Metabolic Syndrome and Fall Risk
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OBJECTIVES

Veterans who are overweight and meet criteria for the metabolic syndrome (MetS) represent a growing majority of the patients who are treated throughout the VA healthcare system (1, 2). While it has long been established that individuals with the MetS are at an elevated risk of developing diabetes and cardiovascular disease, it has recently been discovered that the MetS also significantly increases the risk of neuropathy (3-5). In fact, a surprising finding has been that the risk of neuropathy in the MetS may even be higher than that seen in pre-diabetes (6, 7).

There is also recently published evidence that the MetS is an independent risk factor for falls (8-11). Falls and fall prevention are important areas of research with particular impact on Veterans' health. Falls are one of the most common adverse patient events in the Veteran's Health Administration. In 2003, falls were responsible for approximately 47% of all safety reports and aggregated events within the VA National Center for Patient Safety's database (12). Falls are not only costly in terms of major injuries and healthcare dollars but can result in self imposed activity restrictions and loss of independence. **Identifying patients with the MetS who have an early neuropathy and are at a high risk for falls would be an ideal population to target with focused interventions to reduce future fall risk.**

While it is known that exercise programs successfully reduce the rate of falls and risk of falling in older community-dwelling individuals (13) to our knowledge no one has examined if an exercise program can reduce the risk of falling in patients with the MetS and autonomic neuropathy. **The proposed pilot research project is novel in that this would be the first prospective randomized study to determine if a focused balance exercise program can improve fall risk in patients with the MetS and autonomic neuropathy. Innovative measures of fall risk will also be incorporated as endpoint measures in this pilot study to determine which measurement functions best in this population and could be used in future clinical trials. It is important to the VA mission and relevant to the rehabilitative needs of Veterans in that a targeted program to reduce fall risk at its earliest stages could potentially reduce healthcare costs and improve not only the health, but quality of life of Veterans.**

OUTCOME MEASURES

FSST (primary)

The FSST is a test of proactive dynamic standing balance that clinically assesses an individual's ability to change directions while stepping and has an established cut-off score to distinguish patients at risk for multiple (≥ 2) falls. This test was chosen as the primary efficacy measure because has excellent reliability and strong correlations with other balance measures (the Step Test, the Timed Up and Go test, and the Functional Reach Test). Most importantly it has a higher combined sensitivity and specificity to identify significant differences between groups of multiple fallers, fallers, and nonfallers than any of the other three balance measures that it was compared against in community-dwelling older adults (14). **Although the FSST's sensitivity to change has not been extensively studied, we chose to include it as the primary outcome measure because one of the proposed mechanisms underlying the change that we expect to see as a result of the intervention program is an improvement in dynamic and reactive balance control with more efficient weight-shift during protective stepping.**

DGI instrumented with the GaitRite

The DGI is a validated and reliable measure of functional mobility and gait with established cut off values indicative of fall risk as well as minimal detectable change (15, 16). This measure has been shown to be useful in evaluating gait improvements as a result of interventions (17). However, there are concerns in using the DGI due to limitations including its susceptibility to ceiling effects and relatively low sensitivity to change and responsiveness in community dwelling elderly populations (18). Performing the level walking items of the DGI on the GaitRite will allow for examination of the temporospatial characteristics of gait and the finding could potentially be used to provide novel insights on individual items that may be more revealing in identifying balance and gait deficits than just a timed performance score. [Specifically, time in single or double support, step length and width and gait velocity will be examined. This is because individuals with distal symmetric peripheral neuropathy tend to have increased step width and step time variability, decreased velocity and step length and increased time in double support (19)]

ABC scale

The ABC scale was designed for older adults with higher functioning and includes a wider range of activity difficulty than other commonly used questionnaires such as the Falls Efficacy Scale (20). It is a validated scale

with excellent reliability and a sensitivity of 84%, specificity of 88% to predict falls (21) and demonstrates change with interventions (22). It also has no reported ceiling effect (23).

ActiveStep treadmill system

The ActiveStep will be used to measure the presence and number of recovery steps taken in response to a balance challenge. In contrast to the FSST and the instrumented DGI, which assess proactive balance control, the ActiveStep assesses reactive balance control. This is important to include as an outcome measure because deficits in both reactive and proactive balance control are likely to contribute to falls in this population. While the exercise intervention utilizes proactive balance training, there may be benefits to reactive balance as well.

