**CLINICAL RESEARCH PROJECT**

**Date:** September 23, 2019

**To:** Richard Cannon, MD, Chair, General Medicine 1 IRB

**Protocol Title:**

Pilot Study Characterizing Aerobic Exercise in Women with Systemic Lupus Erythematosus (Exercise SLE Pilot).

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**Estimated Duration of Study:** 36-60 Months
**Estimated Completion Date of Study:** December 2022

| **Subjects of study:** | **Number** | **Sex** | **Age range** |
|---|---|---|---|
| | 20 evaluable subjects | F | 21-80 years |

30 subjects with Systemic Lupus Erythematosus will be recruited in order to accrue 20 evaluable subjects. Enrollment will remain open until 20 subjects have completed the study.

| | |
|---|---|
| **Project involves ionizing radiation?** | No |
| **Offsite project?** | No |
| **Multi-Institutional project?** | Yes, NIH (medical and research testing, and exercise and educational training), George Mason University (collaborating research institution) |
| **DSMB involvement?** | No |
| **Tech Transfer: CRADA, MTA** | No |

**Identifying Words:** Exercise, Systemic Lupus Erythematosus, Rehabilitation

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## Précis

We propose a single-arm exploratory study to characterize the responses and adaptations to aerobic exercise in women who have mild to moderate systemic lupus erythematosus (SLE) uncomplicated by organ damage that would limit participation. This is a pilot study to provide additional preliminary data to support a future U01 application. Persistent, excessive fatigue is among the three most debilitating symptoms of SLE and is cited by as many as 50% of patients as the single most debilitating symptom. We have observed, in women with mild SLE, significant relationships among deficits in work capacity and oxygen consumption obtained during treadmill exercise and patient reported measures of fatigue severity [8]. Clinically significant functional aerobic impairment was present in these women, suggesting an underlying pathophysiological limitation that restricted cardiorespiratory capacity to well below that expected to occur as a result of normal deconditioning due to a sedentary lifestyle and lack of physical activity. We have also observed prolonged rest to steady state metabolic transition during even submaximal exercise in women with SLE [10]. At peak exercise, muscle oxygenation deficiency was apparent despite normal increases in central circulatory oxygen delivery to the active muscles. Muscle tissue studies in other laboratories have implicated muscle capillary basal lamina thickening as an oxygen diffusion barrier, which could possibly diminish the rate of tissue oxygen uptake and restrict cardiorespiratory capacity. Aerobic exercise training could improve cardiorespiratory capacity in women with SLE and with that improvement precipitate a reduction in their fatigability, particularly if that fatigability is mediated by impaired cardiorespiratory function.

Our research team is uniquely qualified to undertake this research and is one of the few teams possessing the experience and background necessary for contributing to this novel, understudied, yet critical field of rehabilitation research. For example, in addition to Dr. Keyser's studies on cardiorespiratory dysfunction in women with SLE, our team has studied the effects of an intense aerobic exercise-training program in individuals who have pulmonary hypertension (PH) [24,25] or interstitial lung disease (ILD) [26,27], two conditions associated with autoimmune diseases such as SLE. In fact, several of the subjects had SLE and the majority had autoimmune diseases of somewhat similar etiology. Our results demonstrated improved cardiorespiratory function and diminished fatigability in these patients, without serious adverse events, following a 10-week regimen of intense aerobic exercise training. Adherence to the protocol was over 90% in both subject subsets and there were no serious adverse events in either of these groups.

Subjects of the proposed research will be between 21 and 80 years of age and living within a reasonable travel distance from the greater Washington D.C. area. Subjects will be recruited from the NIH/NIAMS IRP Lupus Clinics. All tests and exercise training will be conducted at the NIH Clinical Center. There will be a single treatment condition consisting of 12-weeks of supervised treadmill walking, three times a week, for 30 minutes per session, at an intensity of 70-80% of the subject's heart rate reserve.

The primary outcome measure for our trial will be the time taken to attain the anaerobic threshold, which is a performance marker of fatigability that is unaffected by patient motivation or perception. Secondary outcome variables will include other measures of cardiorespiratory capacity measured during a cardiopulmonary exercise test (CPET) with accompanying pulmonary gas exchange, central circulatory function (including heart function and an optional measures of peripheral blood flow) and muscle oxygenation analyses. A number of

questionnaires will also be completed including: Fatigue Severity Scale, Patient Reported Outcomes Measurement Information System (PROMIS). All of these data will be obtained before and after aerobic exercise training.

**Study Impact:** Aerobic exercise is generally safe, inexpensive, and can easily be made available and accessible to almost everyone. It requires no approval by regulatory agencies and is thus available as a medically prescribed and supervised intervention almost immediately following confirmation of its safety and efficacy. Effective use of aerobic exercise training as a cardiorespiratory, rehabilitative intervention could have a high degree of impact on personal and public health outcomes.

## Background

As many as 1.5 million Americans are living with systemic lupus erythematosus (SLE).[1, 2] The disease is most prevalent in young African American women[3, 4], although there is significant prevalence in all races. The SLE population is indeed aging. Moreover, SLE is similar in etiology and symptoms to more than 100 other autoimmune diseases collectively effecting 1 in 5 individuals living in the U.S. One of the most debilitating symptoms of SLE is excessive fatigue (SLE-fatigue), which persists even during periods of negligible disease activity or remission. Nearly all patients who have SLE identify fatigue among their three most debilitating symptoms and as many as half report it to be their single most debilitating symptom.[2, 6, 7] SLE-fatigue is associated with functional limitations such as physical activity intolerance[8, 9] and poor cardiorespiratory fitness[8]. Management of SLE-fatigue and the resultant physical debilitation has become a clinical and social challenge that spans the entire course of the disease and lifespan.

Despite the centrality of this symptom to a patient's experience of the disease, a full understanding of the phenomenon has been hampered by dichotomous scientific perspectives depending on whether "fatigue" is regarded as either a subjective perception of tiredness or as a decrement in performance. The NIH/NIA has defined fatigue as "a subjective lack of physical and/or mental energy that is perceived by the individual to interfere with usual or desired activities" (NIH/NIA PA-08-161). *Fatigability* was defined as a phenotype that associates the degree of fatigue with activity of any kind. Physically active people reporting any given level of fatigue are generally less fatigable than their less active counterparts even if those who are less active report the same level of fatigue. Offering additional clarity, the NIH/NIA further defined *perceived fatigability* as "the change in the feeling of tiredness as a function of duration, intensity and/or frequency of activity" and *performance fatigability* as "the decline in performance as a function of frequency, intensity, and/or duration of activity" (NIH/NIA PA-12-227). Several methods have been proposed to measure perceived and performance fatigability. A better understanding of the complex phenomenon of SLE-fatigue will require integration of knowledge derived from measuring both performance and perceived fatigability. However, it remains that performance fatigability is the most objectively measureable subtype and that certain performance fatigability measurements can link mechanistic functions to acute declines in performance, for example, links between exercise-induced fatigue and cardiorespiratory dysfunction.

Cardiorespiratory function supports all physical activity and is the primary support for engaging in strenuous activities, when these activities are prolonged or when repetitions are frequent. Tench and coworkers,[9] reported that peak total body oxygen consumption ($VO_2$) and physical function scores were significantly lower and fatigue was more severe in 93 patients with mild SLE compared to 41 healthy controls. Peak $VO_2$ correlated significantly with physical function but not with fatigue, whereas fatigue severity and physical function were indirectly associated. Conversely, in a later study of 18 women with mild SLE and 16 healthy controls, Keyser and associates[8] reported that the severity of cardiorespiratory impairment, decline in physical performance, and severity of fatigue were all strongly related. In the women with SLE, cardiorespiratory function was insufficient for sustaining even instrumental activities of daily living and the diminished cardiorespiratory capacity appeared to be linked to an underlying pathomechanism. A subset of the same group demonstrated protracted responsiveness of the cardiorespiratory system to both moderate and vigorous energy demands.[10] These findings provide strong evidence for a potentially mediating influence of cardiorespiratory impairment on performance fatigability in women with SLE.

Three studies have reported improvements in cardiorespiratory function, fatigue and/or physical activity following aerobic exercise training. Robb Nicholson and coworkers[11] reported a significant increase in cardiopulmonary exercise test (CPET) duration over controls following aerobic exercise training. The improvement was associated with decreased patient-reported fatigue severity. A significant within group improvement in cardiorespiratory capacity was present after training, but this was not significant over controls. De Carvalho and associates[12] reported significant exercise training-induced increases in cardiorespiratory fitness that were associated with increases in physical activity in women with SLE. Patient-reported fatigue neither increased nor decreased as a result of training. A third, pilot study with a sample of only six subjects[13] found that aerobic exercise training resulted in improvement in SF-36 vitality score in all six women with SLE. Four of the six had increases in peak $VO_2$ ranging between 2.5 and 3.6 ml/kg/min. The findings of these studies implicated cardiorespiratory fitness as a potential mediator/modulator of performance fatigability in women with SLE and suggested that aerobic exercise may be a sufficient stimulus for evoking a training adaptation in these patients. However, neither performance nor perceived fatigability was directly measured in any of these studies.

The investigators (Drs. Keyser, Chan, and Chin) from the NIH Clinical Center, Rehabilitation Medicine Department have been involved in a clinical trial entitled titled "The NI**H** **E**xercise Therapy for **A**dvanced **L**ung **D**isease Trials (HEALD: 08-CC-0133 and14-CC-0027). HEALD examined the effects of vigorous exercise training on cardiorespiratory function and health related quality of life (including fatigue severity and physical activity) in patients with pulmonary hypertension (PH) and/or interstitial lung disease (ILD). Most of the subjects in HEALD had an advanced lung condition associated with an autoimmune/collagen vascular disease similar to SLE. Several of them had SLE. The preliminary findings of HEALD (24-27) suggested that vigorous aerobic exercise training, similar to that proposed in this pilot study, was well tolerated with a high degree of adherence and safe with no serious adverse events, even in these subjects with advanced pulmonary complications associated with autoimmunity. Furthermore, the exercise-training regimen was effective for improving cardiorespiratory function, exercise tolerance, fatigue and fatigability in a subset of patients. The findings of

HEALD so far have linked the improvements in fatigue and fatigability to increases in cardiorespiratory capacity. In this pilot study we intend to examine the feasibility of translating the methodology used in HEALD to women with SLE who do not have overt cardiac, pulmonary or other systemic complications.

## Specific Aims

1. Generate data that can be used for the planning of larger randomized controlled studies (RCT). This is the primary aim of this pilot study. **Specifically, this pilot study is preliminary to the submission of a U01 clinical trial on exercise training, fatigability and physical functioning in women with SLE.**

2. Preliminary characterization of the performance fatigability and cardiorespiratory adaptation to aerobic exercise training in women with SLE. The data to be used in the development of the RCT are the results of the CPET and square wave cardiopulmonary exercise test (swCPET), which provide physiological markers of performance fatigability. The change in performance fatigability following aerobic exercise training will be the primary outcome variable. Specific markers characterizing performance fatigability are the time taken to attain the anaerobic threshold on the CPET and the oxygen kinetics time constant taken from the swCPET. In addition, we will further characterize the adaptation by evaluating exercise training-induced changes in muscle oxygenation and cardiac function (and optional limb blood flow), measured non-invasively.

3. Preliminary assessment of stability of disease activity and effects of training on disease severity. Disease activity will be monitored at baseline, training mid-point, and after training by physical exam, symptom review, and serology. These assessments will contribute to the Safety of Estrogen in Lupus Erythematosus, National Assessment modification of Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), which will be calculated at each of the pertinent data points. We will also track the number of flares and medication changes during subjects' participation. Here our non-inferiority hypothesis is that the training regimen will have no observable effect on disease activity/severity in this group of women with mild SLE.

4. Assessment of feasibility and patient motivation to participate. We will track and monitor the number of patients participating in the Pathogenesis and Natural History of SLE study, who indicate interest and willingness to participate. We will also monitor compliance and attendance with the exercise sessions as well as adherence to the prescribed intensity and duration of exercise during the training sessions. We will query all participants who drop out of the training regimen in order to compile a list of reasons that may affect participation.

