they will be asked to use the Redcap system to log their exercise activity on a daily basis. With their consent, participants will receive daily email reminders with a Redcap program link to log their aerobic and resistance exercise activity, pedometer steps, and to report any barriers or difficulties with their exercises. Participants will still have the option to complete activity logs on paper and the resistance exercise log of individual exercises will still remain on paper.

REDCap is a mature, secure web application for building and managing surveys and databases. While REDCap can be used to collect virtually any type of data, it is specifically geared to support data capture for research studies. REDCap can accommodate complex relationships among tables, allowing large quantities of data to be integrated into a single database. Relational databases such as REDCap also allow for powerful and flexible queries and reports. These features include more user-friendly interfaces, the ability to specify valid ranges for variables, and double-entry systems for data, all of which help to maintain data integrity. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R). We will use the built-in security features of REDCap to restrict user access.

Furthermore, to monitor for adherence and to screen for any exercise intolerance or exercise barriers, the participants will be counseled face-to-face by our research assistant during their follow up visits regarding their progress of their exercise program. The research assistant will be provided with a list of screening questions to address exercise adherence and to assess for advancing the participant's strengthening program. The research assistant will also implement behavior interventions to encourage continued adherence to the exercise program, which will include education on the benefits of exercise and physical activity. There will be one telephone follow up during week 6 of enrollment to ensure the participants do not have questions about their exercise program. They will receive a reminder to wear the pedometer and to complete the daily exercise logs.

The packet includes a list of exercise precautions and also advises the patients to not use their exercise resistance bands when their platelet counts are less than 20 K/ul.

The participants will also be given the telephone contact information of the research staff in case they encounter problems during the exercise intervention period. In the

event of an acute musculoskeletal injury or cardiopulmonary distress, the patient will be managed with an appropriate medical referral. Participants in the outpatient group who are admitted to the hospital for an acute medical concern will also be followed. They will need clearance from their HSCT physician and/or physical medicine and rehabilitation physician to continue with their exercise intervention. They will be encouraged to continue with their exercise program (and record their activity) if their medical condition allows for it. Furthermore, patients who develop significant functional decline that requires supervision and management from a skilled therapist will be referred to inpatient and/or outpatient physical and occupational therapy when appropriate.

As current standard-of-care, some of the patients who are seen in the ambulatory treatment center (ATC) are referred to outpatient physical therapy for an exercise program. These are usually group sessions for patients who do not required one-on-one treatment sessions with a physical therapist. If a participant in our study is enrolled in this outpatient ATC physical therapy program, they will still utilize our exercise program on their non-therapy days and in some situations, they may perform our exercises (aerobic and/or resistance regimens) during their therapy session to fulfill their exercise requirement for the day. Again, the participant will complete their daily log so we may track how much exercise they are performing each day.

If the patient falls or has an adverse event, they are instructed to call their stem cell transplant physician. These patients receive extensive counseling after their stem cell transplant on when and how to contact their stem cell transplant physician and team. If there are questions and concerns about the exercise regimen or intolerance of certain exercises, the participant should call our research staff directly. The Physical Medicine and Rehabilitation physicians will be communicating directly with research team on a weekly basis to discuss any adverse events or concerns.

It is anticipated that a fully adherent participant would be able to complete 30 minutes of exercise daily, five times per week, which equates to approximately 150 minutes of exercise per week.