Autonomic testing

It is hypothesized that at baseline participants with a history of falls will have a greater proportion of abnormalities on tests of cardiovagal function (30:15 ratio, valsalva ratio, E:I ratio) compared to nonfallers. This is because preliminary data suggests that there is a difference in the 30:15 ratio (cardiovagal function) between fallers and non-fallers, but this difference was not seen in measures of adrenergic function (blood pressure response to valsalva and tilt table testing). This is a highly novel aim because while an autonomic neuropathy is a recognized risk factor for falls, the exact component of the autonomic nervous system that contributes to the increased risk of falls has not been closely examined.

BACKGROUND AND SIGNIFICANCE

Obesity is an ever-growing problem throughout the world and has reached epidemic proportions in the United States and especially among Veterans. Recent data from the United States indicate that approximately 36% of adults are obese (24). The burden of obesity is especially apparent among Veterans. In fact, the prevalence of overweight and obesity among veterans was found to be higher than in the general population with two in three female veterans classified as overweight or obese and nearly three in four male veterans falling into those categories (1, 25).

Closely linked to obesity is the MetS, which is a group of risk factors; hypertension, hyperglycemia, abdominal obesity and hyperlipidemia, that occur together and increase the risk for cardiovascular disease and diabetes. The incidence of MetS is rising due to the rising rate of obesity. Over a third of the United States population meets criteria for MetS and the prevalence is approaching 50%. A pilot, computer-based screening study within the VA found that over one quarter of veterans in the Veteran Affairs Northern California Health Care System were found to have MetS and the actual percent affected is thought to be substantially higher (25). In addition to increasing the risk of developing cardiovascular disease and diabetes, it is increasingly recognized that there is an increase risk for neuropathy and falls associated with the MetS. Falls are a significant public health problem, with approximately one in three adults age 65 and older experiencing a fall each year (26, 27). Falls are the leading cause of injuries among older adults and the direct medical costs of falls in 2010 was $30 billion (28). Furthermore, many people who fall, even if they do no experience an injury, will develop a fear of falling. This fear of falling will often cause people to limit their activities and can lead to deconditioning and increase their risk of another fall.

The metabolic syndrome and peripheral neuropathy

Similar to MetS, peripheral neuropathy is also a common disease throughout the United States and especially within the VA healthcare system. Both conditions also have a rising prevalence with age. Neuropathy is a progressive, potentially disabling condition that results in neuropathic pain, sensory deficits, balance difficulties and frequent falls. There is a growing body of literature that supports the association of obesity and the metabolic syndrome with peripheral neuropathy. Due to the fact that neuropathy is a well recognized and common complication in diabetes the link between the MetS and neuropathy was first examined in patients with diabetes. The Metascreen study showed that the MetS was an independent risk factor for all complications in type 2 diabetes (3). When examining neuropathy in particular, obesity has been shown to be associated with neuropathy (29) and multiple studies have demonstrated that the presence of the MetS in patients with diabetes is associated with a higher risk of neuropathy (3, 30, 31).

The MetS is emerging as an important neuropathy risk factor. The link between MetS and neuropathy has been examined by Smith et al. who examined 219 subjects with an idiopathic neuropathy and found a surprising prevalence of MetS features, other than hyperglycemia, between patients with idiopathic neuropathy and IGT and normal glucose tolerance. They found that 86% of subjects with IGT had the MetS and 54% of subjects with normal glucose tolerance also had the MetS. Furthermore, over 80% of those with normal glucose tolerance had lipid abnormalities (6). The finding of a higher prevalence of dyslipidemia and

hypertension than IGT in the neuropathy cohort was surprising due to the fact that patients with IGT and diabetes are at a higher risk of having the MetS. The finding of similar prevalence of nonhyperglycemia MetS features between neuropathy patients with and without IGT provides further evidence that aspects of the MetS other than hyperglycemia, such as obesity and hyperlipidemia, are independent risk factors for neuropathy.

The metabolic syndrome and autonomic neuropathy

Autonomic dysfunction is a significant problem that is associated with IGT (32-35). The neuropathy associated with impaired glucose regulation (IGR), which includes IGT, impaired fasting glucose, and early type two diabetes, is a small fiber neuropathy that is often accompanied by autonomic signs and symptoms (33-35). If there is cardiovagal involvement, patients may develop resting tachycardia with failure to response to physiological demands. When orthostatic hypotension develops patients often experience considerable morbidity, which is partly due to an increased incidence of falls.