## Study Overview

We propose to enroll 30 sedentary, adult, women with negligible to mild SLE disease activity (SELENA-SLEDAI $\leq 4$) in this pilot study with the goal of accruing 20 evaluable subjects. Subjects must also have a Fatigue Severity Scale (FSS) composite score $\geq 3$. We will restrict our recruitment to women with SLE as this is a small pilot study and would like to eliminate possible

gender-biased confounders of physical activity (approximately 90% of patients with SLE are women).

1. **Visit 1:** During this visit, subjects will sign the informed consent. To determine eligibility, subjects will first undergo medical history, physical exam, echocardiogram, electrocardiogram, pulmonary function tests, and complete the FSS questionnaire to ensure meeting of the inclusion criteria and absence of an exclusion criterion (below). Blood and urine samples for the evaluation of safety and SLE disease activity, and serum or urine pregnancy tests will be drawn at this visit. Research samples will also be collected at this visit. We will do SELENA-SLEDAI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SLICC/ACR-DI) at this visit. This visit will require up to four hours to complete. Pre-screening procedures performed within the past 30 days under the Studies of the Pathogenesis and Natural History of Systemic Lupus Erythematosus protocol (94-AR-0066) may be included in this study. This is to avoid patient inconvenience and repeat testing. Research data from the same subject may also be shared directly with NIAMS investigators on protocol 94-AR-0066. Pre-screening assessments may be collected on multiple days to accommodate the patient's schedule.
2. **Visit 2:** This visit will occur within 14 days of completion of all pre-screening assessments (Visit 1). All eligible subjects will complete a treadmill CPET to volitional exhaustion to evaluate cardiorespiratory capacity and to obtain anaerobic threshold and peak heart rate measures from which the work rate for the $VO_2$ on-kinetics tests and the exercise training target heart range can be determined. Bioimpedance cardiography (ZCG) and arterial occlusion with near-infrared spectroscopy (NIRS) will be performed before the CPET. The subjects will also complete the PROMIS instrument. The visit will require three hours to complete.
3. **Visit 3:** Subjects will undergo one submaximal swCPET, treadmill $VO_2$ on-kinetics test, which is a submaximal, moderate exercise intensity test. Arterial occlusion with NIRS will be performed before the swCPET. Bioimpediance cardiography (ZCG) will be measured during the swCPET. The $VO_2$ on-kinetics tests will be used to evaluate how readily the oxidative metabolic pathway can respond to increased work rates and energy demands. The $VO_2$ on-kinetics test will take place 1-7 days after Visit 2 and will require about two hours to complete.
4. **Visit 4 and Exercise Training Session 1:** This visit will be conducted between 1-7 days after the completion of Visit 3, and may be performed over multiple days to accommodate the patient's schedule. This visit will also include the first exercise session of the 36-session aerobic exercise-training regimen. Subjects who would like to participate in the optional non-invasive vascular studies to examine the effect of exercise on vascular function in patients with SLE will do so at this visit. The methods for these studies are described in the research testing section and will take an additional 1.5 hours to complete. After the vascular studies and a light breakfast (since a 3-8 hour fast is required before vascular study testing), there will be a timed walk test to evaluate performance fatigability by measuring how far the subject can walk over a 10-minute interval (10-minute timed walk test). After another brief rest, subjects will complete 20 additional minutes of treadmill walking exercise at the target heart rate to be used for exercise training (70-80% heart rate reserve calculated from CPET). Target heart rate will

be monitored by Polar® monitor. If the vascular studies, baseline 10-minute walk test, exercise training are all performed at this visit, it will take up to 3 hours to complete.

5. **Exercise Training Sessions 2-35:** All subsequent exercise sessions will be scheduled 1-7 days after the first exercise session and 10-minute walk test (Visit 4). All sessions will be scheduled at regular intervals to achieve a goal of 3 visits per week for 12 weeks. Subjects will undergo a treadmill exercise-training program at an intensity of 70 to 80% of the heart rate reserve calculated from the CPETs for 30 minutes during each of the exercise training sessions.
6. **Visit 5:** During exercise training session 13, 14, or 15, Dr. Hasni or a member of the medical team will reevaluate the subjects, including performing a brief review of medical history and physical exam. Samples for research studies, including serum or urine pregnancy and clinical samples for safety and SLE disease activity, will be drawn. The SELENA-SLEDAI will be repeated. Subjects participating in the optional non-invasive vascular studies will do so at this visit. With the medical evaluations, labs, exercise, and vascular studies, this visit will take up to 4 hours to complete.
7. **Visit 6 and Exercise Training Session 36:** This visit will also include the final exercise session of the 36-session aerobic exercise-training regimen. This visit will be scheduled 1-7 days after the previous training session, and may be performed over multiple days to accommodate the patient's schedule. Subjects participating in the optional non-invasive vascular studies will do so at this visit. After vascular study testing and a light breakfast, subjects will then complete a 10-minute timed walk followed by an additional 20 minutes of treadmill exercise. If the vascular studies, 10-minute walk test, and exercise training session are all performed this visit will require about 3 hours to complete.
8. **Visit 7:** This visit will be scheduled 1-7 days after the final exercise session. The subjects will be evaluated by Dr. Hasni or a member of the medical team, including a brief review of medical history and a physical exam. The subjects will also complete the PROMIS instrument during this visit. Blood and urine samples for safety, SLE disease activity and pregnancy will be drawn at this visit. Research blood will also be collected during this visit. The FSS, SELENA-SLEDAI, SLICC/ACR-DI will also be completed on this visit. After a resting electrocardiogram, subjects will complete a CPET with ZCG and arterial occlusion with NIRS during this visit. This visit will require three hours to complete. Components of this visit may be performed on multiple days to accommodate the patient's schedule.
9. **Visit 8:** This visit will be scheduled 1-7 days after Visit 7. Subjects will undergo a swCPET treadmill $VO_2$ on-kinetics test with ZCG and arterial occlusion with NIRS at the work rate identical to the baseline swCPET*. This visit will require two hours to complete.
10. **Visit 9**: This visit will be scheduled 1-7 days after Visit 8. Subjects will undergo a swCPET treadmill $VO_2$ on-kinetics test with ZCG and arterial occlusion with NIRS at a work rate calculated from the CPET performed during Visit 7*. This visit will require two hours to complete.

*The two work rates for Visits 8 and 9 will be randomized.

## Inclusion Criteria

- Fulfilling 4 of the 11 American College of Rheumatology Criteria for the Classification of Systemic Lupus Erythematosus
- Age 21 to 80
- Female Gender
- BMI less than 40
- No primary or secondary medical conditions that would limit aerobic capacity or make exercise participation unsafe. These conditions are found under the exclusion criteria listed below and include cardiovascular disease and cardiomyopathy, pulmonary and pulmonary vascular disease, stroke, significant hepatic or renal dysfunction, most cancers, diabetes mellitus, HIV infection, and peripheral vascular disease.
- SELENA-SLEDAI score $\leq 4$, maintained for at least three months. (C3 and C4 levels are measured as markers for stability and included in the SELENA-SLEDAI score if abnormal).
- No increase in doses of immunosuppressive medications (hydroxychloroquine, mycophenolate mofetil, azathioprine, methotrexate) for at least three months at the time of screening.
- No increase in the dose of prednisone or equivalent steroid in the past 3 months at the time of screening.
- Physically inactive, not participating in aerobic exercise training at heart rate above 60% maximum heart rate, 20 min/session or more, 2 or more days per week, within the last 6 months at the time of screening.
- FSS composite score $\geq 3$ indicating the presence of clinically significant fatigue
- Subjects must be able to walk on a treadmill.

## Exclusion Criteria

- Prednisone $\geq 15$ mg daily (or equivalent)
- Have started azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide or biologics within 3 months
- Rituximab infusion within 6 months
- Present symptoms of ischemic heart disease, right- or left-sided heart failure, cor pulmonale or pulmonary hypertension, dilated or hypertrophic cardiomyopathy or non-idiopathic cardiomyopathy
- Significant pulmonary dysfunction (obstructive, restrictive, or infectious pulmonary disease)
- Significant hepatic (LFT > 2 times of upper limit of normal) or renal dysfunction (GFR<45 ml/min)
- Deep vein thrombosis
- Chronic anticoagulation, (with the exception of low dose aspirin), or a history of a bleeding disorder
- History or presence of any form of cancer other than skin cancer or cervical in-situ cancer
- History of cerebrovascular accident

- Orthopedic conditions that would limit performance of treadmill exercise tests or treadmill exercise training
- Current smoker or active substance abuse
- HIV infection
- Any medication that limit exercise capacity or the ability to adapt to aerobic exercise training
    - (e.g. beta-blockers, anti-retroviral therapy for the treatment of HIV infection)
- Diabetes Mellitus
- Fibromyalgia determined at Visit 1, as per 2010 ACR criteria for diagnosis of fibromyalgia[31]
- Uncontrolled or untreated thyroid dysfunction: Determined by abnormal Thyroid Stimulating Hormone (TSH) level checked at the time of screening or within 3 months before screening visit.
- Currently pregnant, nursing or plan to become pregnant during the duration of the study
- Anemia (hemoglobin < 9 g/dl)
- Significant peripheral vascular disease
- Severe Raynaud's phenomenon
- Individuals unable to give informed consent

# Methods

## Study Procedures:

Subjects will undergo initial evaluation as an outpatient in either OP-9 outpatient clinical or the 5SW Day hospital at the clinical center of the NIH; to ensure meeting inclusion criteria and absence of an exclusion criterion. The evaluation will consist of a medical history, physical examination, serological evaluation, and completion of the SELENA-SLEDAI, SLICC/ACR-DI and the FSS questionnaire.

Subjects will undergo pulmonary function tests with DLCO to rule out obstructive and restrictive lung disease, and doppler echocardiography to rule out left ventricular dysfunction, cor pulmonale and pulmonary arterial hypertension, and an electrocardiogram to rule out abnormal cardiac rhythm and myocardial injury. Subjects meeting inclusion criteria and not meeting an exclusion criterion will be qualified for participation in the study. Participating subjects will then complete the aerobic exercise training regimen, interim tests, medical evaluations, and post-training tests, which are similar to those completed at baseline.

## Medical Tests:

Blood Draw**:** Patients will undergo a blood draw in the National Institutes of Health Phlebotomy Laboratory or the Department of Rehabilitation Medicine. Nine tests will be run with approximately 5 tablespoons of blood taken via a standard blood draw technique. Additionally, approximately 6 tablespoons of blood will be collected via PAX gene, Serum Separator Tube, sodium heparin and CPT tubes and used for research purposes. 1) Nt ProBNP: N-terminal pro b-type natriuretic peptide assays will be performed before and after the intervention period to objectively monitor for potential myocardial damage. Recent data suggests that high levels of NT-proBNP indicate acute heart failure. This test is used as a standard of care in many

emergency departments when patients exhibit symptoms of heart failure such as shortness of breath and fatigue. 2) Complete Blood Count with Differential: Using the same sample of blood we will perform a test to separate the red blood cells, white blood cells and platelets from the plasma which will help us learn more about the oxygen carrying capacity of the blood. 3) SLE disease activity markers: This includes testing for complement proteins C3, C4, anti-ds-DNA antibody (anti-double stranded DNA), ESR (erythrocyte sedimentation rate) and hs-CRP (high sensitivity C-reactive protein levels), urinalysis, and urine protein creatinine ratio. 4) Lipid panel (preferably fasting 8-10 hours). 5) Chemistry panel including electrolytes, mineral panel, acute care panel, and hepatic panel. 6) Coagulation (PTT, PT/INR) 7) TSH (thyroid stimulating hormone, evaluate thyroid function as part of exclusion criteria). 8) Hemoglobin A1C to evaluate diabetes mellitus as part of the exclusion criteria. 9) HIV Antibody

Pregnancy Testing: Female patients of childbearing potential will undergo serum or urine dip-stick pregnancy testing at the National Institutes of Health Phlebotomy Laboratory during baseline testing following blood draw. Follow-up pregnancy tests will be performed at subsequent testing visits to the National Institutes of Health. In order for a patient to be enrolled or continue with this study, this test must be negative.

