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1. Protocol Title

Spinal Cord Injury Exercise and Nutrition Conceptual Engagement (SCIENCE)

2. Objectives

The specific objectives for the current proposal are to assess the impact of home-based functional electrical stimulation leg cycle ergometry plus diet (HBFESLCE + Diet) versus Diet Alone on (Primary Variables) body composition (%BF, FM and FFM), insulin sensitivity (SI), glucose effectiveness (SG), and BMR, as well as (Secondary Variables) lower extremity bone mineral density, lipid profiles, and hsCRP in adults with motor complete SCI between C4-T4. Specific objectives to be addressed in the current proposal are:

1. To determine the impact of HBFESLCE + Diet on body composition, insulin sensitivity, glucose effectiveness and BMR in adults with motor complete tetraplegia or high paraplegia above T4. Additionally, lower extremity bone mineral density & content, lipid profiles, and hsCRP will be compared before and after intervention.
2. To determine the impact of HB Diet Alone on body composition, insulin sensitivity and glucose effectiveness in adults with motor complete tetraplegia or high paraplegia. Additionally, lower extremity bone mineral density, lipid profiles, and hsCRP will be compared before and after intervention.
3. To compare the efficacy of HBFESLCE + Diet with that of HB Diet Alone relative to the parameters listed above.
4. To create a robust dataset of variables that are associated with visceral adipose tissue (VAT) to predict determinates of epicardial VAT (EAT) and abdominal VAT (AVAT) in subjects with chronic motor complete C4-T4 SCI.
5. To compare the change in epicardial adipose tissue, abdominal visceral adipose tissue, intramuscular fat, and subcutaneous adipose tissue before and after home-based FES-LCE plus diet vs. diet alone in adults with chronic motor complete C4-T4 SCI.
6. To compare changes in circulating proinflammatory adipokines before and after FES-LCE plus diet vs. diet alone in adults with chronic motor complete C4-T4 SCI.

3. Background

There are an estimated 1.5 million persons in the United States with SCI, Men 3x > Women, with ~50% having tetraplegia and recent literature would imply that more than 60% are overweight or obese by BMI standards, more than 50% are glucose intolerant,

while one out of five is frankly diabetic.[1] This special population already has significant functional deficits including reduced mobility, myocardial atrophy, restrictive lung dysfunction, bowel and bladder dysfunction, and a high risk for skin breakdown. The additional deficits of visual impairment, gastroparesis, renal disease, peripheral polyneuropathy, and impaired wound healing associated with obesity and diabetes impacts independence to a much greater extent in SCI than in the able-bodied population. The potential to reverse and prevent obesity, diabetes and heart disease in this population has tremendous implications on quality of life and reduced health care costs. Further, the "side-effects" associated with exercise and diet intervention, including improved cardiovascular fitness, improved cholesterol profiles, improved functional mobility, reduced body fat, improved gastric mobility, and reduced spasticity will also positively impact the SCI person's ability to maintain a greater degree of independence and contribute to the work force and society. Exercise and diet to reduce obesity has tremendous potential, therefore, to improve health and quality of life for persons with high paraplegia and tetraplegia. Additionally, translation of these findings to other persons with disabilities and aging populations with issues of sarcopenia, obesity and glucose intolerance is highly probable.

Energy expenditure is 25-50% lower for persons with spinal cord injury, particularly at levels above T4 due to reduced muscle mass, sympathetic blunting and neuroendocrine dysfunction. Energy intake must match or be lower than energy expenditure in order for an individual to lose weight. However, rapid diet alone without significant muscle overload almost always results in additional muscle atrophy due to selective protein "cannibalism" as the body attempts to meet its "set-point" energy needs. Subsequent weight loss will include not just fat mass, but also significant lean body mass – further compromising metabolic expenditure. In brief, diet alone typically re-sets basal metabolism to a lower level than it had been prior to diet initiation, increasing the likelihood of future fat gain even at similar levels of energy intake. As an example, a man with C5 AIS A tetraplegia will continue to gain fat on a 1200 kcal/day diet if his daily energy expenditure is only 1000 kcal/day. Further dietary restriction to below 1200 kcal/d severely limits palatable food choices of appropriate nutrient density; such that dietary adherence becomes highly unlikely. For those few who have such discipline, "set-point" reduction will ultimately sabotage their attempts at weight loss as they further reduce metabolically active tissue. To preserve or increase basal energy expenditure, exercise most likely must be employed.

1. SCI Limits Exercise: Injury to the spinal cord obstructs the transmission of neural messages through the cord and results in the loss of somatic and autonomic control over trunk, limbs and viscera distal to the site of the lesion. Systemic responses to exercise seen in able-bodied individuals are blunted in persons with spinal cord injury and vary to a greater degree as the level of injury is higher. This causes a diminished ability to

perform physical activity and exercise, at a conscious (somatic) and subconscious (autonomic) level. Problems peculiar to SCI include blunted cardiovascular, ventilatory, thermoregulatory, & hormonal exercise responses, while associated SCI features of autonomic dysreflexia, osteopenia, upper extremity overuse syndromes, spasticity, & pressure injuries make the exercise prescription for this population especially difficult.[2]

2. Energy Balance and Obesity: ‘‘Obesity is a chronic, relapsing, neurochemical disease produced by the interaction of environment and host.”[3] In the late 1970s and 1980s, health researchers began to report an association between body fat and cardiovascular disease comorbidities, including hypertension, hyperlipidemia, and diabetes. Obesity was defined as an accumulation of excess body fat, with thresholds associated with cardiovascular disease > 22% body fat (%BF) for men and > 35% for women.[4] Body fat accumulates when energy intake exceeds energy expenditure, resulting in a positive energy balance.

The concept of energy balance reflects an ever-dynamic relationship between relative rates of change for energy intake and energy expenditure. Energy intake reflects the caloric gain through ingestion of foodstuffs, whereas energy expenditure reflects calories used to sustain life, perform movement and digest food. Energy intake is provided through the ingestion of foodstuffs of varying caloric densities. Fats contain roughly 9 kcal/g, carbohydrates and proteins contain ~ 4 kcal/g and alcohol contains ~7 kcal/g. The perceived need for energy is mediated through the lateral (appetite center) and ventromedial (satiety center) nuclei of the hypothalamus, but afferent signals to these centers may be impaired or blocked after SCI.[5]

Energy expenditure is the sum of basal metabolic rate (BMR), the thermic effect of food digestion (TEF) and the thermic effect of physical activity (TEA). Of the three, BMR contributes the most to total daily energy expenditure (TDEE), representing approximately 60-70% of the total. BMR represents the minimal energy expenditure required to sustain life, and equations developed around the beginning of the 20th century remain in use, although modified in recent decades to reflect a larger anthropometric body type.[6] Fat-free lean mass (FFM), comprised of muscle, bone and organs contributes the greatest energy expenditure of BMR, and of the FFM components, skeletal muscle contributes up to 85% of the variance.[7,8] Practically speaking, this means that increases or decreases in skeletal muscle mass significantly impact not only caloric expenditure during activity, but also total energy expenditure at rest. The TEF is the least variable of the components of TDEE, since digestion, absorption, and sympathetic nervous system activation following consumption of foodstuffs remains relatively constant with normal physiology and is not dependent upon body weight or composition. TEF represent ~ 8% of TDEE in most individuals.[9] Intermediate and most variable among the components of TDEE is the thermic effect of activity (TEA). Not only is it dependent upon total body

and skeletal muscle mass, it varies significantly with the mode, intensity, duration and frequency of activities.

Regardless of genetic influences, a person's energy balance is profoundly impacted by spinal cord injury. Injury to the somatic nervous system results in immediate and sustained loss of neurotrophic influences to skeletal muscles below the level of SCI, while sympathetic blunting to injuries above T6 further impair energy metabolism. Paralyzed muscle atrophies rapidly (obligatory sarcopenia) following acute SCI, drastically reducing BMR and TEA directly with the level of injury such that higher levels of SCI result in greater reductions in BMR and TEA. TEA is further reduced in traumatic SCI because of activity, range of motion (ROM) and weight-bear restrictions associated with surgical repair and bony healing. Subsequently, predicted energy expenditure equations used to determine caloric and nitrogen needs overestimate actual needs by an average of ~ 25% in persons with new SCI. These reductions are sustained following the acute phase of SCI,[10–16] due to reduced FFM, sympathetic blunting, cardiopulmonary dysfunction, reductions in work capacity, diminished anabolic hormones and reduced ability to utilize the relatively large muscle mass of the lower extremities. If equivalent reductions in energy intake are not employed, the person with SCI will rapidly accumulate adipose tissue beyond that expected of non-SCI individuals in similar circumstances.

3. Adipose Pathology & Metabolic Syndrome: Once considered benign, adipose tissue in recent years has been demonstrated to mediate severe metabolic consequences when accumulated in excess, and has been implicated as the causative agent for cardiovascular inflammation, hyperlipidemia, insulin resistance, hypertension, and thromboemboli associated with the metabolic syndrome. Adipose tissue, particularly that in visceral regions, has been demonstrated to secrete large amounts of proinflammatory proteins called cytokines, including interleukin-6 (IL-6) and tumor-necrosis factor-α (TNF-α).[17] IL-6 is a potent proinflammatory cytokine released from both visceral and subcutaneous adipocytes that independently causes low-grade vascular inflammation, stimulates the release of cortisol from the adrenal cortex and stimulates hepatic production of C-Reactive Protein (CRP), an acute phase reactant which is also tied to vascular inflammation.