While IGT is a component of the MetS there has been little research done to characterize the autonomic dysfunction seen in patients with the MetS. This is surprising given that fact that in diabetics the risk of cardiovascular disease is known to be higher when the components of the MetS are present (36). The Steno 2 study showed that treatment of each aspect of MetS reduced the risk of both macrovascular and microvascular outcomes, including autonomic neuropathy, in patients with type 2 diabetes (37). More recently, a study of 2,092 participants from the general Chinese population found that the prevalence of cardiac autonomic neuropathy was significantly increased in patients with the MetS. They also found that MetS and resting heart rate were strongly and independently associated with cardiac autonomic neuropathy in the general population (38). A study of 1,011 elderly subjects (age 65.5 $\pm$ 0.8 years) found that those individuals with MetS had lower heart rate variability and that the severity of the MetS was associated with a decrease in the heart rate variability (38). A separate study of 180 diabetic patients found that the MetS was more strongly associated with cardiac autonomic dysfunction than isolated diabetes (39). In fact, studies have found that abnormal heart rate variability indices were present in patients with MetS before the development of diabetes (40).

Risk of falls

Falls are a major health problem and approximately one third of adults age 65 years or older report at least one fall in the past year (27). 13% of the US population is age 65 years or older and this is projected to reach 25% by the year 2025 (41). In the year 2000 fatal falls resulted in $179 million in direct medical costs and medically treated falls cost an additional $19 billion (41). Falls are associated with increased morbidity, disability, and lower quality of life. There is a well established relationship between the presence of diabetes and the risk of falling. This fall risk is multifactorial and due to the decreased sensorimotor function associated with diabetic peripheral neuropathy, musculoskeletal deficits, the presence of pain in the feet and elsewhere in the body, pharmacological complications, and other effects of diabetes. The sensorimotor deficits associated with diabetic polyneuropathy are often ascribed to the large fiber neuropathy seen in more advanced diabetes. However, at the early stages of diabetes and the MetS the neuropathy that is often seen involves the small nerve fibers that affect pain and temperature sensation and are also involved in the regulation of the autonomic nervous system. This results in not only sensorimotor dysfunction and pain in the feet and legs, but dysautonomia with a raised resting heart rate, low heart rate variability, and orthostatic hypotension.

Orthostatic hypotension is among the recognized risk factors for falls. In fact, it has been shown to be an independent risk factor for recurrent falls in elderly patients (42). Among community dwelling individuals the presence of orthostatic hypotension was found to increase the risk of falls 2.5 times in people with uncontrolled hypertension (43). The increased risk of falls in people with orthostatic hypotension may be at least partly due to changes in arterial structure and function with resulting impairment of auto-regulation of BP. Insufficient cerebral blood supply after standing or while standing or walking.

The MetS was found to be an independent risk factor for falls in a study of 1165 community-dwelling older adults (8). Similar studies of community-dwelling older adults have found that falls are associated with abdominal obesity, which is the core diagnostic criterion of the MetS (9, 10). Obesity has been shown to positively correlate with impaired postural balance, even in individuals under 40 years of age (44). More importantly, obesity, which was defined as a BMI greater than 30 kg/m^2, was found to be associated with a higher prevalence of falls in middle-aged and older adults (11). This definition of obesity (> 30 kg/m^2) is the same used by the International Diabetes Federation in definition of the MetS that states that central obesity can be assumed and waist circumference does not need to be measured (45).

Reducing risk of falls

Weekly balance training sessions have been shown to reduced fall risk in patients with diabetic peripheral neuropathy (46, 47). In a group of patients with moderate diabetes and minimal neuropathy it was found that a 12 week training program resulted in increased gait velocity, balance, muscle strength and joint mobility, and decreased fear of falling (46). The "feet first" trial prospectively observed falls after a home based strength and balance program in individuals with diabetic peripheral neuropathy. This study did not show a reduction in fall occurrence but falls were not the primary outcome, the majority of exercises were performed at home without supervision and less than half (45%) of the participants in the intervention group reported compliance with more than half of the study protocol (48). Evidence for the importance of a group or observed training program come from a study of home based vs. center based balance and strength training for community dwelling adults. This study by Comans et al. showed that the center based exercise program yielded significantly better results in terms of falls prevention (49)

However, to our knowledge there have not been any prospective randomized intervention trials to determine if the risk of falls can be reduced in patients with the MetS. Knowledge gained from this pilot project will determine how the chosen outcome measures perform as part of an intervention study in this patient population and provide information to properly power a future clinical trial.