Electrocardiogram: All subjects will be screened for signs/symptoms of coronary artery disease, cardiomyopathy, or any other underlying cardiovascular diseases that may increase the subject's risk of performing an exercise-based intervention by screening all patients with a 12 lead electrocardiogram (EKG). This will be performed in the National Institutes of Health Electrocardiography Laboratory prior to the subject's inclusion in the study. Subjects will be required to lay supine on an examination table while 12 electrodes are placed on the subject's chest and then connected to an electrocardiogram by an EKG technician. A cardiologist will interpret all electrocardiograms prior to the performance of any exercise testing.

Echocardiogram**:** Cardiac echo is required for this protocol. Subjects must not have pulmonary hypertension (PH) and have an estimated left ventricular ejection fraction (LVEF) of ≥50%. To evaluate both of these measures, all subjects will be required to undergo a Doppler echocardiogram prior to inclusion in the study. This may be performed at the National Institutes of Health Echocardiogram Laboratory. A transducer placed on the subject's chest will allow us to measure the subject's right ventricular size/thickness and systolic pressure. 1) PH causes a retrograde flow of blood from the pulmonary arteries into the right ventricle (RV) which, when chronic, results in ventricular remodeling, increasing the size and thickness of the myocardium, thus increasing the chronic RV systolic pressure. To determine the probability of PH we will use the guidelines as presented in the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH.[29] These guidelines suggest using tricuspid regurgitation velocity (TRV) at rest and the presence of additional pre-specified echocardiographic variables suggestive of PH. The probability of PH may then be judged as low, intermediate, or high (Table A). Echocardiographic 'PH signs' used in addition to criteria based on TRV provide an assessment of the RV size and pressure overload, the pattern of blood flow velocity out of the RV, the diameter of the PA and an estimate of RAP (Table B). Based on echocardiogram interpretation, the patient will be admitted to the study if the probability of pulmonary hypertension is low or intermediate.

Table A

| Peak tricuspid regurgitation velocity (m/s) | Presence of other echo 'PH signs'* | Echocardiographic probability of pulmonary hypertension |
|---|---|---|
| ≤2.8 or not measurable | No | Low |
| ≤2.8 or not measurable2.9-3.4 | Yes | Intermediate |
| | No | |
| 2.9-3.4 | Yes | High |
| >3.4 | Not required | |

Table B

| A. The ventricles [a] | B. Pulmonary artery | C: Interior vena cava and right atrium |
|---|---|---|
| Right ventricle/left ventricle basal diameter ratio > 1.0 | Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching | Inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration) |
| Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole) | Early diastolic pulmonary regurgitation velocity >2.2 m/sec | Right atrial area (end-systole) >18 $cm^2$ |
| | PA diameter >25 mm. | |

a. Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

LVEF will be estimated through echocardiogram volumetric measurements of the left ventricle. Placing the transducer over the subject's left ventricle allows for the measurement of the chamber's size in end-systolic and end-diastolic states thus giving an estimation of LVEF by comparing the difference in size. Subjects in this protocol will be required to have an estimated LVEF of ≥50%, because a decreased LVEF will increase the risk of exercise testing/training in this study population.

**Pulmonary Function Test:** Forced Vital Capacity (FVC), Maximal Voluntary Ventilation (MVV), and Diffusion Capacity (DLCO) tests will be assessed for all subjects. These tests will be performed at the National Institutes of Health Pulmonary Function Laboratory prior to inclusion in the study. FVC is used to evaluate the degree of obstructive and restrictive lung disease. MVV is used to evaluate the subject's ventilatory limitation. Both tests will be obtained while the subject is at rest. We will determine whether the subject's exercise capacity is limited by ventilation by computing the ratio between expired minute ventilation (Ve) measured at maximum exercise and MVV (Ve / MVV must not exceed 0.90). To perform the FVC and the

MVV test the subject will be instructed to stand, plug their nose with their free hand (or wear a nose clip) and create an airtight seal over the mouth piece. For the FVC, the subject will be asked to take in three regular breaths, followed by a deep inhalation and a quick and complete exhalation, blowing air until there is nothing left to expire. This test will be performed 2-3 times. Completion of the test will be when two test results are within 5% of each other. For the MVV, the subject will be asked to breathe in and out normally three times followed by breathing in and out rapidly (90-100 breaths·min$^{-1}$) for 12-15 seconds. The teeth and tongue must refrain from blocking airflow. A DLCO test is used to determine the lungs' ability to exchange gases across this respiratory membrane wall. Using a mouthpiece and nose clip, the subject will be required to inhale air containing a small amount of carbon monoxide and then exhale rapidly for 10 seconds. Exhaled air is then measured to determine the amount of carbon monoxide that is absorbed by the lung tissue and as such determine the subject's diffusion capacity.

## Research Tests:

Fatigability Tests: For this measure, subjects will complete a 10-minute timed walk test. Subjects are instructed to walk as far as they can, in ten minutes. Velocity measurements are taken each minute and at 2.5 minutes. Two fatigability types, perceived and performance, are measured during a 10-minute walk test. Fatigability is best defined as the change in physical performance or/and feelings of tiredness over the duration of a particular intensity, duration or frequency of activity (NIH/NIA PAR-12-227). Performance fatigability is the decline in physical performance over time and is measured directly in the laboratory or as a field test in the clinic by measuring physical performance over, in our case, work intensity sustained for a given duration. A performance fatigability index is calculated by dividing the average velocity of the entire 10-minutes of the test into the average velocity over the first 2.5 minutes (decline in performance) and further dividing the previous quotient in performance by the total distance walked (an index of intensity). Perceived fatigability is simultaneously evaluated by having the subject rate perceived changes in the feeling of tiredness over the 10-minutes of the test on a numerical visual response scale and dividing the change by the total distance walked. This test will take approximately 20 minutes to complete.

Treadmill Cardiopulmonary Exercise Test (CPET): We will be measuring time to anaerobic threshold (AT-time) during this test. The anaerobic threshold is a physiological measure that is unaffected by motivation or the perception of fatigue, which indexes the metabolic intensity at which intracellular buffering capacity is exceeded. For activity intensities above the anaerobic threshold, oxidative metabolism is insufficient for supplying all of the ATP needed to sustain the work rate resulting in increased glycolytic supplementation. The by-products of anaerobic glycolysis and insufficient buffering, particularly free ions and metabolic acids, mediate fatigue. Above the anaerobic threshold, glycolytic supplementation intensifies as the energy demand increases. Measuring the AT-time during CPET further scales the index to exercise duration. Thus, AT-time is a physiological measure of performance fatigability in which its prolongation reflects low fatigability and shortening reflects proportionally higher levels. This test will also include muscle oxygenation and cardiac function measurements described below. Ratings of Perceived Exertion (RPE) will be measured incrementally throughout the CPET. Each CPET will take about 120 minutes to complete and one CPET will be performed at baseline and one will be performed after exercise training (for pre to post-training comparison).

Square Wave CPET (swCPET): The swCPET is a submaximal, moderate treadmill test of 3 moderate bouts of continuous work rate exercise alternated with longer bouts of active rest at low intensity. The bouts are comprised of an initial stabilization period of treadmill walking at 0.7 mph for 3 minutes. The stabilization bout is followed by an increase in walking velocity to that corresponding to 85% of the anaerobic threshold measured on the CPET sustained for six minutes. The 6-minute interval is followed by an 8-minute active rest period. The 6-minute exercise, 8-minute recovery sequence is repeated a total of three times. This test is used to measure $VO_2$ on-kinetics. $VO_2$ on-kinetics is a measure of the rapidity with which the cardiorespiratory and oxidative metabolic systems can respond to increases in energy demand. Prolonged VO2 on-kinetics contributes to increased fatigability whereas more rapid $VO_2$ on-kinetics is associated with lower levels of fatigability. Muscle oxygenation and cardiac function measurements will also be made during this test, as will RPE. One of these tests will be completed at baseline and since the work intensity is based on CPET performance, two will be performed after completing the exercise training regimen: one at the original baseline intensity and one at a new intensity established from the post-training CPET. These tests will each take about 45 minutes to complete.

Near Infrared Spectroscopy: Near infrared spectroscopy (NIRS) will be used to assess microvascular reactivity and muscle oxygen extraction. Both of these components are necessary for optimized cardiorespiratory function. Diminished muscle oxygenation capacity is associated with exercise intolerance and performance and perceived fatigability. The NIRS test will be performed during a gastrocnemius total arterial occlusion to assess muscle oxygenation capacity test just prior to the CPET and swCPET. The NIRS light emitters and sensors will be left in place to assess the muscle oxygenation during the swCPET and CPET. The NIRS analysis will help to determine the relative contribution of muscle oxygenation to overall oxygen kinetics in these women with SLE. Times for preparation and making the occlusion measurements are included in the time estimates for both the CPET and swCPET.

Arterial Occlusion Muscle Oxygenation Capacity Test: NIR light source and receiving sensors will be placed on the belly of the dominant gastrocnemius muscle to record muscle oxygen-hemoglobin flux. A blood pressure cuff will be placed around the distal hamstrings of the dominant leg. Using a Hokanson® rapid inflation vascular testing system, the cuff will be rapidly inflated to a pressure that totally occludes blood flow into the gastrocnemius, typically between 60 and 80 mmHg above systolic pressure. The occlusion will be maintained for up to 10 minutes and tissue saturation will be measured over the time course. The tissue saturation index will be calculated as STI= [O2-Hb] / Tot-Hb. The rate of decline in STI will be the main muscle tissue saturation measure.

Bioimpedance Cardiography (ZCG) Test: Bioimpedance cardiography will be used to measure changes in cardiac function at rest and during exercise and the cardiodynamics associated with VO2 on-kinetics. Data will be collected before and after the 12-week aerobic exercise-training regimen. The primary variables for this test are cardiac output and stroke volume however, other cardiac function variables will also be available. The ZCG analysis will be performed during both the CPET and the swCPET. Aluminum/aluminum chloride (Ag/AgCl) electrodes will be placed on the sternum at the level of the heart and another to the standard precordial V6 position. Two Ag/AgCl electrodes will also be placed on the lateral triangle of the neck and two directly over the spine at the level of the xiphoid process. Data will be measured prior to each CPET after subjects rest for at least 10 minutes in a semi-recumbent position. Measurements will subsequently be taken in the standing position on the treadmill and then

continuously during both the CPETs and the swCPETs. Time requirements have been included in the estimates for both CPET and swCPET.

Biomarkers and Mitochondrial Profile: We will collect samples of whole blood, serum CPT and PAX gene tubes for future exploration biomarkers with fatigability. These include serum cytokine markers such as but not limited to IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-12, IL-15, IL-17, IL-23, IFNα, IFNγ, TNF-α and TGF-β, and interferon gene signature.[30] They also include analysis to look for alterations in the "interferon signature" and the "granulocyte signature" in PBMCs using nanostring and measures of CD3+ T cell expression of IFN regulatory factor-related genes using RNAseq and/or NanoString.

We will collect whole blood samples to assess mitochondrial profile of the PBMCs. This includes testing for the maximum respiratory capacity, spare respiratory capacity, and ATP production of PBMCs.

The amount of blood drawn for clinical care indication and research purposes will be kept within the NIH guidelines of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period for adults. We plan to collect samples during Visits 1, 5 and 7.

Non-Invasive Vascular Function Testing (Optional):

Changes in vascular function, as assessed by the reactive hyperemia index (RHI) using Endopat device, arterial stiffness using cardio-ankle vascular index (CAVI), and by using SphygmoCor device to determine central blood pressures and arterial stiffness. Patients with SLE have vascular endothelial dysfunction and premature atherosclerosis. To date there are no studies looking at effect of exercise on vascular function in patients with SLE. These are surrogate markers of vascular damage and future atherosclerosis development which may be amenable to change within the timeframe of this study.