As adipose tissue accumulates, lipolysis that typically occurs in the fasted state produces non-esterified fatty acids (NEFA) at an accelerated rate, even in the face of rising insulin levels. Circulating NEFA are deposited in the liver and skeletal muscle at increasing rates, contributing to insulin resistance by inhibiting the phosphorylation of insulin receptor substrates (IRS-1 and IRS-2) and subsequently the phosphatidylinositol 3-kinase (PI-3 kinase) cascade necessary for activation of the GLUT1 and GLUT4 receptors that allows them to translocate to the cell membrane and facilitate passage of glucose into the cell.[18]

As NEFA and associated triglycerides accumulate within the liver, hepatic production of very low density (VLDL-c) and low density (LDL-c) lipoproteins increases, as does that of apolipoprotein B, the major protein of LDL-cholesterol.[19, 20] Simultaneously, net apolipoprotein A production is slowed, resulting in reductions of high density lipoprotein (HDL-c), the primary scavenger of peripheral lipids. Whole body lipid profiles reflect the local hepatic changes in lipid metabolism with elevated triglycerides, VLDL-c, LDL-c in the face of diminishing HDL-c, creating an atherogenic environment throughout the vascular tree.[19]

Central obesity causes hypertension through a number of mechanisms. Chronic exposure to adipose derived proinflammatory cytokines can damage the arterial endothelium, resulting in arterial stiffness and dysfunction. Visceral fat also secretes the hormone leptin which directly increases sympathetic nervous system activity, increasing vasoconstriction and subsequently mean arterial pressure.[9,20] Adipocyte secretion of TNF-α increases hepatic synthesis of angiotensinogen, a potent vasoconstrictive agent.[13] Specifically, these agents stimulate aldosterone production from the adrenal cortex with subsequent renal sodium reabsorption and volume expansion.[21] Visceral obesity can also cause direct mechanical compression of the kidneys, which causes elevated intrarenal pressures and sodium retention.[20]

4. Obesity in SCI: Obesity, i.e., body fat relative to body weight of greater than 22% in men, or 35% in women, is a significant risk factor for glucose intolerance and heart disease in SCI, but is poorly identified in this special population.[1] Body Mass Index (BMI) is calculated as a person's weight relative to their squared height (Weight (kg)/Height2 (m2), and is the most commonly used indicator of obesity in our society. For able-bodied individuals, BMI ≥ 25 kg/m^2 is considered overweight, while BMI ≥ 30 kg/m2 is considered obese, and places one at significantly higher risk for coronary artery disease, diabetes mellitus, osteoarthritis and certain types of cancer. When the World Health Organization (WHO) "redefined" obesity according to BMI in 1998, significant sensitivity for the true definition of obesity[4] (%BF > 22 in men, %BF > 35 in women) was compromised, resulting in gross underestimation of obesity in certain populations, including those with SCI.[1,22,23] Additionally, standard body composition assessment techniques are based on non-SCI cadaveric dissections performed over 50 years ago, and have not been validated in SCI. Limitations for each of the current techniques used for body composition assessment in SCI have been reported previously.[1,22,23] Computed tomography (CT) is considered the gold standard for fat assessment, while methods such as BMI and waist circumference serve only as a surrogate marker of fat and do not yield a precise measure of body composition (e.g., fat-free mass (FFM) and fat mass (FM)). CT provides the distribution of fat/adipose tissue (i.e. android vs gynoid or subcutaneous [SAT] vs visceral [VAT] adipose tissue) and is a fast, relatively inexpensive (compared

to MR imaging), and widely used tool for assessment of body composition in the able-bodied population.[24]

Several studies using variable techniques have suggested reduced fat-free body mass (FFB) and increased fat mass in persons with SCI.[25–32] Wang et al have further organized and described up to 5 compartment models, most of which discriminate additional components of the FFB mass.[33] For example, FFB can be further discriminated into protein/mineral and water compartments in the 3- compartment water molecular model, or bone mineral and bone-free lean tissue in the 3-compartment tissue model. The 4-compartment model, which is currently accepted as the gold-standard for body composition assessment in most exercise physiology laboratories, is comprised of fat, mineral, water, and protein. This model is especially appropriate for populations such as those with SCI because it actually measures the components of FFB mass which are otherwise erroneously assumed in the other models.[34]

The true prevalence of obesity in SCI remains unclear. In a sample of 7,959 veterans with SCI managed in VA hospitals in 2001, we reported 53% to have BMI > 25 kg/m2 , while 68% had BMI > 23 kg/m2 .[21] A smaller sample reported from a single mid-western VA hospital similarly demonstrated 255 (65.8%) of 387 veterans with SCI to have BMI > 25 kg/m2; an additional 27.9% were reported to have BMI in “normal” (20-25 kg/m2) range.[35] These studies suggest that at least half of these individuals with SCI and “normal” BMIs also fall into the obese range if %BF were accurately assessed. Nonetheless, the best data available at this time suggests that two of every three persons with SCI is likely obese and appears at risk for the metabolic consequences of obesity.

5. Metabolic Syndrome in SCI: Collectively, the constellation of obesity, vascular inflammation, dyslipidemia, insulin resistance and hypertension has been referred to as a “metabolic syndrome,” although the relative impact of each of the components on overall health has been debated among different groups of physicians and scientists. In 1998, the WHO definition of the metabolic syndrome focused on the central role of diabetes mellitus, plus at least two of the following: obesity (BMI > 30kg/m2 or Waist-to-hip ratio > 1), dyslipidemia (TG ≥ 150 mg/dl &/or HDL-c < 35 mg/dl in men or < 40 mg/dl in men, < 50 mg/dl in women), hypertension (BP ≥ 130/85 mm Hg), and fasting glucose > 110 mg/dl.[30] Most recently, the International Diabetes Federation (IDF) definition of metabolic syndrome has emphasized the role of central obesity (waist circumference ≥ 94 cm in men, ≥ 80 cm in women) plus any two of the following: dyslipidemia (TG ≥ 150 mg/dl or on treatment; HDL-c < 40 mg/dl for men, < 50 mg/dl for women or on HDL-c treatment), hypertension (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic, or on treatment for hypertension), fasting glucose ≥ 100 mg/dl or previously diagnosed with type 2 diabetes mellitus.[36] Obesity is now recognized as the primary mediator of the metabolic consequences of the metabolic syndrome and causative for hypertension, low grade

inflammation, cardiovascular disease, glucose intolerance and dyslipidemia. Despite the recent report on carbohydrate and lipid disorders in SCI of the AHRQ ERTA (2008) which was restricted to large, randomized controlled investigations,[11] it remains our contention that metabolic dysfunction is, in fact, at epidemic proportions in the SCI population, but simply has not received sufficient rigorous attention necessary to identify its true prevalence and significance. Since that report, multiple studies have demonstrated increased incidence of metabolic syndrome in persons with SCI when compared to able-bodied individuals.[12–15,24,37] Specific components of the metabolic syndrome in SCI are addressed below. Interestingly, while SCI neuropathophysiology should lead to neurogenic hypotension, we have recently reported hypertension in 22% of a large veteran cohort with SCI; 68% of the cohort had BMI>23 kg/m2, supporting a relationship between hypertension and obesity in this population.[38] The prevalence of hypertension in veterans with SCI is not clearly known, but may be as high as 45% as recently reported by Lee et al in a smaller veteran cohort.[39]

6. Insulin Resistance & Dyslipidemia in SCI: Glucose intolerance has been reported in a large percentage (50-67%) of SCI patients and is characterized by hyperinsulinemia in response to a glucose challenge for this population. Petry et al found that glycosylated hemoglobin (HbA1c) levels above 6.0 in SCI patients significantly correlated with impaired glucose tolerance or frank diabetes, and recommended routine HbA1c screening for patients with SCI.[40] Aksnes et al noted an association between whole body insulin-mediated glucose uptake and skeletal muscle mass in tetraplegics, suggesting loss of muscle mass as the primary reason for insulin insensitivity. The hyperinsulinemia in these patients may therefore be related to body composition changes as has been reported in the general population.[41,42] Bauman & Spungen reported that 62% of quadriplegics with a mean duration of injury of 17 years had abnormal glucose tolerance tests, as compared to only 18% of age-matched controls with similar body mass index (BMI).[43] That same study failed to demonstrate a significant correlation between insulin resistance and body composition, although body composition was estimated using DXA, and not 4-compartment modeling, now considered the gold standard. Finally, Dearwater et al (1986) compared SCI sedentary controls with SCI athletes and found no significant differences in fasting glucose or insulin concentrations but did not conduct glucose tolerance tests.[44]

Persons with SCI have similar total cholesterol levels, but significantly lower HDL-c when compared to able-bodied controls(42±7.9 vs.47±6.7 mg/dl), particularly noticeable in the male population (39±8.3 vs. 45±7.0).[47] Bauman and Spungen recently reported HDL-c in 224 veterans with SCI; 63% had HDL-c < 40 mg/dl, 44% had HDL-c <35 mg/dl, and 19% had HDL-c <30 mg/dl.[45] Several studies have also demonstrated the inverse relationship between elevated C - reactive protein (CRP) and HDL-c in persons with SCI.[13,15,46] As seen in the able-bodied population, there appears to be a direct

relationship between physical activity and HDL-c in persons with SCI.[47–49] Maki et al noted reduced HDL-c was significantly correlated with abdominal adiposity in 46 men with SCI as measured by waist circumference, although correlation with visceral fat imaging was not performed.[50] Similar findings have recently been reported in additional SCI cohorts.[13,15] Few training interventions have actually been examined for changes in cholesterol profiles in the population with SCI, however. A few studies have demonstrated no significant improvement in lipid profiles following 10-16 weeks of aerobic upper extremity exercise in persons with SCI. Few training interventions have actually been examined for changes in cholesterol profiles in the population with SCI, however. A few studies have demonstrated no significant improvement in lipid profiles following 10-16 weeks of aerobic upper extremity exercise in persons with SCI.[51,52] However, Hooker & Wells(1989) demonstrated improved cholesterol profiles(TC/HDL-c from 5.0 to 4.0, HDL from 39 to 47 mg%) in SCI patients who had completed 8 weeks of moderate upper extremity exercise training.[53]

7. Exercise on Insulin Sensitivity: Aerobic exercise has been shown to improve glucose tolerance and reduce insulin resistance in the able-bodied.[54–56] Dengel et al examined the effects of moderate aerobic exercise three times weekly for 6 months on obese sedentary men, and found oral glucose tolerance significantly improved, and glucose disposal rate increased by 22% as determined by the hyperinsulinemic euglycemic clamp.[54] A previous study by Dengel's group (1996) investigating the combination of aerobic exercise and caloric restriction for weight loss found similar improvements in glucose tolerance and glucose disposal rates.[55] A significant correlation was noted between area under the glucose curve and change in percent body fat. A large, multicenter, multicultural epidemiological trial examined the relationship between physical activity and insulin as determined by the frequently sampled intravenous glucose tolerance test (IVGTT) developed by Bergman.[57] and found that while higher intensity physical activity improved insulin sensitivity to a greater extent, even low levels of activity were related to improved insulin sensitivity in this population of normal to mild non-insulin-dependent diabetes mellitus.[56] Similarly, Smutock et al reported improved glucose tolerance and reduced insulin AUC during oral glucose tolerance tests following 20 weeks of moderate aerobic exercise consisting of treadmill walking and/or jogging when compared to controls.[58]