Possible Mechanisms Underlying Expected Reduction in Fall Risk

In order to maintain balance and avoid a fall one must constantly adjust the body's position in space so that the center of mass is kept over the base of support. This represents a complex task that involves the detection and central integration of multimodality sensory inputs to then plan and execute complex motor tasks. Therefore there are multiple compensatory mechanisms, many of which respond to training, which can overcome deficits in another area of the system.

Falls often occur due to internal or external perturbations experienced by the body. Insights into the strategies used in these situations have been obtained through moving platform and waist-pull experiments and have shown that protective stepping is a commonly used and important reaction to instability that attempts to maintain balance. Impairments in protective stepping are an important contributor to fall risk (50) and a predictor of future falls among community dwelling older adults (51). However, in order for the steps to be effective they must be properly timed, directed, and executed. Older individuals tend to have longer first steps and take multiple shorter steps and falls are also associated with early first step initiation and a lower force threshold for stepping (52). These findings suggest that individuals who are at a high risk for falls are more likely to use an ineffective stepping strategy and support the theory that stepping can be a reflex-like action that is associated with a fear of falling (50). Repeat exposure to perturbations can result in learning to resist loss of balance and several studies have suggested that training programs result in a reduction in the reactive response and might be an effective fall prevention intervention (52-54). This improvement in balance and fall risk may be due to anticipatory control of stepping and enhanced central mechanisms of neuromotor control.

Lateral stability is especially important because falls to the side are frequent among older adults and can be detrimental due the risk of hip fracture. Waist-pull perturbations experiments have shown that in addition to using multiple steps, older adults are least likely to use single steps in purely lateral directions (50). In fact, measures of mediolateral postural sway have been associated with past falls (55), future risk of falls (56), and recurrent falls (57). Older people also tend to use a cross-step strategy, which is a more complex and hazardous strategy, as opposed to a side-step. This likely occurs due to the inability to shift weight and unload the leg ipsilateral to the perturbation direction due to lack of muscular strength and central processing mechanisms (52). Additional explanations for the lateral instability and falls associated with aging include a disproportional decline in hip abductor-adductor muscle strength related to age related sarcopenia (58). These changes in skeletal muscle and decreased joint flexibility are risk factors for falls. The resulting decrease in trunk mobility and hip abductor joint torque among fallers may contribute to differences in stepping performance.

The participants in the proposed study with the MetS are more likely to have sarcopenia (59, 60). Sarcopenia is a recognized contributor to functional decline and mobility loss. It has been found that intramuscular adipose tissue is an important variable related to performance on several mobility measures including the Timed Up and Go (61). It is believed that physical activity may prevent fat infiltration into skeletal muscle and exercise programs may be an effective intervention for the decline in mobility. The exercises proposed will also target distal lower extremity strength, which is expected to be declined in the MetS but required to generate adequate stabilizing torques around the ankles, and engage more proximal balance control mechanisms that are involved in counterbalance/postural movements. In addition to sarcopenia the

participants are likely to have mild sensory deficits involving dysfunction of skin mechanoreceptors. Previous studies have shown that neuropathy patients with sensory loss have widened base widths and increased gait variability (62). Exercise programs may enhance executive function and motor learning and lead to adaptations that improve balance control.

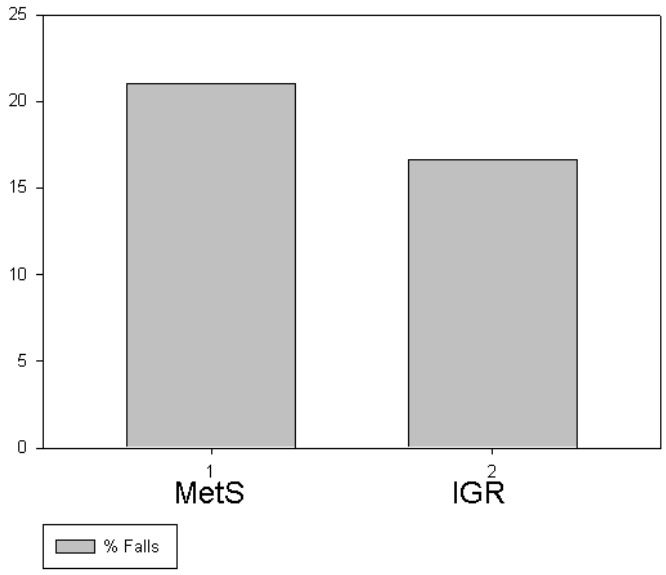
In addition the presence of autonomic neuropathy predisposes these individuals to not only orthostatic hypotension but orthostatic intolerance. In a study of patients with diabetic autonomic neuropathy orthostatic complaints, which characterize the syndrome of orthostatic intolerance, were associated with previous falls even after adjusting for orthostatic hypotension (63). Deconditioning has been shown to be present in almost all (93%) patients with orthostatic intolerance (64). Previous studies have reported improvement of orthostatic tachycardia and symptoms after implementation of a structured exercise program (65, 66). Exercise is a frequently prescribed and effective treatment for the postural orthostatic tachycardia syndrome and physical counter-maneuvers involving contraction of the proximal lower extremity muscles is an effective symptomatic treatment for orthostatic intolerance. Preliminary studies reviewed in this proposal and obtained during the CDA1 indicate that abnormalities of autonomic function and cardiovagal function in particular as measured by the 30:15 ratio, are associated with falls. The autonomic nervous system plays a key role in regulation of heart rate and blood pressure and exercise training may improve autonomic nervous system functioning (67) and therefore improve fall risk.