Pulse wave analysis *(SphygmoCor):* This optional procedure will be performed duringVisits 4, 5 and 6. SphygmoCor is a set of non-invasive tools used to determine central blood pressures and arterial stiffness. It (1) derives the pressure wave from the ascending aorta to the carotid artery and (2) gives an accurate measurement of pressure at the heart, brain, and kidneys. However, it cannot be used on patients who may suffer from heart arrhythmias or arterial stenosis. The SphygmoCor consists of the following:

*SphygmoCor Px Pulse Wave Analysis System* – a diagnostic tool to measure central blood pressure.

*SphygmoCor Pulse Wave Analysis System* – an algorithm used to determine central aortic pressure and visualize ventricular- vascular interactions.

*SphygmoCor Pulse Wave Velocity System*- a tool that derives a pressure pulse waveform using the pressure tonometer and an ECG signal simultaneously. Arterial tonometry uses a pressure sensor to detect the speed of a pulse wave and may indicate a problem in the arteries.

*SphygmoCor Pulse Wave Monitoring System*– a tool that provides an estimated pressure waveform from the ascending aorta.

Cardio-ankle vascular index *(CAVI):* This optional procedure will be performed the morning of Visits 4, 5 and 6. For this procedure, placement of ECG electrodes on both wrists and a microphone for phonocardiograph on second intercostal space and 4 blood pressure cuffs wrapped around 4 extremities. Arterial stiffness is calculated followed specified formulas. Main advantage of this procedure versus other procedures to measure arterial stiffness is that it is not altered by blood pressure. In addition, it is simple to perform. All vasodilators, antihypertensives

and statins will be held the morning of the test and will be restarted after the procedures are completed. This is in order to avoid having additional variables interfering with the readings of the vascular measurements. The test takes approximately 20 minutes to be performed.
Peripheral arterial tonometry *(Endopat)**:*** This optional procedure will be performed the morning of Visits 4, 5 and 6. EndoPAT™ quantifies the endothelium-mediated changes in vascular tone, elicited by a 5-minute occlusion of the brachial artery (using a standard blood pressure cuff). When the cuff is released, the surge of blood flow causes an endothelium-dependent. Flow Mediated Dilatation (FMD). The dilatation, manifested as Reactive Hyperemia, is captured by EndoPAT as an increase in the PAT Signal amplitude. A post-occlusion to pre-occlusion ratio is calculated by the EndoPAT software, providing the EndoPAT index. The test takes approximately 15 minutes to complete, is very easy to perform, and is both operator and interpreter independent. It is a noninvasive test, providing automatic analysis, office-based procedure. The five-minute blood pressure cuff inflation is an accepted standard test to cause reactive hyperemia (the increase of blood flow after a temporary restriction in blood supply) for the assessment of endothelial function. While the occlusion may cause some minor discomfort, and tingling in the fingers, the test is absolutely harmless. It is recommended that the patient fast 3 to 8 hours before the test. Subjects will be requested to hold all medications including but not limited to all vasodilator, antihypertensive and statin on the morning of the test. Subjects will be requested to bring their medication with them on the day of the procedure they will resume their medications right after the completion of procedures. This is in order to avoid any possible confounding variables interfering with the readings of the vascular measurements.
Heart rate variability (HRV): HRV may be calculated during rest and exercise using the ECG and HR data collected during the CPET, swCPET, exercise sessions and/or vascular function tests to examine autonomic functioning. Patients with SLE have been reported to have decreased HRV at rest, suggesting autonomic dysfunction in this population. There have been no studies that examined HRV during exercise and as a result of exercise training in patients with SLE.

## Health Related Quality of Life Measures

PROMIS and FSS-: These are validated patient reported outcome measures. The fatigue, physical function, mental and sleep domains will be scored for each of these scales. Use of PROMIS and FSS, will permit an assessment of the relative contributions of factors, other than cardiorespiratory fitness and physical activity, such as mental and social functioning, to fatigue. Examining the relationships among fatigue and physical function provides an index of general fatigability. PROMIS will provide a venue for characterizing health related quality of life. These questionnaires are estimated to take 30 minutes to complete.

**Treadmill Exercise Training**: After the above baseline tests are completed, subjects will undergo aerobic exercise training. The training regimen used in this project is known to elicit improvements in cardiorespiratory function in healthy cohorts and in those who have chronic illnesses in general. This training regimen has been shown to improve cardiorespiratory function and fatigue/fatigability in patients with autoimmune disease comorbid with pulmonary hypertension and/or interstitial lung disease, with subject adherence to the protocol at over 90% in both subject subsets and with no serious adverse events in either group. The target training heart rate range is 70-80% of heart rate reserve, computed as: 0.7 and 0.80 (peak heart rate minus resting heart rate) + resting heart rate. This method allows for the target heart rate range to be determine relative to each subject's own capacity since it accounts for both the resting as well as

the measured maximum heart rate. The 70-80% range defines performance of physical activity that is within the recommendations for prescription of safe, effective, and enjoyable exercise put forth by the American College of Sports Medicine (ACSM).[28] The frequency of the visits will be on average three times per week, unless make up visits are needed in order to attend 80% or 29 visits in 12 weeks. During the training session, heart rate, treadmill speed, treadmill inclination, and RPE will be recorded. In the event that subjects cannot sustain 30 minutes of continuous treadmill walking at the target intensity, an interval approach will be used in which walking at the target will be sustained at smaller training interval durations of no shorter than 5 minutes followed by an active rest interval that is no longer than 1.5 times the training interval until the subject achieves a total exercise time of 30 minutes, excluding the rest intervals. Each of these sessions will last about 60 minutes but slightly longer if an interval approached is used.

**Post Training Protocol**: After completing the 12-week aerobic exercise training regimens, subjects will repeat the medical examinations, 10 MWT, vascular studies, CPET with muscle oxygenation and cardiac function measures, swCPET, fatigability tests, PROMIS, Fatigue Severity Scale, SELENA-SLEDAI, and SLICC/ACR-DI. Pre-post differences in the outcome measures will then be compared between the groups and analyzed for clinical and biological relevance.

## Statistical Analysis

Pre-post differences in the outcome measures will be analyzed for clinical and biological relevance using *t* tests or ANCOVA to control for confounding or intervening modulators if discovered. The primary outcome variable for this study is the change in performance fatigability as determined by pre to post exercise training changes in the time taken to attain the anaerobic threshold on the CPET and oxygen kinetics time constant measured during the swCPET. We also assess changes in the performance fatigability index (PFI) and the perceived fatigability index. Secondary outcome measures will include exercise training induced changes in muscle oxygenation and cardiac function, as well as changes in questionnaire responses, including the PROMIS and Fatigue Severity Scale. Changes in disease activity and severity will be assessed by comparing post-training to baseline scores on the SELENA-SLEDAI and SLICC/ACR-DI. As change in these measures are expected to be small, Chi-square tests or logistic regression after dichotomizing changes into categories of up to no change and increase by at least 3 points will be used.

## Subject Withdrawal

Subjects may withdraw voluntarily anytime during the study. Any subject who misses more than 7 exercise training sessions without making them up before the end of the study or missing more than 2 consecutive weeks of exercise at the NIH Clinical Center will be withdrawn. Subjects who develop a SLE flare, defined as an increase in SELENA-SLEDAI score of ≥4 compared to baseline during the study or any other medical condition as determined by the clinician that will impair their ability to participate in the study will be withdrawn. In addition, the emergence of any of the exclusion criteria after subject enrollment or any changes in medications that may make subject participation unsafe or interfere with the study interpretation will lead to that subject's withdrawal. Any subject withdrawn after completion of more than 12 visits will not be replaced.

## Risks and Discomforts to Subjects:

1. CPET: The most serious risks of participating in vigorous exercise are cardiovascular abnormalities including sudden cardiac arrest, myocardial infarction, angina and electrocardiographic abnormalities, shortness of breath, dizziness, early fatigue onset and exhaustion. These risks are slight and the likelihood of their occurrence is small even in individuals with known coronary atherosclerosis or chronic heart failure during maximal exercise testing. The general risk of serious adverse events during CPET is low at 0.0 to 8.3 per 10,000 tests.[14-23] Pre-screening minimizes the risk to almost negligible levels. Exercising at submaximal intensities, such as during aerobic exercise training, carries with it an even lower risk of serious adverse events that is not greater than that occurring during routine activities or exercising in unsupervised settings.
   To minimize risk and maximize safety, subjects will be evaluated by medical history and physical examination, ECG, Doppler cardiac echocardiography, and pulmonary function tests with DLCO, to exclude those with contraindications to exercise prior to initial CPET. During CPETs, subjects will be monitored by continuous 12-lead EKG and before beginning the tests subjects will be informed of the signs and symptoms of heart disease and questioned frequently during the test regarding their presence. Staff with training appropriate for exercise testing and training will supervise CPET and training sessions for individuals with chronic illnesses, credentialed by the NIH Clinical Center, Rehabilitation Medicine Department, in which the testing and training procedures will take place.
2. PROMIS and FSS: These questionnaires are generally not provocative and used to describe overall domains relative to health quality of life. The major risk associated with their use is accidental identification of the data. To avoid this, no names or other personal identification information will be written or attached to the questionnaire forms. To de-identify the data, the completed questionnaires will be linked to other study data only by a study identifier, which will be a number assigned to each subject's information. The identification key will be kept in secure files in the offices of Dr. Chin, Dr. Keyser and Dr. Hasni and available only to Drs. Chin, Keyser and Hasni.
3. Square wave CPET (swCPET): This test does not require vigorous levels of exertion, is of moderate intensity and does not use an exercise intensity greater than that encountered in routine daily activities. As such the risk to patients is minimal. The major risk of this test is tripping and falling on a moving treadmill belt or falling off the treadmill. This could result in contusions and bruising, lacerations, abrasions from the treadmill belt, concussion, and sprains, strains and fractures. Again these risks are minimal.
   To optimize safety, swCPETs will be conducted after first completing the CPETs as described above. Thus, subjects will have demonstrated their ability to safely exercise at a severe intensity that is much higher than the moderate intensity used for the swCPET. The tests will be conducted by trained and experienced staff all of whom are credentialed to supervise cardiopulmonary testing in the NIH Clinical Center, Rehabilitation Medicine Department after physician clearance of the subject for testing. The treadmill itself is equipped with 2/3 length handrails to enable the subject to maintain balance or catch herself in the event of a stumble. At least two staff members will be present for the swCPET and subjects will have been pre-screened for all exercise and tests by a physician prior to participation.

4. Fatigability Tests: Subjects are instructed to walk as far as possible around an 80-meter circular corridor in 10 minutes. The major risks to this test are stumbles and falls, which could result in sprains, strains, fractures, contusions, and concussion. Additional risks include chest pain, shortness of breath, nausea, pallor, diaphoresis, heart attack, cardiac arrest and sudden death similar to the CPET.
   To maintain the safety of participation in this test, all Fatigability tests will be conducted after the CPET, which imposes volitionally maximum cardiovascular stress. Only subjects able to tolerate the CPET without clinical signs and symptoms of cardiovascular disease will be enrolled in the study. Therefore, subjects will have demonstrated their ability to tolerate exercise intensities and stress greater than that imposed by the 10-minute walk test. Credentialed staff with expertise in exercise testing will conduct the 10-minute walk test. Subjects will sit immediately following the test to avoid falling in the event they would become dizzy after strenuous exercise.
5. NIRS Test with Arterial Occlusion Muscle Oxygenation Capacity Test: The near infrared spectroscopy (NIRS) test involves placing infrared light emitters and sensors on the belly of the gastrocnemius (calf) muscle. These are held in place by a sticky cement and are often covered with an elastic wrap to help hold them in place. The light itself does not cause burns and we could find no reports of any untoward events regarding the use of NIRS. Some very minor risk may be due to minor skin breakdown under the emitter/sensor patches. This usually resolves in a few hours to several days and is usually not painful or uncomfortable.
   This test also involves total occlusion of blood flow just above the knee. Subjects may experience pain, tingling, and/or numbness in the lower leg during the test. To diminish these effects, occlusion time will be kept minimal, after observing complete deoxygenation of the gastrocnemius muscle (not more than 10 minutes). No ischemic injury is associated with this test due to the high anaerobic capacity of skeletal muscle and the short occlusion time.
   Arterial occlusion for measures of reactive hyperemia is a non-invasive and safe technique commonly used in patients with peripheral vascular disease. We are using arterial occlusion in our current interstitial lung disease (ILD) protocol. Of the 16 participants who have completed the ILD study, three participants did not participate in the arterial occlusion due to Raynaud's Syndrome and one requested to stop due to discomfort. All participants fully recovered within minutes of cuff removal with no reports of residual pain or discomfort after leaving our facility. There have been no adverse events from arterial occlusion in our lab. It is a well-accepted procedure deemed safe and tolerable.
6. Bioimpedance Cardiography (ZCG) Test: This test involves passing a small, unnoticeable electrical current between electrodes of known distance on the thorax and back. The voltage and amperage of the current is below the threshold for perception or stimulation of action potentials in skeletal, smooth, or cardiac muscle and sensory, motor or CNS neurons. We could find no reports of adverse events due to use of the ZCG. Risks are basically those associated with skin breakdown due to sliver/silver chloride electrode patch contact with the skin. Some slight itching has been reported in some subjects. These symptoms are minimal and last only for a few hours to a few days.
7. Treadmill Exercise Training: The risks are those associated with aerobic exercise and treadmill walking in general. These are the risks of provocation of signs and symptoms of

cardiovascular disease including chest pain, shortness of breath, dizziness/syncope, diaphoresis, sweating, nausea, heart attack and sudden death. Risks also include contusions, abrasions, concussion, sprains, strains and fractures associated with falling on a moving treadmill. Subjects are likely to experience immediate or delayed muscle soreness due to initiating an exercise-training program after having been sedentary. The onset of muscle soreness typically occurs immediately or within 48 hours and lasts a few days to a week.