8. Functional Electrical Stimulation for SCI: Computerized functional electrical stimulation (FES) has been developed as a neuromuscular aid to restore purposeful movement of limbs paralyzed by upper motor neuron lesions. In use for over 40 years, it has been refined with sophisticated computer technology to be used as an exercise enhancement tool for patients with spinal cord injury. Phillips in 1987 proposed medical guidelines for patient participation in FES rehabilitation, including medical criteria for inclusion and exclusion.[59] Briefly, FES of the lower extremities can be used to stimulate

strength[60–62] and endurance,[53,60,61] and has the potential to improve energy expenditure, increase stroke volume,[63,64] increase total body peak power output (PO_{Peak}), VO_{2Peak} and ventilatory rate,[53,65,66] reverse myocardial disuse atrophy,[70] increase HDL levels and improve body composition,[67,68] and possibly increase lower extremity bone mineral density.[68,69]

9. FES on Insulin Sensitivity and Bone Mineral Density: Atrophied lean body mass, particularly skeletal muscle, is not as metabolically active in SCI compared to able-bodied individuals. A few recent studies have evaluated the effect of lower extremity functional electrical stimulation (FES) on glucose tolerance and insulin sensitivity in SCI. One year of FES performed 3 days per week for 30 minutes sessions resulted in a 25% increase in insulin sensitivity, as assessed by a hyperinsulinemic, euglycemic clamp, in ten subjects with a SCI in the cervical or thoracic region.[70] Similarly, eight weeks of daily lower extremity FES resulted in 33% improvement in insulin sensitivity for 5 men with cervical spinal cord injury.[64] Euglycemic, hyperinsulinemic clamps were performed 48 hours after a single exercise bout to determine if a single bout of moderate intensity exercise would alter tissue sensitivity to insulin in SCI. With low statistical power, results showed no change in insulin sensitivity with the SCI or controls in response to the single exercise bout. Both groups were insulin sensitive, however, and the SCI group was active at the onset of the study, so it is not surprising that neither group responded to the exercise stimulus with augmented capacity for glucose disposal following a single exercise bout. Atrophied lean body mass, particularly skeletal muscle, is not as metabolically active in SCI compared to able-bodied individuals.

10. SCI Dietary Guidelines: There is a paucity of information about dietary interventions for SCI, particularly motor complete high paraplegia and tetraplegia. The few studies that have been performed have demonstrated relatively high caloric consumption (though significantly lower than for non-SCI), poor nutrient density and relatively high BMI.[76-81] BMR or TDEE are rarely reported, and dietary adjustments have previously been based on estimates of energy expenditures done more than a decade ago.[82, 83] Although the American Dietetic Association (ADA) recently provided dietary guidelines for persons with SCI, they are relatively broad and note that best practices would include indirect calorimetry to estimate true caloric needs.[84] Lieberman et al (2014) has tried to characterize dietary intake for persons with SCI, and his findings indicated mean caloric intake of >2600 kcal/d without reference to energy expenditure or body composition.[85] A recent 7-month randomized, controlled trial (Online: ahead of print) demonstrated no improvement in lipid profiles or weight loss in persons with SCI provided nutritional education alone, without regard to true energy expenditure or body composition.[86] Our three recent manuscripts have provided more detail for managing diet in SCI, including the need for indirect calorimetry and body composition monitoring.[87-89]

3.2 Previous Data

1. Body Composition & Energy Expenditure: A preliminary investigation in our laboratory has demonstrated the accuracy of using DXA as a proxy for 4-compartment modeling (Heymsfeld, 1990) to assess body composition in SCI adults.[26] In comparing body composition analyses techniques in 72 individuals with SCI, we recently found Total Error to be 4.8% with Dual X-ray Absorptiometry, 5.7% with hydrodensitometry, 16.0% with bioelectrical impedance analysis), and 6.2% with standard skinfold equations when compared to 4-compartment modeling, the currently accepted gold standard for body composition assessment. We also participated in a multisite trial to develop a compendium of physical activity energy expenditures for SCI, and provided significant data demonstrating reduced energy expenditure at rest and during activities when compared to AB literature.[90]

2. Prevalence of Metabolic Syndrome in Persons with SCI. We have previously reported on the incidence of obesity and hypertension in a large cohort (n=7959) of veterans with SCI in which 53% had BMI>25, and a surprising 22% had clinically significant hypertension.[27] Additionally, we conducted a nationwide survey that demonstrated diabetes prevalence is greater among veterans with an SCI/D compared with the civilian population, but similar to that of other veterans, although it may occur at a younger age in those with an SCI/D.[40] Our lab previously reported retrospective data on 477 veterans with SCI screened for metabolic syndrome using the International Diabetes criteria previously reported. Within the sample, 56.5% had BMI > 25 kg/m2 , 63.4% had HDL-c < 40 mg/dl, 48.7% had fasting blood glucose > 100 mg/dl, 56.5% had hypertension, and 44.8% met criteria as having the metabolic syndrome.[91] We have recently reviewed an expanded data set of the same variables and have a manuscript in preparation with similar results.

3. Fat Mass & Glucose Tolerance: Previous work in our laboratory demonstrated a strong relationship ($r=0.67$, $p<0.001$) between body composition and glucose area under the curve following OGTT in SCI subjects at all levels of injury. Glucose AUC was more strongly correlated ($r=0.86$, $p<0.001$) with %BF in those persons with T6-L2 SC. Additional work in our laboratory (Figure 1) has demonstrated significant relationships between visceral adipose tissue (VAT) and plasma glucose levels.[92, 93] Although relationships were also demonstrated for subcutaneous abdominal adipose tissue (SAT) and plasma glucose, these were not significant. Plasma insulin was somewhat variable presumably due to the nature and longevity of the person's glucose intolerance; those with acute glucose impairments were more likely to have hyperinsulinemia. For Individuals with SCI, increases in VAT, SAT, or VAT/SAT ratio are associated with an adverse metabolic profile, manifested by impaired glucose tolerance, insulin resistance, and dyslipidemia. [92, 93]

4. OGTT & Level of SCI. In 20 non-diabetic SCI subjects tested before exercise intervention, mean % Body Fat determined by 4-compartment modeling was 35.9 ± 6.7,

whereas %BF for able-bodied (AB) adults generally ranges from 12-25%. Further, Glucose AUC during 3-hour OGTT was significantly elevated in C7- T5 (965 ± 102 mg%•min) and T6-L2 SCI (723 ± 52) compared to non-diabetic AB adults (679 ± 18), and significantly different from each other ($P<0.05$); see figure 2. Of note, the glucose:insulin AUC ratio, a gross measure of insulin sensitivity, appeared elevated in our SCI subjects compared to AB adults (3.68 ± 3.02 vs1.41 ± 0.89), although not significantly so.

5. Intravenous Glucose Tolerance Test (IVGTT). Dr. Gater learned the IVGTT procedure during his VHA and NIH Career Development Awards and has been proficient performing IVGTTs for over 18 years. Dr. Gater has supervised over 150 IVGTTs in the past 4 years, and the U Miami CTSI CRC staff routinely performs IVGTTs for several of the metabolic protocols being done there. Based on our recent results from FESLCE on glucose kinetics, HBFES LCE + Diet is expected to reduce % Body Fat and improve insulin sensitivity and glucose effectiveness during intravenous glucose tolerance tests.

6. Bone Mineral Density (BMD) in SCI. We've previously demonstrated a strong relationship between time since SCI and lower extremity BMD using DXA.[94] The regional bone measurements were determined using specified region of interest (ROI) analyses specified by the DXA manufacture (Lunar DPXIQ; Software version 4.3, Madison, WI). The resulting precision of the arm, leg, and trunk BMD measurements was 0.0202, 0.0128, and 0.0086 g/cm2, respectively, while % coefficient of variation of arm, leg and trunk BMD were 1.92 %, 0.86 %, and 0.86 %, respectively. Although we did not see a significant increase in BMD with our most recent FES interventional trial, it appeared that BMD remained constant or slightly increased over the 4-month intervention. We will be monitoring for similar trends in the Home-based interventional trial.

7. Novel Home Based FES (HBFES): Dr. Gater was a co-investigator on several FES trials while at the U Kentucky, U Michigan, and Virginia Commonwealth University and has authored several publications about patient selection criteria, potential complications and rate of exercise progression required for functional electrical stimulation.[95-99] He was part of a VA multi-site grant on implanted neuroprostheses for standing with the lead group at the Cleveland FES Center of Excellence, and a paper summarizing that data was recently published.[100] His group utilized FES in several protocols for paraplegia which have recently been completed and additional manuscripts are in preparation. In comparison with arm crank ergometry, paraplegic subjects assigned to the FES-LCE group demonstrated similar improvements in body composition, glucose effectiveness and insulin sensitivity. Our lab has continued to demonstrate positive body composition changes, as well as response to different FES stimulation patterns. [98, 99, 101-103]

Dr. Gater's lab recently piloted a program for VACO Prosthetics and Orthotics of rent-to-purchase RT300s for veterans in whom 90-day exercise compliance with the equipment can be documented. Patients were screened by their physicians and initial exercise trials monitored in the SCI Exercise Laboratory before sending the RT300 (Restorative Therapeutics, Inc., Baltimore, MD) to the veteran's home for the 3-month trial. Preliminary work with n=17 veterans with paraplegia over 12 months has demonstrated ease of use, ability to monitor and adjust settings by internet, and 80% successful completion by those participating. The telemedicine program has demonstrated capacity to use the VitelCare® T400 (Bosch, Vienna, VA) to monitor HR & BP during home-based exercise, and we will purchase similar systems and web cams to monitor our subjects at home. As preliminary work for the current proposal, we demonstrated improvements in several individuals with tetraplegia using HBFES 5 days/week for 1 year up to 56 months, with increased FFM and RMR, but %BF didn't decrease as expected, likely due to unmonitored dietary intake. [104, 105] Previous studies have not used persons with high SCI due to concern of autonomic dysreflexia and inability to monitor exercise in the home.