Equipment provided:

- Notebook for the exercise activity log ($10-20 each x 40)
- Pedometer: EKHO One Pedometer http://www.amazon.com/Ekho-1277210-EKHO-One-Pedometer/dp/B002MACRUC/ref=sr_1_2?ie=UTF8&qid=1449008114&sr=8-2&keywords=ekho+one+pedometer
- Resistance exercise bands: therabands in 3 different levels of resistance http://www.amazon.com/Thera-Band-Latex-Exercise-Bands-YELLOW/dp/B00SX165ZC/ref=pd_sim_328_1?ie=UTF8&dpID=415g8eKmdtL&dpSrc=sims&preST=_AC_UL160_SR160%2C160_&refRID=1HQKCG0DCF55KPZRVKRC

Equipment needed:

- Handheld dynamometer: microFET 2 Hoggan Health Industries ($1095) http://www.hogganhealth.net/microfet2.php
- Stop watch

The participants will not receive monetary compensation for their participation in this study as this is an unfunded pilot study. The patients are not returning for any follow-up visits as they will be seen during their normally scheduled clinic visit. There would be no burden of extra return visits specifically for the study. However, the participants' benefit and incentive for participating in this study is they will receive exercise education and an exercise regimen, which will be beneficial in these newly-diagnosed GVHD patients.

VI. STATISTICS:

The objective of this study is to estimate change in the six functional/physical measures (described in Section VI) over time. The information gained in this study will be used for future larger studies. These measures will be collected at baseline, two weeks, 4 weeks, and 8 weeks. Other secondary endpoints, such as patients' Self Reported Improved (or PROMIS) Health Assessment Questionnaire, PROMIS Short Form v1.0 – Physical Function 12a, MDASI, FACT-Fatigue, GVHD associated measures and corticosteroid dose will also be collected over the same time course. We plan to approach 70 patients (3 patients each month for an approximate period of 24 months of accrual). We expect that about 85% (60 patients) will agree to participate in the study. Further if 10 (20%) out of 60 patients drop out early due to developing significant weakness, disease progression, or have a prolonged and complicated inpatient hospital course, we expect 50 patients to complete the 8 week measures. With 50 patients, we will have an 80% power to detect an effect size of 0.404 in a functional measure change from baseline to 8 weeks using a paired t-test with a 0.05 two-sided significance level.

To explore the possible corticosteroid dose effect on the functional measures, graphical methods will be used to present data and the cumulative steroid exposure may be correlated with functional measures over time in a repeated measures analysis when appropriate. Furthermore, 2-week or 4-week cumulative steroid exposure may be compared between 6-month non-relapse deaths and others, provided patients all survive past 2 weeks or 4 weeks.

We expect about 20% non-relapse mortality rate at 6 months (NRM6). With about 10 non-relapse deaths, we will explore potential difference in baseline and/or the change of functional/physical measures between 6-month non-relapse deaths vs others. With 10 non-relapse deaths and 40 others, we will have an 80% power to detect an effect size of 1.011 in the difference of a functional measure at baseline between two groups using a two-sample t-test with a 0.05 two-sided significance level.

We will also evaluate adherence rates to the exercise regimen and drop-out rates/patterns, which is very important for the future larger study planning.

At the end of the study, we will summarize the pattern of the functional/physical measure change, pattern of exercise and other secondary measures, using collected information from all 50 patients. Repeated measures analysis or generalized estimating equation maybe applied to estimate the magnitude of the measure change over time. In the same model we will also evaluate the correlation between/among different measures. These models incorporate the intra-patient correlation into consideration when these measures are recorded multiple times from each patient.

VII. PROTOCOL MONITORING AND SAFETY

Trained research staff will be performing study assessments and monitoring the patient carefully throughout the study period. A study physician will also be available by pager to address any concerns, distress, or questions, and will attend to the patient as needed. Regulatory monitoring will be provided by the principal investigator and the Institutional Review Board. Patient confidentiality will be ensured by use of patient initials, secure storage of clinical data, and anonymous reporting.

Health information will be protected and we will maintain the confidentiality of the data obtained from the patient's chart.

Collection of identifiers: We will collect and securely store patients' identifiers (including name and medical record number). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be guaranteed. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principle investigators, co-investigators, and research staff will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities. The data will be kept by the principle investigator in a locked file cabinet.

Final disposition of study records: These data will be used only for this research study. Data files will be destroyed within 5 years after publication of the findings.

VIII. REFERENCES

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