As a method of establishing her exercise training regimen is within the ranges recommended for safe and effective exercise by the ACSM and as a safety precaution, subjects will have undergone CPET prior to beginning exercise training. The intensity for training will be well below the maximum attained on the CPET and subjects presenting clinical signs and symptoms on the CPET will be excluded from the study. All subjects will be pre-screened and approved for participation by a medical staff member before beginning participation. In addition, treadmills used for training will have handrails and an emergency stop button easily accessible for the subject in the event they begin to fall or need to stop immediately. The stop button is linked to a clip worn on the subject's clothing and in the event she falls the treadmill will stop immediately preventing further abrasions from a moving treadmill belt. Subjects' treadmill exercise training sessions will be overseen and monitored by staff specifically credentialed for the supervision of aerobic exercise.

8. Echocardiography: The use of diagnostic transthoracic ultrasound is not associated with significant risk. There is however the possibility of an allergic response to the gel used to optimize contact of the ultrasound transducer with the skin in a few people. The allergy may present as a rash and/or itching localized to the area of contact and subsides after a few hours to a few days.
9. PFT with DLCO: Serious risks are not associated with pulmonary function tests or lung diffusion tests. Patients may experience perceptions associated with exertion on the PFT and may feel dizzy and short of breath for a short time after completion of the test. Patients may also experience slight dizziness and shortness of breath during and shortly after the DLCO procedure. In both cases these symptoms are not specific to any emergent condition, unless severe and persistent, and should only last a few minutes following the tests.
10. Blood draw: The risks are those associated with routine blood draws. These include infection, vein collapse, and the need for multiple sticks. These risks will be minimized by personal credentialed at the Clinical Center for obtaining and handling blood samples. On occasion, some subjects may be come dizzy, nauseous, or may faint at the sight of their own blood. We will instruct subjects to face a different direction during the draws if they are prone to these reactions. If these reactions do occur, subjects will be given appropriate instructions for managing them by the trained technician acquiring the sample.
11. Electrocardiogram: There is no clinically significant risk associated with this procedure. There may be minor discomfort, when the ECG electrodes taped to chest are removed. Rarely, a reaction to the electrodes may cause redness or swelling of the skin.
12. Vascular function studies: SphygmoCor, CAVI, and Endopat, (optional). These procedures are very well tolerated. Other than potential transient minimal discomfort with blood pressure cuff, no side effects are expected.

## Benefits to Subjects:

This research involves greater than minimal risk with the prospect of direct benefit to individual subjects. Potential benefits of participation include improvements in cardiorespiratory capacity that may enable individuals to accomplish a given amount of activity or work at a lower percentage of maximum capacity and with less fatigue. Moreover, improvement of exercise tolerance generally increases quality of life by permitting individuals to engage more easily in daily physical activities and perhaps full or part time employment. Improved cardiorespiratory fitness may also decrease the risk for cardiovascular disease, stroke, cancer, obesity and diabetes mellitus.

## Human Subject Research Protections (HSRP)

## Subject Selection

**Rationale:** Patients referred from the Baltimore/Washington/Northern Virginia area will be potential subjects for this study. All subjects will be classified by SELENA-SLEDAI score, which measures Lupus disease activity. No participants will be excluded based on race or ethnicity.

**Recruitment:** Subjects will be primarily recruited from the pool of subjects available at National Institute of Health's, National Institute of Arthritis, Musculoskeletal, and Skin Diseases clinic. The majority of these subjects are enrolled in the Pathogenesis and Natural History of Systemic Lupus Erythematosus (SLE) study, which has been ongoing since the early 1990's and currently has approximately 1100 enrollees. Other recruitment efforts may be directed toward presentations to Lupus support groups and an introductory study letter for local private rheumatology practices. We may also utilize NIH Clinical Center-sponsored digital media resources such as Twitter, Facebook, CC Radio, CC TV, Photo Gallery; databases such as NIH Search the Studies, ClinicalTrials.gov, and Research Match; and local newspapers such as the Washington Post to disseminate information about the study to potential participants and their healthcare providers.

The recruitment strategy offered by the NIH/CC Office of Patient Recruitment, including sample recruitment messages and advertisements in the form of study flyers will be used. IRB-approved flyers may be left with clinics for interested treating physicians to refer subjects to this study with approval of the venue or in accord with their policy; self-referral is also permitted. Recruitment flyers may also be given directly or sent electronically to those requesting study information. Flyers may be made available at outreach exhibits, speaking engagements, support group meetings, professional meetings or association/trade meetings with approval of the venue or in accord with their policy.

### Pre-Screening Process in the NIAMS Clinic

If any physicians in NIAMS feel they have a patient that may be an appropriate candidate for enrollment based on inclusion/exclusion criteria, then an associate investigator will be introduced to the patient after a brief overview of the study. If she is interested, they will be consented at that time or make an appointment for a future date in order to be consented and tested.

**If the NIH Study Coordinator or Associate Investigator interviews a potential subject from any source the following script will be followed**:

"Thank you for your interest regarding the research we are conducting to determine the benefits of an exercise program on Lupus. We are accepting volunteers 21-80 years of age who have been diagnosed with Lupus, with moderate to severe fatigue, and are currently stable in their disease and treatments. If you are enrolled in the study we would ask that you come to NIH for 3 days of testing, which do not have to be in a row, which would include a test to determine how far you can walk in 10 minutes, breathing tests and a treadmill exercise test. During the treadmill test you will have 16 electrodes on your chest, we will ask that you wear a neoprene mask to collect data on the amount of oxygen you breathe in and out, as well as an electrode on your calf to determine the amount of oxygen your muscle utilizes for energy. After testing you will begin an exercise regimen that will include 36 exercise training sessions over 12 weeks. Does this sound like something that you would like to participate in?"

If they answer "yes," we ask if they have time to answer a short questionnaire that would allow us to evaluate their eligibility and safety for inclusion into the study.

If, based on this interaction, we think the subject might meet the inclusion criteria for the study, we will request medical records such as (recent history, medication list, pulmonary function test, resting EKG, six-minute walk and echocardiogram) to further evaluate their eligibility for the study. Their medical records will be reviewed and, if it appears that the patient meets the inclusion criteria, we will set up an appointment for the patient to come to the NIH Clinical Center for consent and testing. If, after obtaining a patient's medical records it is clear that the patient does not meet inclusion criteria, the information may be used to refine our inclusion and exclusion criteria; however, these medical records will not be used for any research purposes.

Upon arriving at the NIH, the patient will proceed through admissions and then consented to the study, followed by a history and physical examination, blood draw, ECG, transthoracic echocardiogram, pulmonary function testing, arterial occlusion muscle oxygenation capacity test, cardiopulmonary exercise test, questionnaires, and ten minute walk test.

## Exclusions:

**Exclusion of Children:** Individuals younger than 21 years will not be included in the protocol because reference ranges for normative aerobic capacity and aerobic fitness have not been established for children and adolescents. The objectives of this project do not include establishing these normative reference ranges. Moreover, far less is understood about Lupus in children and the mechanisms by which it occurs. This lack of information could introduce critical levels of bias into the interpretation and cause the interpretation of our results to be

misleading. Exercise response and adaptation in children with Lupus should be studied in separate and specific protocols.

**Exclusion of Males:** Males account for less than 10% of those diagnosed with Lupus and this accounts for less understanding of Lupus as it relates to males. Due to the limited access of male patients and decreased likelihood to find willing male subjects we chose to exclude them because they will not be a viable comparison for this study.

**Exclusion of Pregnant Women:** Women of childbearing age will undergo urine pregnancy testing during screening and follow-up visits and will be excluded from the study should results be positive. Pregnant women will necessarily be excluded from the study for safety reasons. Women who do not exercise before pregnancy should not begin a rigorous exercise during pregnancy and would not be able to achieve the target heart rate required as part of the testing and training.

**Exclusion of Those Who Are Unable to Provide Informed Consent:** Individuals unable to give informed consent will necessarily be excluded from the study because of the risk to subject safety and the need to maintain integrity of the study. Subjects must be able to comprehend and follow directions, and express their own needs adequately during all testing and retesting procedures, and exercise and educational training sessions.

## Participation of NIH employees:

We anticipate eligible NIH employees may participate in this study. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the "NIH information sheet on Staff Research Participation" as per NIH SOP 14F, "Research Involving NIH Staff as Subjects." If the employee is within the same branch, section, or unit such that the individual obtaining consent is a supervisor then independent monitoring of the consent process through Clinical Center Department of Bioethics Consultation Service will be requested. Study staff will be trained that communication of any personal or medical information about an NIH employee, including the fact that they are participating in this study, should be restricted to those investigators who need to know this information, and such information will not be discussed with anyone outside of the study without permission from the subject.

We will discuss the following applicable safeguards to the eligible NIH employee:

- Unbiased participation for protocol integrity and participant risk assessment.
- Ensure there is no perceived workplace pressure or expectation on either participation or deciding not to participate on the protocol in regards to a benefit or adverse effect on their NIH employment or staff position.
- Protection of privacy and confidentiality will be maintained, but also with acknowledgement of the limits due to sensitive information that may be in their NIH file.
- Discussion of time commitments of the study and compensation in accordance with NIH policy 2300-630-3, *Leave Policy for NIH Employees Participating in NIH Medical Research Studies*.

**Data and Safety Monitoring Plan:** As the PI, Dr. Chan will closely monitor patient safety throughout the duration of the study. As the medically responsible physician, Dr. Sarfaraz Hasni, will monitor the patient's condition as it relates to their Lupus disease activity.

Since the risk of performing several exercise tests on patients with SLE is unknown, our plan may need more than just PI monitoring, but fails to meet the criteria for the involvement of a full DSMB. We suspect that the risk is a minor increase over minimal risk, but we are not sure. For this reason, we have enlisted the assistance of Michael M. Ward M.D., Senior Investigator in the Clinical Trials and Outcomes Branch of NIAMS, as the independent medical monitor (IMM) for this study. He will be apprised of all significant adverse events. In addition, this monitor will also have access to the study data. RMD's Epidemiology and Biostatistics Department will examine the results on an interim basis. If, at any point, they feel that the study should be stopped because of concern for safety of study subjects, they will inform the PI, the IRB, and the clinical and scientific directors of CC and NHLBI.