8. Novel Home Based Dietary Approach for SCI: Early in his career, Dr. Gater conducted exercise and dietary interventional studies assessing changes in body composition and glucose tolerance in able-bodied populations.[106, 107] He has utilized dietary assessments in his most recent studies, and has contributed to the sparse literature on dietary interventions for persons with SCI.[1, 5, 87-90] Of note, BMR for high SCI often falls below 1,000 Kcal/day. Dr. Gater's group recently published a review article on the role of nutrition after SCI further elucidating the need for this research, [88] and another demonstrating the relative efficacy of 24-hour dietary recall in persons with SCI. [87]

3.3 Study Rationale

Spinal cord injuries (SCI) predispose individuals to impaired fitness, obesity, glucose intolerance and insulin resistance, placing them at greater risk for diabetes and coronary artery disease. These health risks are only moderately reduced with upper extremity exercise, due to the relatively small muscle mass utilized, and upper extremity exercise has very limited potential for persons with high paraplegia or tetraplegia. Functional electrical stimulation leg cycle ergometry is likely to improve whole body composition, energy expenditure and glucose metabolism. Closely monitored diet intervention may also reduce body weight but is more likely to result in loss of lean tissue, i.e., metabolically active muscle tissue, with subsequent reductions in energy metabolism and the re-accumulation of adipose tissue. Both types of interventions have been tried in institutional settings previously, but compliance has typically been an issue due to distance and environmental barriers that prevent easy access. The purpose of this proposal is to evaluate and compare the health benefits of home-based functional

electrical stimulation leg cycle ergometry plus diet (HBFESLCE + Diet) to home-based (HB) Diet alone.

4. Inclusion and Exclusion Criteria

Inclusion criteria:

- Adults 18-65 years of age (inclusive)
- Sex: male or female
- Women of child-bearing potential who agree to refrain from getting pregnant during the trial
- C4-T4 motor complete (AIS A, B & C) spinal cord injury for duration greater than 12 months
- <5% change in body weight over the past 12 months

Exclusion criteria:

- <22% body fat
- Unresponsive to neurostimulation
- Those who have participated in a FES or ACE exercise program (>60 minutes/week) within the past 3 months
- Known orthopaedic limitations
- Coronary artery disease
- Type 1 diabetes mellitus, insulin-requiring Type 2 or untreated diabetes mellitus (fasting glucose>126 or HgbA1c>7.0)
- Uncompensated Hypothyroidism (Stable on medication >1 year or not on medication)
- Renal disease
- Uncontrolled autonomic dysreflexia, recent (within 3 months)
- Deep vein thrombosis (within the past 3 months)
- Anticoagulation therapy

- Pressure ulcers > Grade II
- Decisional impairment
- Any potential causes of autonomic dysreflexia at the discretion of the PI
- Prisoners
- Pregnant or nursing women

5. Number of Subjects

Forty (40) subjects will participate in the study; however, it may be necessary to screen up to 60 subjects to allow for those who do not meet inclusion/exclusion criteria.

Study Timelines

It is anticipated that subjects will be enrolled in the study for 21weeks.

It is anticipated that enrollment of subjects will occur between August 15, 2020 and December 31, 2024.

6. Study Endpoints

Primary Study Endpoints:

1. Body composition (%BF, FM and FFM)
2. Insulin sensitivity
3. Glucose effectiveness
4. BMR
5. Thickness of epicardial adipose tissue as measured by echocardiography
6. Volumes of subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), intramuscular fat, (IMF) as measured by CT.

Secondary Study Endpoints

1. Lipid profiles
2. Lower extremity bone mineral density
3. hsCRP in adults

4. Proinflammatory adipokines: tumor necrosis factor-α, interleukin-6, monocyte chemoattractant protein-1, plasminogen-activator inhibitor-1, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1

5. Anti-inflammatory adipokines: Adiponectin and Interleukin-10

7. Procedures Involved

Overview:

Primary outcome measures will include body composition by iDXA, CT, Echocardiography, insulin sensitivity, glucose effectiveness and BMR, while secondary outcomes will include lower extremity BMC and density, lipid profiles, hsCRP, fasting insulin, TNFα, IL-6, PAI-1, ICAM-1, VCAM-1 MCP-1,adiponectin and IL-10, Non-esterified free fatty acids determined before and after the 16-week interventions. Subjects will be randomly assigned (50% chance) to either HBFES LCE + Diet on an RT300 ergometer or Home-based (HB) Diet Alone intervention as determined by a random number generator.

Study Procedures include:

- **History and Physical Examination:** Each subject will undergo a complete history and physical examination by a physiatrist board certified in SCI medicine. This will include general demographics, past medical history, medications, family and social history, race and ethnicity. Subjects will undergo an AIS exam which is a system of tests used to define and describe the extent and severity of a patient's spinal cord injury. 28 key sensory points will be tested on each side of the body for light touch and pinprick sensations. There will also be a strength assessment of ten muscles on each side of the body. The subject will be graded based on their sensations and strength assessment. Subjects who have had a neurological physical exam with ASIA completed in the last year by a licensed physiatrist board certified, will not need a repeat exam. Women of childbearing potential will have a pregnancy test obtained.
- **ECG:** A resting 12-lead ECG will be performed on each subject to rule out any coronary artery disease.
- **Surface Neurostimulation:** The physical exam will conclude with a surface neurostimulator trial to determine muscle response to electrical stimulation at bilateral gluteus maximus, hamstrings, vastus lateralis, and vastus medialis. If there is no muscle response, the patient may not be included in the study.
- **Dobutamine Echocardiogram/Epicardial Adipose Tissue**

- **Screening Labs:** A full electrolyte panel (fasting sodium, potassium, chloride, bicarate), BUN, creatine, glucose and HgbA1c will be drawn at the Clinical Translational Research Site, 7th floor during the IVGTT.
- **Blood labs**
    - **Blood Lipids, hsCRP and inflammatory panels:** Each subject will have lipid profiles (HDL-c, LDL-c, total cholesterol, and triglycerides). hsCRP, insulin, non-esterified free fatty acids, IL-6, TNFα, MCP-1, PAI-1, ICAM-1, VCAM-1, Adiponectin, IL-10 assessed before and after the 16-week intervention. Lipids and hsCRP will be determined by standard analyses procedures employed by the CRC. Secondary variables of particular note include HDL-c, total cholesterol:HDL-c ratio and hsCRP.
    - **Genetic Testing:** A separate sample will be collected and stored for future analysis to assess genetics in relation to body composition and metabolism after spinal cord injury.

  A total of approximately 26 ml of blood (approximately 5 teaspoons) will be collected for all the aforementioned tests.
- **Body Composition:** Dual Energy X-Ray Absorptiometry (DXA): Total body and regional (lumbarspine, proximal femur, and forearm) dual-energy x-ray absorptiometry (DXA) scans will be performed using a Lunar iDXA bone densitometer at the Lynn Rehabilitation Center Physical Medicine and Rehabilitation (Lynn PM&R) Research Lab. DXA scans will be completed at screening, baseline, and at the midpoint and end of the study intervention to assess for changes in body composition. All scans will be performed and analyzed by a trained, certified DXA operator. A single trained investigator will analyze all scans. The DXA total bone mineral content measurements will be used to correct for the mineral fraction in the criterion body composition model (4-compartment model) [39]. Anthropometric measures (skinfolds, girths and circumferences) will be obtained for pilot data using a CRC adjunct proposal. Primary variables will include %BF, Absolute Fat Mass (FM), and Absolute FFM determined by DXA.
- **Weight:** Subjects will be weighed at each visit to the Lynn PM&R Research Lab.
- **Lower Extremity bone mineral density (BMD) and bone mineral content (BMC):** Lower extremity bone mineral density will be determined by dual-energy x-ray absorptiometry (DXA) using a Lunar iDXA (Lunar Inc., Madison, WI) bone densitometer at the Clinical Translational Research Site, 7th floor as described above. All scans will be performed and analyzed by a trained, certified DXA operator using the Lunar software version 13.4. A single trained investigator will analyze all scans. Secondary variables of particular note include femoral neck and proximal tibial BMD (areal density) and BMC.
- **BMR:** Subjects will have their basal metabolic rate measured by indirect calorimetry using a canopy COSMED Quark RMR gas exchange measurement

system. They will be woken early in the day before eating or drinking and lie still for 20 minutes while the measurement is in progress.

- **IVGTT:** An IVGTT will be used to determine insulin sensitivity and glucose effectiveness using standard protocols established at the University of Miami Towers: Clinical Translational Research Site, 7th floor. After a 10 to 16-hour fast, an indwelling catheter with an intravenous saline drip (0.9% NaCl) will be placed in an antecubital vein, and another intravenous line will be placed in a contralateral vein or hand vein between the hours of 0630 and 0800 to facilitate infusion of glucose and blood sampling during the IVGTT. Glucose samples will be taken at –6, -4, -2, 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes after the rapid glucose injection (0.3 gm/kg IV over 30 seconds at time zero). In addition, 20 minutes after the glucose injection a bolus of insulin (0.02 U/kg) will be injected to determine insulin sensitivity. Blood pressure and heart rate will be assessed at minutes 22, 23, and 24 of the protocol. Plasma glucose will be measured by the Autoanalyzer glucose oxidase method and plasma insulin concentrations will be determined by electrochemiluminescence (ECL). The S_i (glucose disposal rate per unit of secreted insulin per unit time) and S_G (glucose mediated glucose disposal rate) are calculated from a least-squares fitting of the temporal pattern of glucose and insulin throughout the IVGTT using the MINMOD program.[60, 104] Reproducibility studies from our group comparing entry (screening) IVGTT SI data with studies done following placebo treatment have indicated that the coefficient of variation is approximately 15% (Gater, unpublished results) The acute insulin response to IV glucose (AIRG) is calculated as the mean rise in plasma insulin above baseline at 3, 4 and 5 minutes after IV glucose administration. KG, a measure of glucose tolerance, is calculated as the least square slope of the natural log of absolute glucose concentration between 5 and 20 minutes after the glucose bolus. Primary variables will include S_I and S_G. The total amount of blood drawn during the entire study is about 1/2 pint, which is less than donating a unit (1 pint) of blood.
- **Stress Test & Energy Expenditure:** This procedure will be performed on all subjects at the UMH Echocardiography Laboratory under the supervision of Dr. Martin Bilsker. A dobutamine echocardiogram stress test will be performed prior to exercise to rule out significant cardiovascular disease and to establish peak heart rate that will be used to prescribe peak exercise intensity for the HBFES exercise intervention as per ACSM guidelines; this is a standard procedure at our SCI Center for persons desiring exercise. Before the administration of the dobutamine, epicardial adipose tissue will be measured. A post-intervention echocardiogram will also be performed to measure epicardial adipose tissue following the intervention [109]. The COSMED Quark RMR (Rome, Italy) gas

exchange measurement system will be used with canopy to determine basal metabolic rate (BMR) as described above, and exercise energy expenditure by mask indirect calorimetry during the aerobic exercise (in target heart rate zone) for exercise sessions 1, 41 and 80. BMR will be utilized to assess caloric needs for the dietary intervention proposed. Primary variables will include BMR and exercise energy expenditure.

- **Non-contrast CT images:** Abdominal/pelvic/thigh scans will be performed at UM/Sylvester Department of Radiology, these will be obtained pre and post intervention using a 128-slice multidimensional whole body scanner before and after the intervention. Prior to undergoing the scan subjects will have their lower extremities ranged and stretched as described above. Images will be attained from the xiphoid process to the superior aspect of the patella. All images will be analyzed at a separate workstation using TeraRecon iNtuition imaging software. Images are automatically segmented into adipose tissue, skeletal muscle, and bone/background based on location and then their attenuation properties, with adipose having the lowest attenuation and bone/background having the highest attenuation. A CT attenuation range of -120 to -40 Hounsfield units (HU) will be used to encompass abdominopelvic adipose tissue, -190 to -30 HU will be used for IMF, and -29 to +150 HU will be used for skeletal muscle (needed for IMF quantification).[71] Cross sectional area (CSA; cm^2) will be automatically calculated by the software by summing the pixels of the tissue and multiplying it by the pixel surface area for each adipose tissue depot, while volume (cm^3) will be computed by multiplying the CSA by the image slice thickness and inter-slice space. Visual distinction will be used to determine VAT versus SAT based on the anatomical locations of the tissues and CSA and volumes will be summed together from consecutive slices. Total VAT mass and total SAT mass (in grams) will be the product of the total volume and fat density (0.9196 g/cm^3). For the CSA of IMF, the outer perimeter of the thigh muscle group will be traced and the femur will be excluded. A bimodal graph will be used to determine pixel differences between muscle (higher attenuation) and IMF (lower attenuation). To account for muscle size, IMF CSA will be normalized to muscle CSA. Volume of IMF will be calculated as described above.

- **Exercise Training Intervention:** Within approximately two weeks of testing, subjects will be randomly assigned to either HBFES-LCE + Diet or Diet alone (Diet) group. Prior to each exercise bout, all participants will have lower extremities ranged and stretched according to a standard protocol (Appendix 5), to reduce risk of injury and to reduce spasticity and tone. The exercise protocol will include an initial accommodation period of 4 weeks, during which four 10-minute exercise bouts/day will be interspersed with 5 minutes of rest, gradually

lengthening bouts until at least continuous 40-minute sessions are tolerated. However, subjects will have the flexibility to advance through the accommodation period at their own pace, as tolerated. Exercise intensity during the remaining 12-week intervention will be set at 70% maximal heart rate (HRmax), as determined by the initial dobutamine stress test, or as close to that as tolerated / capable by the subject based on stimulation intensity and resistance (see below). Exercise training will consist of three to five, 40-67-minute sessions (200 minutes at target intensity) each week for a total of 16 weeks; 10-minute warm-up and cool-down sessions will accompany each exercise session. An intent-to-treat protocol will be employed, and thus all subjects randomized will be used in the final data analyses. FES leg cycle ergometry (LCE) training will be induced on the RT300 FES-LCE ergometer (Restorative Therapeutics, Inc., Baltimore, MD) through wires connected to silastic surface electrodes over bilateral quadriceps, hamstring and gluteal muscles. Electrodes will be placed on the skin of the following corresponding skeletal muscle groups. Quadriceps: One electrode will be placed on the skin approximately 3 finger widths above the superior aspect of the patella, and the other 4-5 finger widths from the inguinal crease. The Q-angle should be kept in mind when centering the electrodes over the quadriceps. Hamstrings: One electrode will be placed 2-3 finger widths above the popliteal fossa and the other electrode approximately 1 hand width apart but no further than 3-4 finger widths from the gluteal fold. Gluteus Maximus: Two electrodes will be placed parallel and on the bulk of the muscle belly with at least 2 finger widths between electrodes. The medial electrode will be placed approximately 2-3 finger widths from and parallel to the gluteal cleft and the lateral electrode approximately 2-3 finger widths posterior to the greater trochanter. The above are guidelines and due to anatomical differences among subjects, slight modifications may be required at the discretion of the Physical Therapist in order to achieve optimal tetanic contraction. Subjects will be provided with a pictorial instructional guide on proper electrode placement. (FES Protocol for Patient and Families Appendix 6).

In the event of an unforeseen interruption or pause in a subject's intervention due to illness or other personal reasons, the PI will manage the course of the remaining sessions at his discretion. This includes extending or restarting the intervention as appropriate with the goal of ensuring that subjects are able to experience the full intervention while also preserving data integrity**.** Accommodations to conduct the exercise sessions and other FES related activities at an alternative site (e.g., home, office, The Miami Project gym) may be made at the discretion of the PI and study team to mitigate any extreme unforeseen circumstance impacting the home-based sessions and facilitate the participation in

the protocol. The ability to make these accommodations will facilitate data collection and minimize transportation and caregiver burden for the subject.

- The RT300 FES-LCE computer sequences functional electrical stimulation impulses which induce contractions of the quadriceps, hamstrings, and gluteal muscles in an order that allows for the hip, knee, and ankle joints to combine to create the repetitive circular motion of pedaling. The RT300 has HIPAA Compliant internet connectivity that allows clinicians to follow results and make alterations to the exercise and cycle parameters remotely. Once a session is completed the performance data including time, distance, power, energy expenditure and the session parameters such as current amplitude, pulse width, current frequency, cycling speed and resistance are displayed and stored. The HIPAA compliant internet connectivity allows for the optimization of training and safety. The RT300 also allows the participant to cycle from his or her own wheelchair eliminating the need to transfer onto a cycle. Prior to starting home based FES-LCE, subjects will undergo 1-3 FES-LCE sessions in the Lynn PM&R Research Lab so that electrode application, ergometer function can be taught, and heart rate, blood pressure and possible autonomic dysreflexia symptoms could be monitored. A baseline blood pressure and heart rate reading will be obtained prior to beginning an exercise session and then every 10 minutes thereafter (for a total of three readings) while monitoring for symptoms of autonomic dysreflexia. Subjects will continue to be assessed for symptoms of autonomic dysreflexia during the session. After completion of the laboratory trial without incident, the subject will be cleared to begin home based FES-LCE. The PT and at least one other member of the research team will assist with delivery and set-up of the RT300 ergometer, cardiovascular monitoring and audiovisual teleconference equipment in the subject's home. The initial 1-2 sessions in-home will be monitored by in-person PT and/or RN, as well as by telemonitoring by research coordinator / graduate student in the lab and dietician on the CRC to ensure real-time audiovisual communication is intact. At any time during the 16-week intervention, should audiovisual monitoring equipment malfunction, telephone or Zoom communication initiated by a UM study team member) will allow for immediate home-evaluation of equipment by PT, RN and/or technicians. Study team members and participants will be protected from COVID-19 by observing standard precautions as is the practice when at the Lynn PM&R Lab. These include mask-wearing, handwashing, the use of sanitizer and/or sanitizing wipes, additionally social distancing to the extent possible. All subjects will be

asked to participate in 3-5 cycling sessions per week of 40-67 minutes for a total of 200 minutes/week in target intensity zone, plus 10-minute warm-up and 10- minute cool-down. Sessions will be monitored by the research staff via internet connection and telemedicine VitelNet and web cam (HR & BP q 10 minutes). Cycle parameters will be individualized depending on the amount of current needed to perform the cycling activity and depending on the comfort of the participants. The cycling parameter ranges will include maximum values not to exceed the following: 140 mA for current amplitude, 500 μs for pulse width, and 100 Hz for frequency. Speed will be advanced between 30 and 50 rpm with an initial resistance of 0.5 Nm. The resistance will be set on automatic so that the RT300 cycle would vary the resistance to allow the set speed. For example, if the speed is set at 40 rpm and the resistance is at 1.0 Nm, if the participant cannot sustain the set speed at that resistance, the cycling system will automatically decrease the resistance to allow the participant to maintain the selected speed. Cycling duration will be increased over the 16-week period until a goal of between 40 and 67 minutes of continuous active FES cycling was attained. Subject and home assistants will be provided training concerning the placement of electrodes and the FES-LCE procedures. Medical guidelines proposed by Phillips will be employed at all sessions. [62]

- **Dietary analyses** will be completed through a comprehensive dietary assessment (Appendix 1) and by 24-hour (Appendix 2) and 72-hour recall on the CRC (Food Frequency Questionnaire) (Appendix 3) analyzed by NDS-R software, with immediate feedback provided by a registered dietician. An individualized, detailed dietary plan consistent with My Healthy Plate Dietary Guidelines of America (http://www.choosemyplate.gov/) (Appendix 4)will be used based on estimated caloric needs determined by indirect calorimetry (BMR) as described above; daily multivitamins will recommended for all subjects and additional supplements, e.g. Vitamin D will be prescribed as necessary to ensure a homogenous sample. Both groups (HBFES LCE + Diet and Diet alone) will receive daily (M-F) electronic dietary education, assessments and consultation via trained Nutrition Coaches using the MyFitnessPal dietary app, as well as weekly dietary assessments and consultation done with the Nutrition Coaches and RD via audiovisual teleconference. For the HBFES LCE + Diet group and the Diet alone group, once weekly dietary sessions will occur on a mutually agreed upon time over teleconference. In the event of a technical malfunction, telephone or Zoom communication will be used as an alternate method of communication. Zoom will be initiated by a UM study team member. The HBFES LCE + Diet group will

have diet modified based on their energy expenditure during their exercise sessions. Diet modifications in both groups will be individualized to ensure appropriate nutrient/vitamin density and 200 Kcal/day energy deficit to yield ~1/2 pound fat loss per week, i.e., ~ 8 lb. fat loss over the 4- month study, in accord with the PI's previous work.[87, 90] Throughout the study, all subjects will be informed of high quality proteins and instructed on the importance of including protein throughout the day (at each meal). In addition to daily electronic and weekly telemedicine caloric and nutrient counseling (both groups), the Nutrition Coaches and registered dietician will provide health tips from the "choose my plate" website (Appendix 4) and individualize the subject's diet for the desired weight loss.