## NIH IRB and CD reporting:

Adverse events, non-compliance, protocol deviations, unanticipated problems (UP), and serious adverse events are defined as described in NIH HRPP SOP Policy 801 ("Reporting Research Events"). All adverse events and deviations occurring during the study, including those observed by or reported to the research team, will be recorded. Reporting research events to the IRB will conform to the reporting requirements and timeframes as specified in Policy 801. Specifically, any actual or suspected non-compliance, major deviations, or UPs will be reported within 7 calendar days. Deaths that are possibly, probably or definitely related to the research will be reported to the IRB within 24 hours of an investigator becoming aware of the death. Minor deviations, adverse events and SAEs that are not UPs will be summarized and reported to IRB at the time of continuing review, or when otherwise requested by IRB or OHSRP office of Compliance and Training.

**Conflicts of Interest**: This study does not include any commercial interests, technology transfer, or any products made by a commercial interest. No conflicts of interest have been identified for any NIH employees associated with this study.

**Travel and Compensation**: No travel reimbursement will be provided.
Subjects will receive a total of $2015 upon completion of the protocol as compensation for the following research activities and interventions*:

| | |
|---|---|
| Prescreening visit | $140 |
| Baseline Exercise Testing Visit 1 | 110 |
| Baseline Exercise Testing Visit 2 | 90 |
| Exercise Training Visit #1 (including 10-minute-walk test and vascular studies | 110 |
| Interim Evaluation Study Visit (including exercise training session and vascular studies | 125 |

| | |
|---|---|
| Final Exercise Training Session (including 10-minute-walk test and vascular studies | 110 |
| Post-Exercise Testing Visit #1 | 160 |
| Post-Exercise Testing Visit #2 | 90 |
| Post-Exercise Testing Visit #3 | 90 |
| 33 Exercise Training Visits at $30/visit | 990 |
| TOTAL | $2015 |

*Subjects withdrawn before completing the study will be pro-rated for the portion of the study completed. Subjects will be compensated for the total number of exercise training sessions attended.

## Informed Consent:

*Consenting*: NIH research staff will interview interested candidates. Those deemed appropriate will both read and sign the NHLBI NIH approved consent form. A copy of the signed informed consent shall be given to the individual signing the consent and the original consent document will be retained in the medical record. Upon giving consent, the subject will undergo a full examination by a physician, and a review of available medical records will be performed to confirm their suitability for the trial. Additionally, they will undergo an echocardiogram, EKG, PFT with DLCO and a pregnancy test to ensure the patient is safe to exercise and do not meet any exclusion criteria. After this, they will begin the baseline research tests including: treadmill cardiopulmonary exercise test, arterial occlusion muscle oxygenation capacity test, pulmonary gas exchange analysis, heart rate measurement, bioelectrical impedance plethysmography, near infrared spectroscopy, six-minute walk and fatigability tests, and patient self-report instruments. All tests will be performed again post rehabilitation for outcome comparisons.

**Management of Data and Samples**: Data will be collected using appropriately calibrated computer-assisted instrumentation, commercial software programs, data collection sheets and self-reported outcome questionnaires.

Clinical Trials Survey System (CTSS) will be used to manage data collection of the following subject self-reported outcome questionnaires and subjects will have the choice of using an NIH mobile device or paper format to complete the questionnaires. All digital CTDB forms will be considered source documentation.

| **CTDB** | **Source** |
|---|---|
| Fatigue Severity Scale | Digital or Paper |
| PROMIS | Digital or Paper |

Clinical Trials Database (CTDB) will be used to manage data collection and tracking of the intervention through the use of an NIH mobile device. Paper source may be used should capability of digital entry not be available. All Digital CTDB forms will be considered source documentation.

Upon enrollment, subjects will be assigned a protocol number that will be used as a subject identifier for all subject files and data collection sheets. All computer software with associated data files is kept on password-protected computers that are off-network and are stored in a locked laboratory with restricted access. Paper data collection sheets will be kept in de-identified subject folders in locked filing cabinets in secure areas. Patient consent forms and other relevant medical records with patient names and other identifiable data are kept in separate folders and locked in separate filing cabinets. No information will be kept in either folder that could be used to link a subject's medical record file to a subject's study data file.

Electronic data collected in the laboratory will be transferred to a restricted access folder on the Clinical Center network with appropriate firewall protection. Only study PIs and AIs will have access to this folder. A password protected USB device will be used to transfer data. Email communication with patient information or data will be transmitted via encrypted email as per NIH guidelines.

Data will be analyzed as discussed in the Data Analysis section of this document. Analysis will be conducted using an assigned protocol number as the subject identifier described above. Analysis of de-identified data may be performed at George Mason University by approved associate investigators on this protocol. This includes de-identified data from the treadmill exercise tests, 10 MWT, fatigability tests, exercise training data and questionnaires.

## **Sample Storage**:

As described under the biomarkers section we will collect samples of whole blood, serum CPT and PAX gene tubes for future exploration biomarkers with fatigability and other related research studies. These include serum cytokine markers such as but not limited to IL-2, IL-6, IL-10, TNF-α and TGF-β, and interferon gene signature.[30]

The amount of blood drawn for clinical care indication and research purposes will be kept within the NIH guidelines of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8 week period for adults.

Research samples collected from subjects consenting to this protocol will be stored in locked secure freezers belonging to NIAMS. The freezers are located in Building 10 at the NIH. Only study investigators and participating research personnel will have access to the samples. Samples will be kept indefinitely unless there is a significant justification for destroying them. The Principal Investigator will report the loss or destruction of samples collected under this protocol to the Institutional Review Board (IRB).

All samples will be coded and will not have personal identifiers. The codes for identifiers will be contained in a secure electronic database (CTDB) and a subject code log that is maintained in secure research files. An electronic record log with identifiers of all collected research specimens will be kept. These will be stored in secure NIH computers.

Coded samples may be shared with collaborators within and outside the NIH. Any remaining samples will be stored in the NIAMS locked freezers. Stored samples may be used for studies

related to systemic lupus erythematosus.  Approval from the IRB will be obtained prior to any research use of stored samples beyond the scope of this study.

All patient samples will be coded and used for research purposes without sharing identifying information and all collaborators will follow federal rules for clinical research.

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## Appendices
## Appendix 1 – Study Protocol Timeline Checklist

| | Visit 1 | Visit 2 | Visit 3 | Visit 4/Exercise Training 1 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | X | | | |
| Medical History and Physical Exam | X | | | |
| Inclusion/Exclusion Criteria | X | | | |
| SELENA-SLEDAI | X | | | |
| ACR Damage Index (SLICC/ACR-DI) | X | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene | X | | | |
| 2) Doppler Echocardiogram | X | | | |
| 3) Pulmonary Function Test with DLCO | X | | | |
| 4) Electrocardiogram | X | | | |
| 5) Serum or Urine Pregnancy test | X | | | |
| 6) Clinical labs and urine | X | | | |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | X | | | |
| 2) PROMIS | | X | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | X | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | X | X | |
| Square Wave CPET (swCPET) | | | X | |
| Fatigability Test (10 minutes) | | | | X |
| Near Infrared Spectroscopy (NIRS) | | X | X | |
| Bioimpedance Cardiography Test (ZCG) | | X | X | |
| Modified Treadmill Exercise Training 20 minutes | | | | X |
| Treadmill Exercise Training 30 minutes | | | | |
| Non-Invasive Vascular Function Testing (Optional) | | | | X |

| | Exercise Training 2 | Exercise Training 3 | Exercise Training 4 | Exercise Training 5 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | | | | |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | | | | |
| ACR Damage Index (SLICC/ACR-DI) | | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | | | |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | |
| 5) Serum or Urine Pregnancy test | | | | |
| 6) Clinical labs and urine | | | | |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | |
| - | | | | |
| 2) PROMIS | | | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | | |
| Near Infrared Spectroscopy (NIRS) | | | | |
| Bioimpedance Cardiography Test (ZCG) | | | | |
| Modified Treadmill Exercise Training 20 minutes | | | | |
| Treadmill Exercise Training 30 minutes | X | X | X | X |
| Non-Invasive Vascular Function Testing (Optional) | | | | |

| | Exercise Training 6 | Exercise Training 7 | Exercise Training 8 | Exercise Training 9 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | | | | |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | | | | |
| ACR Damage Index (SLICC/ACR-DI) | | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | | | |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | |
| 5) Serum or Urine Pregnancy test | | | | |
| 6) Clinical labs and urine | | | | |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | |
| 2) PROMIS | | | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | | |
| Near Infrared Spectroscopy (NIRS) | | | | |
| Bioimpedance Cardiography Test (ZCG) | | | | |
| Modified Treadmill Exercise Training 20 minutes | | | | |
| Treadmill Exercise Training 30 minutes | X | X | X | X |
| Non-Invasive Vascular Function Testing (Optional) | | | | |

| | Exercise Training 10 | Exercise Training 11 | Exercise Training 12 | Exercise Training 13 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | | | | Training Visit 13, 14 or15 |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | | | | Training Visit 13, 14or 15 |
| ACR Damage Index (SLICC/ACR-DI) | | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | | | Training Visit 13, 14or 15 |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | |
| 5) Serum or Urine Pregnancy test | | | | Training Visit 13, 14 or 15 |
| 6) Clinical labs and urine | | | | Training Visit 13, 14 or 15 |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | |
| 2) PROMIS | | | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | | |
| Near Infrared Spectroscopy (NIRS) | | | | |
| Bioimpedance Cardiography Test (ZCG) | | | | |
| Modified Treadmill Exercise Training 20 minutes | | | | |
| Treadmill Exercise Training 30 minutes | X | X | X | X |
| Non-Invasive Vascular Function Testing (Optional) | | | | Training Visit 13, 14 or 15 |

| | Exercise Training 14 | Exercise Training 15 | Exercise Training 16 | Exercise Training 17 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | Training Visit 13, 14 or 15 | Training Visit 13, 14 or 15 | | |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | Training Visit 13, 14 or 15 | Training Visit 13, 14 or 15 | | |
| ACR Damage Index (SLICC/ACR-DI) | | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | Training Visit 13, 14 or 15 | Training Visit 13, 14 or15 | | |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | |
| 5) Serum or Urine Pregnancy test | Training Visit 13, 14 or 15 | Training Visit 13, 14 or 15 | | |
| 6) Clinical labs and urine | Training Visit 13, 14 or 15 | Training Visit 13, 14 or 15 | | |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | |
| 2) PROMIS | | | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | | |
| Near Infrared Spectroscopy (NIRS) | | | | |
| Bioimpedance Cardiography Test (ZCG) | | | | |
| Modified Treadmill Exercise Training 20 minutes | | | | |
| Treadmill Exercise Training 30 minutes | X | X | X | X |
| Non-Invasive Vascular Function Testing (Optional) | Training Visit 13, 14 or 15 | Training Visit 13, 14 or 15 | | |

| | Exercise Training 18 | Exercise Training 19 | Exercise Training 20 | Exercise Training 21 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | | | | |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | | | | |
| ACR Damage Index (SLICC/ACR-DI) | | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | | | |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | |
| 5) Serum or Urine Pregnancy test | | | | |
| 6) Clinical labs and urine | | | | |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | |
| 2) PROMIS | | | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | | |
| Near Infrared Spectroscopy (NIRS) | | | | |
| Bioimpedance Cardiography Test (ZCG) | | | | |
| Modified Treadmill Exercise Training 20 minutes | | | | |
| Treadmill Exercise Training 30 minutes | X | X | X | X |
| Non-Invasive Vascular Function Testing (Optional) | | | | |

| | Exercise Training 22 | Exercise Training 23 | Exercise Training 24 | Exercise Training 25 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | | | | |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | | | | |
| ACR Damage Index (SLICC/ACR-DI) | | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | | | |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | |
| 5) Serum or Urine Pregnancy test | | | | |
| 6) Clinical labs and urine | | | | |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | |
| 2) PROMIS | | | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | | |
| Near Infrared Spectroscopy (NIRS) | | | | |
| Bioimpedance Cardiography Test (ZCG) | | | | |
| Modified Treadmill Exercise Training 20 minutes | | | | |
| Treadmill Exercise Training 30 minutes | X | X | X | X |
| Non-Invasive Vascular Function Testing (Optional) | | | | |