- Methods: Each subject will undergo a complete physical examination by a physiatrist board certified in SCI medicine, with 12-lead resting ECG and dobutamine echocardiogram stress test (reviewed by the cardiologist) and comprehensive dietary assessment prior to participation. Echocardiograms (transthoracic two-dimensional guided M-mode) will be performed by standard techniques with subjects in the left lateral decubitus position. The thickness of EAT will be measured perpendicular to the free wall of the right ventricle at the end of systole in three cardiac cycles using parasternal long-axis or short-axis view. Echocardiographically, EAT is identified as the echo lucent (echo-free) space between the superficial/external wall of the myocardium and the visceral layer of the serous pericardium. Measurement of EAT on right ventricle was chosen for two reasons: 1) this point is recognized as the greatest absolute epicardial fat layer thickness, and 2) parasternal long-and short-axis views allow the most accurate measurement of epicardial adipose tissue on the right ventricle with optimal cursor beam orientation in each view. The baseline measurement of EAT will precede the dobutamine stress echocardiogram. The physical examination by Dr. Gater will conclude with a surface neurostimulator trial to determine muscle response to electrical stimulation at bilateral gluteus maximus, vastus lateralis, and vastus medialis. During this visit, participants will also be screened for total body fat percentage by DXA. Screening labs will be obtained including fasting sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose and HgbA1c. Within approximately, two weeks, depending on subjects' availability, eligible participants will return to the University of Miami medical campus. This visit will include the remaining DXA scans for estimation of body composition. After DXA completion, participants will be escorted to the UM Towers: Clinical Translational Research Site (CTRS), 7th floor and will be asked to remain in the CTRS overnight. At 6 am the following morning, the subject will be gently awakened for determination of basal metabolic rate (BMR) by indirect calorimetry using a canopy COSMED Quark RMR (Rome, Italy) gas exchange

measurement system for 20 minutes. The 3-hour intravenous glucose tolerance test (IVGTT) will be completed between the hours of approximately 7 and 11am. Once assigned to an intervention group, HBFES LCE + Diet subjects will begin monitored exercise (4-week initial accommodation described below), proceeding with a target heart rate @ 70% HRMax for 40 minutes, 5 times weekly for 16 weeks. Energy expenditure for exercise sessions 1, 41 and 80 will be determined using by indirect calorimetry using a COSMED Quark RMR (Rome, Italy) gas exchange measurement system. Post-testing will ensure within approximately 1 week of the last exercise bout, to optimize IVGTT responses. Both groups will receive daily (M-F) electronic dietary education, assessments and consultation via Nutrition Coaches, as well as via audiovisual remote teleconference weekly to maintain a daily 200 Kcal/d energy deficit.

Screening Visit (Week 1)

The screening visit will take place Lynn PM&R Research Lab. Potential participants will be encouraged to ask questions, thoroughly review the consent document and discuss the decision to participate with their family and caregivers. An additional visit will be scheduled to complete the screening procedures in the event the potential participant does not consent at the initial visit.

After obtaining written consent, subjects will undergo the following procedures:

- History and Physical Examination
- An ASIA exam for those who may not have had one within the last year
- Surface Neurostimulation
- Total body scan by DXA to determine total body fat percentage
- ECG & Dobutamine Stress Echocardiogram
- Pregnancy test for women of childbearing potential

The aforementioned procedures will be completed at the Lynn PM&R Research Lab. The dobutamine echocardiogram/epicardial fat and adipose tissue measurements will be performed at the UHealth Tower. The dobutamine stress echocardiogram is intended to rule out any significant cardiovascular disease and to establish peak heart rate that will be used to prescribe peak exercise intensity for the HBFES-LCE exercise intervention.

The Screening Visit and procedures are expected to take approximately 3 hours to complete and can be arranged at the subject's convenience.

Baseline Assessment (Weeks 2-3)

Once the subject has completed the screening visit and their eligibility for continued participation has been confirmed, they will be asked to return for a baseline assessment. At this visit, subjects will undergo the following procedures:

- Anthropometric measures performed at Lynn PM&R Research Lab)
- Remaining DXA scans (performed at Lynn PM&R Research Lab)
- CT (Abdomen/pelvis/thigh performed at UM/Sylvester Department of Radiology)
- BMR (following an overnight stay at CTRS)
    - A registered nurse will be available to stay with the subject during the overnight stay. A family member or caretaker will also be allowed to stay overnight.
- IVGTT (performed at CTRS)
  A full electrolyte panel will be obtained (fasting sodium, potassium, chloride, bicarbonate), BUN, creatine, glucose and HgbA1c (performed at CTRS). Blood Lipids, hsCRP insulin, non-esterified free fatty acids, IL-6, TNFα, MCP-1, PAI-1, ICAM-1, VCAM-1, adiponectin, IL-10 and a separate blood sample for genetic analysis (performed at CTRS) will also be obtained. This process is expected to take approximately 18 hours to complete and will require an overnight stay at the CTRS. This visit can be arranged at the subject's convenience but must be scheduled within 2 weeks of the Screening Visit.
- COVID-19 PCR testing with a negative result within 48 of admission to CTRS for subjects and their caregiver if applicable

Randomization

Directly after the baseline visit subjects will be randomly assigned to the HBFES LCE + Diet or Diet alone intervention groups using a random number generator.

Exercise Trial and Mask Indirect Calorimetry Session 1: (Week 4)
HBFES LCE + Diet subjects will undergo at least 1 FES-LCE session in the Lynn PM&R Research Lab this week so that heart rate, blood pressure and possible autonomic dysreflexia symptoms can be monitored. Subjects' energy expenditure during aerobic exercise will be measured at this time by mask indirect calorimetry. This assessment represents Session 1 of the intervention. If another session is required, the subject will return within 5 days to perform another FESLCE session. After completion of the laboratory trial without incident, the subject will be cleared to begin home based FES-LCE.

Accommodation Period (Weeks 5-8)
The FES-LCE subjects will have an accommodation period of 4 weeks, during which four 10-minute exercise bouts/day will be interspersed with 5 minutes of rest, gradually

lengthening bouts until at least continuous 40-minute sessions are tolerated. Both groups (HBFES LCE + Diet and Diet alone) will have weekly dietary assessments and consultation done with the RD via teleconference. For both groups, these weekly sessions will occur at a mutally agreed upon time.

Mask Indirect Calorimetry Sessions 21, 41 and 61 (Subject-Specific)
Exercise energy expenditure by mask indirect calorimetry during aerobic exercise will be measured additionally at Sessions 21, 41and 61 of the intervention. We anticipate the timing of these assessments will be subject-specific depending on the frequency of the weekly exercise routine established by each subject. They will occur at varying timepoints during the intervention as subjects work through their weekly exercise sessions. For example, subjects who maintain a 5-day/week schedule, exercise session 41 will occur at about week 8 of the intervention. For those who exercise on a 3-day/week schedule, session 41 will occur later in the intervention at about week 13. Subjects will return to the Lynn PM&R Research Lab for this assessment.

Exercise Intervention & Mask Indirect Calorimetry Session 80 (Weeks 9-20)
For the following 12 weeks the HBFES LCE + Diet subjects will exercise 3-5 times each week in order to achieve 200 minutes at target intensity. Both intervention groups will continue to meet with the RD via teleconference once per week. For both groups, these weekly sessions will occur at a mutually agreed upon time. Session 80 represents the conclusion of the exercise intervention and the timing of the final assessment of energy expenditure during aerobic exercise by mask indirect calorimetry. Subjects will perform their final FES-LCE session for this assessment at the Lynn PM&R Research Lab.

End of Study Assessment (Week 21)
All subjects will return to the Lynn PM&R Research Lab and CTRS within 1 week of study completion. At this visit subjects will repeat the same procedures they did during the baseline assessment:

- Anthropometric measures (performed at Lynn PM&R Research Lab)
- DXA (performed at Lynn PM&R Research Lab)
- BMR (overnight stay at CTRS) A registered nurse will be required to stay with the subject during the overnight stay. A family member or caretaker will also be allowed to stay overnight.
- IVGTT (performed at CTRS after overnight stay)
- Blood Lipids, hs-CRP, insulin, non-esterified free fatty acids, IL-6, TNFα, MCP-1, PAI-1, ICAM-1, VCAM-1, adiponectin, IL-10 (performed at CTRS)
- Echocardiogram (non-dobutamine, performed at UMH Echocardiography Laboratory)

- CT imaging - Abdomen/Pelvis/Thigh (performed at UM/Sylvester Department of Radiology)
- COVID-19 PCR testing with a negative result within 48 of admission to CTRS for subjects and their caregiver if applicable

The End of Study Assessment is expected to take approximately 18 hours to complete and will require an overnight stay at the CTRS.

Subjects who were randomized to the Diet only cohort will be offered an opportunity to experience HBFES LCE by enrolling in the TEAM-SCI protocol #20220652 once they have completed their participation in SCIENCE.

9) Data and Specimen Banking

Genetic Testing

As part of our baseline blood collection during the overnight stay at the CTRS, we will also obtain a sample for genetic testing. Subjects' samples will be stored indefinitely for future analysis to assess genetics in relation to body composition and metabolism after spinal cord injury. Samples will be labeled via a deidentified mechanism but linked to the subject by a unique study ID that will be assigned to them when they enter the study. The link to each subject's identity and/or other identifiable information will be maintained separately from the research data.

The data will be kept at the Lynn PM&R Research Lab 3rd Floor located at 1611 NW 12th Avenue Miami, FL 33136. The blood samples for genetic testing will be kept frozen at the Biomarker and Immunoassay Laboratory located at the Diabetes Research Institute, 1450 NW 10th Avenue, Room 3033 Miami, FL. 33136. Extracted samples will be analyzed at the Hussman Institute for Human Genomics (HIHG) Biorepository, 1501 NW 10th Avenue Biomedical Research Building (BRB) Room 448 Miami, FL. 33136.

Subjects may be contacted to inform them of their results.

10) Data Management

Sample size determination

Sample size estimates were determined for the primary variables most important to the investigation, notably % Body Fat and the Insulin Sensitivity Index (SI) determined using Bergman's Minimal Model to interpret IVGTT data. For the purpose of statistical analyses, we will assume a dropout rate of 15%, although we are optimistic that persons participating in the project will actually demonstrate a better compliance rate than usual, due to the Home-Based interventions. Sample size consideration for % Body Fat (%BF) as determined by DXA was based upon body composition changes noted by Bauman et al (1994) in response to a 12-week FES leg ergometry training. % BF (Mean± SE) decreased from 31.8± 2.3 to 28.5± 2.4 for the 12 subjects monitored. Assuming a similar

change in the %BF for our HBFES LCE + Diet group and a minimal change in %BF of -0.06 for our Diet alone group, with an $\alpha = 0.05$ significance level using a Mixed Linear Model (MLM) to fit a Repeated Measures ANOVA (RMANOVA) with one between subjects factor (Group), one within subjects factor (Time) and the interaction between Group and Time and assuming both a correlation of 0.70 between the Pre and Post measurements and a correlation of 0.50 between the Pre and Post measurements. In addition, simulations were performed with the variance seen in the pilot data as well as with this variance doubled; these results are presented in Table 3. In all scenarios considered a sample size of 20 subjects per group would provide over 80% power to detect a significant Group by Time interaction. Even if 5 subjects dropped out we would still have over 80% power to detect a significant Group by Time interaction in all but one scenario.

Power Calculation for BF%				
$\alpha = 0.05$	Var(Pre)=Var(Post)=6.250		Var(Pre)=Var(Post)=12.500	
Sample Size	Empirical Power ρ=0.70	Empirical Power ρ=0.50	Empirical Power ρ=0.70	Empirical Power ρ=0.50
n=10 per group	95%	80%	76%	53%
n=15 per group	99%	95%	86%	67%
n=20 per group	100%	97%	95%	80%

The sample size consideration for IVGTT was based on group comparisons of changes in mean response levels of insulin sensitivity to exercise between the spinal cord injury group and the able-bodied group noted within our institution in response to an exercise regime in 13 subjects with spinal cord injury. Differential equations are employed to describe glucose kinetics (assuming a single compartment model for glucose distribution) and insulin effects (assuming a separate compartment, remote from plasma) using insulin and glucose concentrations determined during the IVGTT. The resulting information provides a good estimate of glucose effectiveness, i.e., the effect of glucose at basal insulin to enhance glucose disposal, and insulin sensitivity, i.e., whole body responsiveness to an insulin challenge.[145] In these 13 subjects insulin sensitivity increased 8.24 μU/ml with a calculated standard deviation of change of 19.74 μU/ml. A large part of both the mean chance and the variability in the 13 observed patients was attributable to two extreme responders. To be conservative we assumed both a “large” change in insulin sensitivity of 3.2 μU/ml and a “small” change of 1.6 μU/ml and a “large” standard deviation of 6 μU/ml and a small standard deviation of 3 μU/ml. Using a linear regression model to predict the change scores (post-score minus pre-score) with one between subjects factor (Group) and assuming both a correlation of 0.70 between the Pre and Post measurements and a correlation of 0.50 between the Pre and Post measurements and assuming both a correlation of 0.70 between the Pre and Post

measurements and a correlation of 0.50 between the Pre and Post measurements. The results of the power calculations based on the simulation is shown in table 4 (next page). In all but the most extreme scenarios considered (small mean change, large variance or low correlation) a sample size of 20 subjects per group would provide over 80% power to detect a significant Group by Time interaction. Even if 5 subjects dropped out we would still have over 80% power to detect a significant Group by Time interaction in all but the three extreme scenarios noted.

Statistical methods

Forty subjects will be randomly assigned to either HBFES LCE + Diet or Diet alone. All tests will be two-sided at the $\alpha = .05$ level of significance. Effects will be reported with a point estimate and 95% confidence intervals in addition to p-values. We will examine the distributions of all measures and identify possible outliers. Dependent variables that are found to be non-normally distributed will be transformed to more closely approximate normality before analysis. Outliers will be thoroughly checked for collection or data entry errors before being used in the analysis. A linear regression model will be used to fit a model to assess the effects of exercise training (independent variable) on the change scores (post-score minus pre-score) for body composition, insulin sensitivity, glucose effectiveness, serum lipids and lower extremity bone mineral density (dependent variables). The linear regression model will have one between subjects (independent) factor, Group (HBFES LCE + Diet or Diet alone). While this model is exactly the same as a two-sample t-test for the change scores it allows for the adjustment of other explanatory variables that might have an impact on the dependent variable (i.e. age, time since injury, etc.). While we anticipate that randomization will balance out the groups with respect to covariates that may have an impact on dependent variables, if this is not the case the linear regression model for the change scores will allow for the inclusion of these covariates to adjust for the Group predictor variable, which are the real variables of interest in the study. Specific variables for body composition will include per cent and absolute BF, as well as per cent and absolute FFM mass, as determined by 4-compartment modeling. Insulin sensitivity (SI), glucose effectiveness (SG) will be the primary variables assessed from the IVGTT, and BMR will be assessed as a primary variable. Specific variables for serum lipids will include total cholesterol, HDL-C, LDL-c, triglycerides; hsCRP will be measured separately. Areal density (BMD) and bone mineral content (BMC) will also be considered secondary variables of interest.

Power calculations for Insulin Sensitivity (Si)				
Mean Diff(T2-T1) Group 1=0.0, Group 2=3.2				
$\alpha = 0.05$	Var(Time1)=Var(Time 2)=3.00		Var(Time1)=Var(Time 2)=6.00	
Sample Size	Empirical Power ρ=0.70	Empirical Power ρ=0.50	Empirical Power ρ=0.70	Empirical Power ρ=0.50
n=10 per group	99%	98%	95%	79%

n=15 per group	100%	100%	99%	90%
n=20 per group	100%	100%	100%	97%
Mean Diff(T2-T1) Group 1=0.0, Group 2=1.6				
α = 0.05	**Var(Time1)=Var(Time 2)=3.00**		**Var(Time1)=Var(Time 2)=6.00**	
Sample Size	**Empirical Power ρ=0.70**	**Empirical Power ρ=0.50**	**Empirical Power ρ=0.70**	**Empirical Power ρ=0.50**
n=10 per group	72%	49%	45%	31%
n=15 per group	88%	68%	57%	40%

All primary and secondary outcomes will be visually assessed (boxplots, histograms, etc.) for normality and/or continuous data will be examined with a Shapiro-Wilk test. We will use a 2-way (group x time) mixed-model analysis of variance (ANOVA) to assess group interaction. Where significant interaction effects are observed, paired and independent t-tests will be used to determine significant differences within and between groups. Alpha will be set at < 5%.

11) Provisions to Monitor the Data to Ensure the Safety of Subjects

Please refer to the attached document DSMB 0719

12) Withdrawal of Subjects

12.1 Criteria for removal from study

Subjects will be removed from the study for the following reasons:

- Withdrawn Consent
- Non-compliance with study requirements
- Recurrent Autonomic Dysreflexia

12.2 Follow-up for withdrawn subjects

Subjects withdrawn from the study prior to the 16-week assessment will be asked to return to the lab for an End of Study visit. These subjects will be asked to complete all baseline assessments. Subjects may refuse any or all of the End of Study procedures. At a minimum, investigators will require subjects to return the exercise equipment.

Subjects who are withdrawn early will not be replaced; we anticipate an Intent-to-Treat analysis of all subjects who complete screening and are randomized.

Subjects removed from the study for adverse events or safety concerns will be followed for resolution of the event. No additional follow up of withdrawn subjects will be performed.

13) Risks to Subjects

- Venous catheter Insertion may result in localized swelling, soreness, bruising, chance of infection, bleeding, pain, lightheadedness or possible fainting.
- Insulin Sensitivity Tests may result in hypoglycemia (low blood sugar) with occasional dizziness, sweating, and nausea. Seizures, coma or death may occur, but are highly unlikely during medical monitoring.
- Dobutamine echocardiogram may cause anxiety or dizziness.
- Anthropometrics may cause discomfort or bruising.
- Basal metabolic rate determination may cause anxiety or shortness of breath.
- Functional electrical stimulation may result in a fracture of the lower extremity and cause redness and skin lesions affecting the areas of electrode placement. The severity of the lesions may range from mild skin irritation to lesions that require treatment. Adherence to the *recommended* protocol for treatment and prevention of skin lesions will be provided to subjects. This protocol is as follows:
    - During the FES session in the first few weeks we will gradually increase amplitude while keeping a narrow pulse width. Pulse width will be gradually increased thereafter.
    - After each FESLCE session participants will be instructed to 1) wash the areas with soap and warm water, 2) thoroughly dry and apply over-the-counter Neosporin or any other over-the-counter triple antibiotic ointment or cream to the affected areas, and 3) cessation of fabrifoam wraps. After each session, the research team will request photos of the skin where the electrodes are placed for a post-session skin assessment.
    - Prior to the start of the FES sessions and throughout the protocol we recommend that all participants clip their hair.
    - When lesions begin to appear, stimulation will be decreased.
- DXA scan may cause anxiety and excessive exposure to radiation
- CT Imaging may cause anxiety and some exposure to radiation
- Exercise training may cause light-headedness, shortness of breath and altered heart rate and blood pressure. Muscle soreness at the neck, upper back, shoulders, arms and hands rarely occur.
- Autonomic dysreflexia may occasionally occur during functional electrical stimulation but will be closely monitored for, and stimulation diminished or stopped if unresolved with usual measures.
- Training may also cause pressure ulcers, but close monitoring during and after sessions should prevent such wounds.
- Extreme exercise may cause fainting, heart attack or (almost never) death.

14) Potential Benefits to Subjects

Potential benefits may include weight loss, improved body composition, improved glucose tolerance and lipid profiles, and improved mobility and self-efficacy and appear to largely outweigh the potential risks listed on the previous page. This population is especially at risk for metabolic dysfunction, obesity and metabolic syndrome including glucose intolerance, dyslipidemia, hypertension and vascular inflammation.

15) Vulnerable Populations

No vulnerable populations will be recruited or enrolled in the study.

Some subjects may present with a caregiver who assists them with certain activities such as completing and signing documents. These subjects may have limited use of their upper extremities as a result of their spinal cord injury, making it difficult or impossible to sign for themselves. It is usual and customary, in this scenario for the caregiver to sign on their behalf, e.g. the informed consent form, however these subjects will not have any cognitive deficits.

16) Sharing of Results with Subjects

Overall study results are expected to be published in peer-reviewed scientific journals at the conclusion of the study.

Clinically significant research results will be shared with subjects during the course of the study. Subjects will likely be self-aware of some study findings, such as weight loss, increased muscle mass. There are no plans to share overall study findings directly with subjects.