| | Exercise Training 26 | Exercise Training 27 | Exercise Training 28 | Exercise Training 29 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | | | | |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | | | | |
| ACR Damage Index (SLICC/ACR-DI) | | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | | | |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | |
| 5) Serum or Urine Pregnancy test | | | | |
| 6) Clinical labs and urine | | | | |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | |
| 2) PROMIS | | | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | | |
| Near Infrared Spectroscopy (NIRS) | | | | |
| Bioimpedance Cardiography Test (ZCG) | | | | |
| Modified Treadmill Exercise Training 20 minutes | | | | |
| Treadmill Exercise Training 30 minutes | X | X | X | X |
| Non-Invasive Vascular Function Testing (Optional) | | | | |

| | Exercise Training 30 | Exercise Training 31 | Exercise Training 32 | Exercise Training 33 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | | | | |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | | | | |
| ACR Damage Index (SLICC/ACR-DI) | | | | |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | | | |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | |
| 5) Serum or Urine Pregnancy test | | | | |
| 6) Clinical labs and urine | | | | |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | |
| 2) PROMIS | | | | |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | | |
| Near Infrared Spectroscopy (NIRS) | | | | |
| Bioimpedance Cardiography Test (ZCG) | | | | |
| Modified Treadmill Exercise Training 20 minutes | | | | |
| Treadmill Exercise Training 30 minutes | X | X | X | X |
| Non-Invasive Vascular Function Testing (Optional) | | | | |

| | Exercise Training 34 | Exercise Training 35 | Exercise Training 36 /Visit 6 | Visit 7 |
|---|---|---|---|---|
| **Time Frame** | | | | |
| Consent Form | | | | |
| Medical History and Physical Exam | | | | X |
| Inclusion/Exclusion Criteria | | | | |
| SELENA-SLEDAI | | | | X |
| ACR Damage Index (SLICC/ACR-DI) | | | | X |
| **Labs and Imaging**: | | | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | | | X |
| 2) Doppler Echocardiogram | | | | |
| 3) Pulmonary Function Test with DLCO | | | | |
| 4) Electrocardiogram | | | | X |
| 5) Serum or Urine Pregnancy test | | | | X |
| 6) Clinical labs and urine | | | | X |
| **Questionnaires:** | | | | |
| 1) Fatigue Severity Scale (FSS) | | | | X |
| 2) PROMIS | | | | X |
| **Procedures:** | | | | |
| Cardio Pulmonary Exercise Test (CPET) | | | | X |
| Arterial Occlusion Muscle Oxygenation Capacity Test | | | | X |
| Square Wave CPET (swCPET) | | | | |
| Fatigability Test (10 minutes) | | | X | |
| Near Infrared Spectroscopy (NIRS) | | | | X |
| Bioimpedance Cardiography Test (ZCG) | | | | X |
| Modified Treadmill Exercise Training 20 minutes | | | X | |
| Treadmill Exercise Training 30 minutes | X | X | | |
| Non-Invasive Vascular Function Testing (Optional) | | | X | |

| | Visit 8 | Visit 9 |
|---|---|---|
| **Time Frame** | | |
| Consent Form | | |
| Medical History and Physical Exam | | |
| Inclusion/Exclusion Criteria | | |
| SELENA-SLEDAI | | |
| ACR Damage Index (SLICC/ACR-DI) | | |
| **Labs and Imaging**: | | |
| 1) Research Blood Tests (Whole Blood, Serum, CPT, PAX gene tubes) | | |
| 2) Doppler Echocardiogram | | |
| 3) Pulmonary Function Test with DLCO | | |
| 4) Electrocardiogram | | |
| 5) Serum or Urine Pregnancy test | | |
| 6) Clinical labs and urine | | |
| **Questionnaires:** | | |
| 1) Fatigue Severity Scale (FSS) | | |
| 2) PROMIS | | |
| **Procedures:** | | |
| Cardio Pulmonary Exercise Test (CPET) | | |
| Arterial Occlusion Muscle Oxygenation Capacity Test | X | X |
| Square Wave CPET (swCPET) | X | X |
| Fatigability Test (10 minutes) | | |
| Near Infrared Spectroscopy (NIRS) | X | X |
| Bioimpedance Cardiography Test (ZCG) | X | X |
| Modified Treadmill Exercise Training 20 minutes | | |
| Treadmill Exercise Training 30 minutes | | |
| Non-Invasive Vascular Function Testing (Optional) | | |

## Appendix 2. Fatigue Severity Scale (FSS)

### Fatigue Severity Scale (FSS)

Name _____ Date _____

The Fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue on you. The FSS is a short questionnaire that requires you to rate your level of fatigue.

The FSS questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you. A score of 1 indicates you disagree and a score of 7 indicates you agree.

| **FSS Questionnaire** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **During the past week, I have found that:** | **Disagree <--------> Agree** | | | | | | |
| My motivation is lower when I am fatigued. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Exercise brings on my fatigue. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| I am easily fatigued. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fatigue interferes with my physical functioning. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fatigue causes frequent problems for me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| My fatigue prevents sustained physical functioning. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fatigue interferes with carrying out certain duties and responsibilities. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fatigue is among my three most disabling symptoms. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fatigue interferes with my work, family, or social life. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

# Appendix 3: SELENA SLEDAI

LE-NUM:_____

Name of Patient:_____MRN: _____

Date SLEDAI Performed: / / _____
mm/dd/year)

| Wt. | Present | Descriptor | Definition |
|---|---|---|---|
| 8 | | Seizure | Recent onset (last 10 days). Exclude metabolic, infections or drug cause, or seizure due to past irreversible. |
| 8 | | Psychosis | Altered ability to function in normal activity due to severe disturbances in the perception of reality. Include hallucination, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes. |
| 8 | | Organic Brain Syndrome | Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and Syndrome fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least two of the following: Perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic infectious or drug causes. |
| 8 | | Visual Disturbance | Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes. |
| 8 | | Cranial Nerve Disorder | New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus. |
| 8 | | Lupus Headache | Serve persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia. |
| 8 | | CVA | New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes. |
| 8 | | Vasculitis | Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or an angiogram proof of vasculitis. |
| 4 | | Arthritis | More than 2 joints with pain and signs of inflammation. |
| 4 | | Myositis | Proximal muscle aching weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis. |
| 4 | | Urinary Casts | Cellular casts. |
| 4 | | Hematuria | >10 red blood cells/high power field. Exclude stone, infection or other cause. |
| 4 | | Proteinuria | New onset or recent increase of more than 0.5h/24hr. |
| 4 | | Pyuria | >5 white blood cells/high power field. Exclude infection. |
| 2 | | Rash | Ongoing inflammatory lupus rash. |
| 2 | | Alopecia | Ongoing abnormal, patchy or diffuse loss of hair due to active lupus. |
| 2 | | Mucosal Ulcers | Ongoing oral or nasal ulcerations due to active lupus. |
| 2 | | Pleurisy | Classic and Severe pleuritic chest pain or pleural rub or effusion, or new pleural thickening due to lupus. |
| 2 | | Pericarditis | Classic and Severe pericardial pain or pleural rub or effusion, or electrocardiogram confirmation. |
| 2 | | Low Complement | Decrease in C3 or C4 below the lower limit of normal for testing laboratory. |

| | | | |
|---|---|---|---|
| 2 | | Increased DNA Binding | Above normal range for testing laboratory. |
| 1 | | Fever | >38 C. Excluding infectious causes. |
| 1 | | Thrombocytopenia | <100,000-platelets/mm3. |
| 1 | | Leukopenia | <3,000 white blood cells/mm3. Excluding drug causes. |
| | | **TOTAL SCORE** | (Sum of weights next to description marked present) |

Please Return To: _____

# Appendix 4: SLICC/ACR DAMAGE INDEX FOR SLE

**Obs. Num: _____**
**Name of Patient:_____ MRN:_____**
**Date SLICC Performed:_____/_____/_____ LE-Num:_____**

| Wt | Score | Item |
|---|---|---|
| | | **Ocular (either eye, by clinical assessment)** |
| 1 | | Any cataract ever |
| 1 | | Retinal change or optic atrophy |
| | | **Neuropsychiatric** |
| 1 | | Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration,--difficulty in spoken or written language, impaired performance level) OR major psychosis |
| 1 | | Seizures requiring therapy for 6 months |
| 1(2) | | Cerebrovascular accident ever (score 2 if >1) |
| 1 | | Cranial or peripheral neuropathy (excluding optic) |
| 1 | | Transverse myelitis |
| | | **Renal** |
| 1 | | Estimated or measured glomerular filtration rate < 50% |
| 1 | | Proteinuria > 3.5g/24h |
| 3 | | OR End-stage renal disease (regardless of dialysis or transplantation) |
| | | **Pulmonary** |
| 1 | | Pulmonary hypertension (right ventricular prominence, or loud P2) |
| 1 | | Pulmonary fibrosis (physical and radiograph) |
| 1 | | Shrinking lung (radiograph) |
| 1 | | Pleural fibrosis (radiograph) |
| 1 | | Pulmonary infarction (radiograph) |
| | | **Cardiovascular** |
| 1 | | Angina OR coronary artery bypass |
| 1(2) | | Myocardial infarction ever (score 2 if > 1) |
| 1 | | Cardiomyopathy (ventricular dysfunction) |
| 1 | | Valvular disease (diastolic murmur or systolic murmur > 3/6) |
| 1 | | Pericarditis for 6 months, OR pericardectomy |
| | | **Peripheral vascular** |
| 1 | | Claudication for 6 months |
| 1 | | Minor tissue loss (pulp space) |
| 1(2) | | Significant tissue loss ever (e.g. loss of digit or limb)(score 2 if > 1 site) |
| 1 | | Venous thrombosis with swelling, ulceration, OR venous stasis |
| | | **Gastrointestinal** |
| 1(2) | | Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if > 1 site) |
| 1 | | Mesenteric insufficiency |
| 1 | | Chronic peritonitis |
| 1 | | Stricture OR upper gastrointestinal tract surgery ever |
| | | **Musculoskeletal** |
| 1 | | Muscle atrophy or weakness |
| 1 | | Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis) |
| 1 | | Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) |
| 1(2) | | Avascular necrosis (score 2 if > 1) |
| 1 | | Osteomyelitis |
| | | **Skin** |
| 1 | | Scarring chronic alopecia |
| 1 | | Extensive scarring of panniculum other than scalp and pulp space |

| | | |
|---|---|---|
| 1 | | Skin ulceration (excluding thrombosis for > 6 months) |
| 1 | | **Premature gonadal failure** |
| 1 | | **Diabetes** (regardless of treatment) |
| 1(2) | | **Malignancy** (exclude dysplasia) (score 2 if >1 site) |
| | | **TOTAL Score** |

# Appendix 5: PROMIS–57 Profile v2.0

**Please respond to each question or statement by marking one box per row.**

| | **Physical Function** | **Without any difficulty** | **With a little difficulty** | **With some difficulty** | **With much difficulty** | **Unable to do** |
|---|---|---|---|---|---|---|
| 1 | Are you able to do chores such as vacuuming or yard work?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2 | Are you able to go up and down stairs at a normal pace? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3 | Are you able to go for a walk of at least 15 minutes? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4 | Are you able to run errands and shop?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | | **Not at all** | **Very little** | **Somewhat** | **Quite a lot** | **Cannot do** |
| 5 | Does your health now limit you in doing two hours of physical labor? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6 | Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7 | Does your health now limit you in lifting or carrying groceries?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8 | Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Anxiety**<br>**In the past 7 days…** | **Never** | **Rarely** | **Sometimes** | **Often** | **Always** |
| 9 | I felt fearful..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10 | I found it hard to focus on anything other than my anxiety ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11 | My worries overwhelmed me..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12 | I felt uneasy ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13 | I felt nervous..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14 | I felt like I needed help for my anxiety ..... | ☐ | ☐ | ☐ | ☐ | ☐ |

| | **Anxiety**<br>**In the past 7 days…** | **Never** | **Rarely** | **Sometimes** | **Often** | **Always** |
|---|---|---|---|---|---|---|
| 15 | I felt anxious..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16 | I felt tense ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Depression**<br>**In the past 7 days...** | **Never** | **Rarely** | **Sometimes** | **Often** | **Always** |
| 17 | I felt worthless ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 18 | I felt helpless ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 19 | I felt depressed ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 20 | I felt hopeless ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 21 | I felt like a failure ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 22 | I felt unhappy ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 23 | I felt that I had nothing to look forward to. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 24 | I felt that nothing could cheer me up..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Fatigue**<br>**During the past 7 days…** | **Not at all** | **A little bit** | **Somewhat** | **Quite a bit** | **Very much** |
| 25 | I feel fatigued ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 26 | I have trouble <u>starting</u> things because I am tired..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **In the past 7 days…** | | | | | |
| 27 | How run-down did you feel on average? ... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 28 | How fatigued were you on average? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 29 | How much were you bothered by your fatigue on average?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 30 | To what degree did your fatigue interfere with your physical functioning? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |

**Fatigue**

| | **In the past 7 days…** | **Never** | **Rarely** | **Sometimes** | **Often** | **Always** |
|---|---|---|---|---|---|---|
| 31 | How often did you have to push yourself to get things done because of your fatigue? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 32 | How often did you have trouble finishing things because of your fatigue? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |

**Sleep Disturbance**

| | **In the past 7 days…** | **Very poor** | **Poor** | **Fair** | **Good** | **Very good** |
|---|---|---|---|---|---|---|
| 33 | My sleep quality was..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **In the past 7 days…** | **Not at all** | **A little bit** | **Somewhat** | **Quite a bit** | **Very much** |
| 34 | My sleep was refreshing..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 35 | I had a problem with my sleep ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 36 | I had difficulty falling asleep ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 37 | My sleep was restless ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 38 | I tried hard to get to sleep..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 39 | I worried about not being able to fall asleep ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 40 | I was satisfied with my sleep..... | ☐ | ☐ | ☐ | ☐ | ☐ |

**Ability to Participate in Social Roles and Activities**

| | | **Never** | **Rarely** | **Sometimes** | **Usually** | **Always** |
|---|---|---|---|---|---|---|
| 41 | I have trouble doing all of my regular leisure activities with others ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 42 | I have trouble doing all of the family activities that I want to do ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 43 | I have trouble doing all of my usual work (include work at home) ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 44 | I have trouble doing all of the activities with friends that I want to do ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 45 | I have to limit the things I do for fun with others ..... | ☐ | ☐ | ☐ | ☐ | ☐ |

## Ability to Participate in Social Roles and Activities

| | | Never | Rarely | Sometimes | Usually | Always |
|---|---|---|---|---|---|---|
| 46 | I have to limit my regular activities with friends..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 47 | I have to limit my regular family activities .. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 48 | I have trouble doing all of the work that is really important to me (include work at home)..... | ☐ | ☐ | ☐ | ☐ | ☐ |

## Pain Interference

| | **In the past 7 days…** | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 49 | How much did pain interfere with your day to day activities? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 50 | How much did pain interfere with work around the home? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 51 | How much did pain interfere with your ability to participate in social activities? ... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 52 | How much did pain interfere with your enjoyment of life?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 53 | How much did pain interfere with the things you usually do for fun?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 54 | How much did pain interfere with your enjoyment of social activities? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 55 | How much did pain interfere with your household chores? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 56 | How much did pain interfere with your family life? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |

## Pain Intensity

**In the past 7 days…**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 57 | How would you rate your pain on average? ..... | ☐ 0 **No pain** | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 | ☐ 7 | ☐ 8 | ☐ 9 | ☐ 10 **Worst imaginable pain** |

# Appendix 6: Fatigue Severity Score (Spanish)

## Escala de Intensidad del Cansancio
## Fatigue Severity Scale (FSS) (Spanish)

Nombre _____ Fecha_____

La Escala de Intensidad del Cansancio (FSS) es un método para evaluar el efecto del cansancio en usted. La FSS es un cuestionario corto para el que es necesario que califique su grado de cansancio.

El cuestionario de la FSS contiene nueve oraciones con las que se evalúa la intensidad de sus síntomas de cansancio. Lea cada oración y marque con un círculo un número del 1 al 7, con base en qué tan exactamente refleja su situación en la última semana y hasta qué punto está de acuerdo o en desacuerdo con que la oración le concierne. Un puntaje de 1 indica que no está de acuerdo y un puntaje de 7 indica que está de acuerdo.

| **Cuestionario FSS** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **En la última semana, noté que:** | **En desacuerdo <--------> De acuerdo** | | | | | | |
| Mi motivación es menor cuando estoy cansado(a). | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| El ejercicio me cansa. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Me canso con facilidad. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| El cansancio interfiere con mi funcionamiento físico. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| El cansancio me causa problemas frecuentes. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| El cansancio impide mi funcionamiento físico sostenido. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| El cansancio interfiere con el cumplimiento de ciertos deberes y responsabilidades. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| El cansancio está entre mis tres síntomas más incapacitantes. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| El cansancio interfiere con mi trabajo, familia o vida social. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

# Appendix 7: PROMIS 57 v2 (Spanish)

## PROMIS–57 Profile v2.0

**Responda a cada enunciado marcando una casilla por línea.**

| | Capacidad de funcionamiento físico | Sin dificultad | Con poca dificultad | Con alguna dificultad | Con mucha dificultad | No puedo hacerlo |
|---|---|---|---|---|---|---|
| 1 | ¿Puede realizar tareas, como pasar la aspiradora o trabajar en el jardín? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2 | ¿Puede subir y bajar escaleras a un paso normal?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3 | ¿Puede salir a caminar durante 15 minutos por lo menos? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4 | ¿Puede hacer mandados y compras? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | | **Nada** | **Poco** | **Algo** | **Mucho** | **No puedo hacerlo** |
| 5 | ¿Limita su salud en este momento su capacidad para realizar dos horas de trabajo físico? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6 | ¿Limita su salud en este momento su capacidad para realizar trabajos moderados en el hogar, como pasar la aspiradora, barrer el piso (suelo) o entrar a la casa las compras del mercado?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7 | ¿Limita su salud en este momento su capacidad para levantar o llevar las bolsas del supermercado?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8 | ¿Limita su salud en este momento su capacidad para realizar trabajos pesados en el hogar, como fregar (restregar) los pisos (el suelo), o levantar o mover muebles pesados? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **<u>Ansiedad</u>**<br>**En los últimos 7 días…** | **Nunca** | **Rara vez** | **Algunas veces** | **A menudo** | **Siempre** |
| 9 | Sentí miedo ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10 | Tuve dificultad para concentrarme en otra cosa que no fuera mi ansiedad ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11 | Mis inquietudes fueron demasiado para mí ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12 | Me sentí intranquilo/a ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13 | Me sentí nervioso/a ..... | ☐ | ☐ | ☐ | ☐ | ☐ |

| | | | | | | |
|---|---|---|---|---|---|---|
| 14 | Sentí que necesitaba ayuda para mi ansiedad..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15 | Sentí ansiedad ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Ansiedad**<br>**En los últimos 7 días…** | **Nunca** | **Rara vez** | **Algunas veces** | **A menudo** | **Siempre** |
| 16 | Me sentí tenso/a..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Depresión**<br>**En los últimos 7 días...** | **Nunca** | **Rara vez** | **Algunas veces** | **A menudo** | **Siempre** |
| 17 | Sentí que no valía nada..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 18 | Me sentí indefenso/a (que no podía hacer nada para ayudarme)..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 19 | Me sentí deprimido/a..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 20 | Me sentí desesperanzado/a ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 21 | Me sentí fracasado/a ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 22 | Me sentí descontento/a ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 23 | Sentí que nada me ilusionaba ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 24 | Sentí que nada me podía animar..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Agotamiento**<br>**En los últimos 7 días…** | **Nada** | **Un poco** | **Algo** | **Mucho** | **Muchísimo** |
| 25 | Me siento agotado/a ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 26 | Tengo dificultad para <u>comenzar</u> las cosas porque estoy cansado/a ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **En los últimos 7 días…** | | | | | |
| 27 | ¿Qué tan rendido/a se sintió en promedio?... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 28 | ¿Qué tan agotado/a estuvo en promedio?.... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 29 | ¿En qué medida le molestó el agotamiento en promedio? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 30 | ¿En qué medida el agotamiento interfirió en su funcionamiento físico? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **En los últimos 7 días...** | **Nunca** | **Rara vez** | **Algunas veces** | **A menudo** | **Siempre** |

| | | | | | | |
|---|---|---|---|---|---|---|
| 31 | ¿Con qué frecuencia se tuvo que forzar para hacer sus actividades debido al agotamiento?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Agotamiento**<br>**En los últimos 7 días...** | **Nunca** | **Rara vez** | **Algunas veces** | **A menudo** | **Siempre** |
| 32 | ¿Con qué frecuencia tuvo dificultad para terminar las cosas debido al agotamiento? .... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Alteración del sueño**<br>**En los últimos 7 días…** | **Muy mala** | **Mala** | **Pasable** | **Buena** | **Muy buena** |
| 33 | La calidad de mi sueño fue... ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **En los últimos 7 días…** | **Nada** | **Un poco** | **Algo** | **Mucho** | **Muchísimo** |
| 34 | Mi sueño fue reparador..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 35 | Tuve problemas para dormir ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 36 | Tuve dificultad para dormirme. ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 37 | Tuve el sueño inquieto..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 38 | Hice un gran esfuerzo por lograr dormirme .. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 39 | Me preocupó no poder quedarme dormido/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 40 | Me sentí satisfecho/a con mi sueño ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| | **Capacidad para participar en roles y actividades sociales** | **Nunca** | **Rara vez** | **Algunas veces** | **A menudo** | **Siempre** |
| 41 | Tengo problemas para realizar con otras personas todas mis actividades habituales de tiempo libre..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 42 | Tengo problemas para realizar todas las actividades con mi familia que quiero hacer | ☐ | ☐ | ☐ | ☐ | ☐ |
| 43 | Tengo problemas para realizar todo mi trabajo habitual (incluya el trabajo en el hogar)..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 44 | Tengo problemas para realizar todas las actividades con mis amigos/as que quiero hacer ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 45 | Tengo que limitar las cosas que hago para divertirme con otras personas..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 46 | Tengo que limitar mis actividades habituales con mis amigos/as ..... | ☐ | ☐ | ☐ | ☐ | ☐ |

| | | | | | | |
|---|---|---|---|---|---|---|
| 47 | Tengo que limitar las actividades habituales con mi familia..... | ☐ | ☐ | ☐ | ☐ | ☐ |

| | **Capacidad para participar en roles y actividades sociales** | **Nunca** | **Rara vez** | **Algunas veces** | **A menudo** | **Siempre** |
|---|---|---|---|---|---|---|
| 48 | Tengo problemas para realizar todo el trabajo que es verdaderamente importante para mí (incluya el trabajo en el hogar)..... | ☐ | ☐ | ☐ | ☐ | ☐ |

| | **Efectos del dolor**<br>**En los últimos 7 días…** | **Nada** | **Un poco** | **Algo** | **Mucho** | **Muchísimo** |
|---|---|---|---|---|---|---|
| 49 | ¿En qué medida el dolor interfirió en sus actividades diarias?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 50 | ¿En qué medida el dolor interfirió en el trabajo en el hogar?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 51 | ¿En qué medida el dolor interfirió en su capacidad para participar en actividades sociales?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 52 | ¿En qué medida el dolor interfirió en su capacidad para disfrutar de la vida? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 53 | ¿En qué medida el dolor interfirió en las actividades que hace habitualmente para divertirse? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 54 | ¿En qué medida el dolor interfirió en su capacidad para disfrutar de actividades sociales?..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 55 | ¿En qué medida el dolor interfirió en sus tareas domésticas? ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| 56 | ¿En qué medida el dolor interfirió en su vida familiar?..... | ☐ | ☐ | ☐ | ☐ | ☐ |

**Intensidad del dolor**
**En los últimos 7 días…**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 57 | En promedio, ¿cómo calificaría su dolor? ..... | ☐ 0 **Ningún dolor** | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 | ☐ 7 | ☐ 8 | ☐ 9 | ☐ 10 **El peor dolor imaginable** |