If requested, results can be shared with a subject's PCP and a note will be put in the patient's EMR about their participation in the research study.

17) Setting

- Activities related to recruitment, consent, and some baseline data collection will occur at the University of Miami .
- Data collection and other related procedures will occur within the Department of Physical Medicine & Rehabilitation at the UM Miller School of Medicine (CTRS 7th floor) or the Lynn PM&R Research Lab.

Data storage, administrative, and data analysis activities will occur in the offices of the PI, collaborators, and study staff at the UM Miller School of Medicine Department of Physical Medicine & Rehabilitation.

18) Resources Available

As PI, Eduard Tiozzo, PhD, MSCTI, FAHA will devote 30% of his time (6 calendar months) and have primary responsibility for project implementation. He has more than 10 years of experience in clinical research trial implementation, particularly, in the role of Exercise Physiologist as it relates to exercise and nutrition interventions, and body composition assessment (DXA Certified)

As Co-Investigator, Dr. Jose Ramon Vives-Alvarado will perform history and physical and ASIA examinations, admissions and discharges, intravenous glucose tolerance tests, provide medical supervision of all subjects, , presentations and manuscript submissions. Meghan Cochrane will also assist with performing history and physical and ASIA examinations, determination of eligibility and general medical supervision of subjects.

Other co-investigators are included on the project that fulfill several roles: clinical experts in SCI, and in pain management, research experts in SCI, and in pain measurement and assessment. The study staff also includes a Clinical Research Nurse (Dinorah Rodriguez, RN, BSN, CCRC), physical therapists (Cristina Segredo Thurston, PT, DPT, NCS and Thomas Pelaez DPT, CSCS), registered dietician Alicia Sneij, PhD, MS, RDN, nutrition coaches, named in the study team section of the IBIS application, research associate one postdoctoral associate (Gary J. Farkas, PhD), and research assistants, named in the study team section of the IBIS application. All staff that will participate in conducting the study, including recruitment, data collection, data review, etc., and their associated duties, are listed within the IRB application in IBIS. Regularly-scheduled meetings will be held with all study staff in order to ensure that all are up-to-date on study procedures, training, and oversight efforts.

Financial resources for this work, including study staff effort, device procurement, subject payments, and miscellaneous supplies are provided for as appropriate via grant funding obtained by the Department of Physical Medicine and Rehabilitation.

19) Prior Approvals

N/A

20) Recruitment Methods

20.1 Identification of subjects

- Subjects will be actively recruited from the South Florida Spinal Cord Injury Model System, a database of the Department of Physical Medicine and Rehabilitation under the Directorship of Elizabeth Felix, PhD. (ePROST #20100501). Subjects will also be recruited from the Miami Project to Cure Paralysis using a telephone script. Participants enrolled in the Miami Project to Cure Paralysis database were recruited by word-of-mouth, casual contact, online advertisement on The Miami Project to Cure Paralysis website, and via phone or

email contact for those individuals who have filled out the intake form on the Miami Project to Cure Paralysis Website. The intake form contains a provision for participants to opt in to receive updates on research projects.

https://redcap.miami.edu/surveys/index.php?s=P9T87MYKH4

- Through the intake form, The Miami Project maintains a database of persons who have volunteered their participation in research studies. This is a searchable database under the management of David McMillan Director of Education and Outreach. This database contains self-reported information, such as age, date of injury, level of injury, and impairment scale score that will allow us to screen potential participants. In addition to these two sources, we are also requesting a Waiver of Authorization for pre-screening for the purpose of reviewing subjects' medical records.

- Direct response from subjects responding to the study flyer will be recruited/screened using a telephone script.

20.2 Recruitment process

Potential subjects will be contacted via phone calls, and in the clinic to provide information for participation in this research study. Flyers and ads will be posted throughout the University of Miami campus as well as on the department's website. As a result, subjects inquiring about this study may be offered participation in other PM&R studies for which they may be eligible. The Clinical Trials Search Tool will be used.

20.3 Recruitment materials

- Flyers: posted at the University of Miami hospital, websites, clinic sites and community centers.
- Telephone Script
- Clinical Trials Search Tool – https://umiamihealthresearch.org

20.4 Eligibility/screening of subjects

We anticipate most subjects will be known to us through the SCI database. Prior to consent, we will confirm with potential subjects, by review of the database or their medical chart the location and date of their SCI. All other screening assessments, physical exam, surface neurostimulation, lab tests, and body composition measurement, will be performed only after subject's written consent has been obtained

20.5 Payment

Each subject will be paid $50 for completing the Baseline Assessments, and $50 for completing the final assessment for a total of $100. In addition, we will pay subjects $25

per completed CT scan, pre and post intervention for a total of $50. If the Week 22 visit is not completed, there will be no pro-rated payments for the completion of the other visits.

21) Local Number of Subjects

We anticipate that, over the recruitment period (Aug 2019 – Dec 2022) 40 subjects will participate in the study. To allow for a percentage of subjects who will not meet inclusion/exclusion criteria, it may be necessary to screen up to 60 subjects. We will not consent more than 60 subjects without prior approval by the IRB.

22) Other Physical Medicine and Rehabilitation Research Studies

Subjects will be offered participation in other PM&R studies for which they may be eligible (as described in the recruitment process above). The possibility of dual enrollment or partial overlap of participation in more than one study is conceivable. This could result in duplication of required assessments subjects would need to complete. However, in an attempt to simplify subjects' participation, reduce the number of visits to our research lab, and mitigate testing redundancy, we may apply test results completed for one study to another in those cases.

23) Confidentiality

Check all that apply:

☒ Data obtained or created for this research will be stored on an encrypted electronic device or system owned by the University of Miami or on a cloud storage system that has been approved by the University of Miami for storage or research data.

☐ The Investigator (or research staff) will record (e.g. write down, abstract) data collected in a manner that **does not include** any indirect or direct identifiers and the recorded data **will not be linked to the individual's' identity.**

☒ The investigator (or research staff) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers of the subject. The investigator **will assign a code to each subject and link the code to the subject's identity**. The research team will maintain the link to the subject's identity on a document separate from the research data. Both documents will be stored in separate files on a University of Miami encrypted device or on a University of Miami approved cloud storage system. The research team will destroy the identifiers at the earliest opportunity.

☒ The research team will maintain the research data for at least six years.
☐ *Bio*-Specimens obtained for this research will be stored without any direct or indirect identifiers.
X *Bio*-Specimens obtained for this research will be stored in a de-identified coded manner.
X When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

Data that is collected on paper will be stored securely in a locked cabinet in a locked office that is accessible only to study staff as described in Section 23, Provisions to Protect the Privacy Interest of Subjects. Electronic data will be collected and stored on a secure server within the University of Miami network with access limited only to those personnel listed on the IRB application for this study.

24) Provisions to Protect the Privacy Interests of Subjects

For recruitment purposes, the study team physician(s) and approved staff will access information from medical records to assess eligibility for the study, therefore we are requesting a Waiver of Authorization. These source documents will be retained and the information confirming inclusion and exclusion criteria will be noted in the subject's study records/documents.

During the initial consenting procedures, a history and physical will be obtained as part of standard of care which may include questions sensitive in nature. Subjects will be ensured that they do not have to respond to all of these questions. If they are not comfortable answering, they may still participate in the study. Subjects will be reminded of this throughout assessment sessions as needed. Research staff will make every effort to provide a friendly atmosphere and assurances of privacy and confidentiality in any way possible. Paper documents for data collection will only include assigned subject ID numbers that cannot be easily linked to subject identity. A password-protected log of subject ID numbers associated with subject identity and contact information will be maintained only until all activities of the study are completed.

All study-related interviews or completion of questionnaires and assessments will be conducted in private areas where others will not be able to see or hear participant responses, and study staff will not discuss personal information with other study staff members unless they are in a private location where others cannot hear. Patients' study-related information will not be discussed or disclosed to anyone that is not a part of the research study unless indicated by law.

25) Compensation for Research-Related Injury

If you are hurt or get sick due to being in this study, treatment will be available in most cases. If you are hurt because of a correctly done study procedure the Sponsor will pay for the cost of treating the injury. The University of Miami and the sponsor are not planning to pay for pain, lost wages, and other costs you incur because you were hurt. You do not give up any of your legal rights to obtain payment for an injury if you sign this consent document. If the sponsor pays any of your medical expenses, we may be required to give the sponsor your name, date of birth, and Medicare ID or social security number.

26) Economic Burden to Subjects

The subjects will not be responsible for any costs due to participation in the research study.

27) Consent Process

26.1 Obtaining Informed Consent

- Subjects will complete the consent process at the Lois Pope Life Center, Christine Lynn Rehabilitation Hospital, or the Clinical Research Center (CRC) in a private room during a time that is convenient for them.
- Subjects will be given plenty of time to consider participation and to ask any and all questions they have. They will have the opportunity to take the consent form home and consider it further if needed. The subjects will be assured that participation is voluntary, that they may withdraw from participation at any time, and that current and future health care will not be affected by the participants' choice to participate or not.
- Waiver of Authorization is requested to review medical records for eligibility prior to the subject signing informed consent for participation.

26.2 Consent Documentation

- Written documentation of consent will be completed for each subject. For subjects who are unable to sign as a result of their spinal cord injury, verbal consent will be obtained from the subject and the consent form will be signed by the subject's legally authorized representative. The consent document will be included in this submission.

26.3 Consent – Other Considerations

- Cognitively Impaired Adults

- Capability of Providing Consent: Not Applicable
- Adults Unable to Consent: Not Applicable
- Assent of Adults Unable to Consent: Not Applicable

- Subjects who are not yet adults (infants, children, teenagers)
  - Parental Permission: Not Applicable
  - Assent of subjects who are not yet adults: Not Applicable

28) Process to Document Consent in Writing

The subject's consent to participate in this research study will be documented in writing according to standard UM IRB SOP (HRP-091).

29) Authorization for Use and Disclosure of Protected Health Information (HIPAA)

Type of Request:

☒ Waiver of Authorization for access to medical record for subject identification/recruitment.

☐ Waiver of Authorization for access to medical record to obtain data for the research.

Confirm that you will destroy or de-identify the information you collect at the earliest opportunity.

☒ ***I confirm***

Confirm that the information you collect will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

☒ ***I confirm***

30) Drugs or Devices

The devices used in this study do not require an IDE. Please refer to 9.) Procedures Involved for information about the devices and where they will be held.

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