PRELIMINARY STUDIES

Risk of Falls is Increased in Subjects with the MetS

Pilot data from the INMED study demonstrates a difference in the proportion of subjects who reported a fall prior to enrollment into the study. Data regarding the prevalence of falls was collected for 44 participants (38 with MetS and 6 with IGR) and was found to be 20.45% (9 fallers). Eight of the subjects with MetS (21.1%) had reported a fall prior to enrolling in the INMED study compared to only one of the subjects with IGR (16.7%) (**Fig. 1**). Although this difference is not statistically significant, it does support previously published data that the MetS and abdominal obesity are independent risk factors for falls (8-10).

Fig. 1: %Falls in pts with MetS vs IGR



One published study retrospectively examined the relationship between the MetS with falls in community dwelling older adults (8). A total of 1,165 participants (54.3% women) with a mean age of 74.9 ± 6.7 years were asked about a history of falls in the preceding year. In this sample, 17.9% had experienced a fall and the prevalence of MetS was 27.3%. Compared to those who did not experience a fall, the fallers had a higher prevalence of the MetS (45.7% vs. 23.3%). After adjusting for age, gender and performance status the MetS was a significant independent risk factor for falls (OR=2.56, 95%CI 1.86-3.51).

Individual components of the MetS have also been examined as potential risk factors for falls. A study of 1,377 community dwelling older adults (mean age 74.9 ± 6.8 years, 48% women) were retrospectively asked about their fall history in the past year. In this sample 22.7% (313) had experienced a fall. There was no difference in the prevalence of diabetes between group of fallers and non-fallers. However, the fallers were found to have a larger waist circumference compared to non-fallers (88.5 ± 10.4cm vs. 86.7 ± 9.2cm respectively, p=0.004). A multivariate analysis found that waist circumference was independently correlated with falls. The adjusted odds ratio of waist circumference was 1.03 (95%CI = 1.01-1.05, p=0.003) (9).

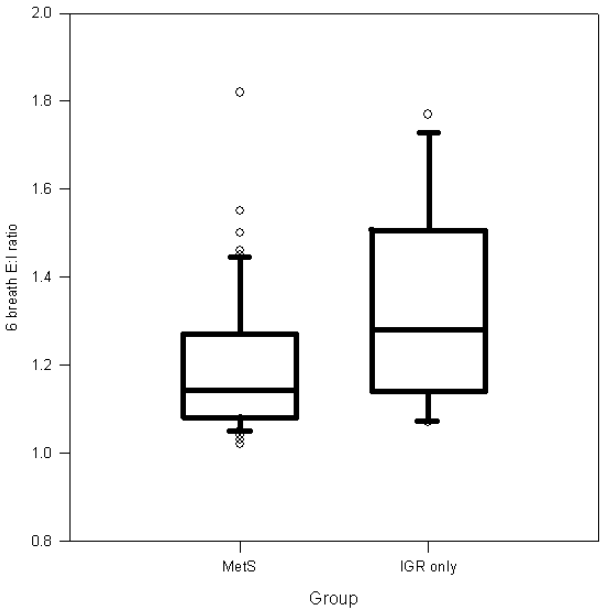
A more recent study of 671 ambulatory, community dwelling participants (mean age of 75 years) also found that increased waist circumference/central obesity is a risk factor for falls (10). Participants were retrospectively asked about falls in the previous year and 21.0% (141) reported a history of falls. In this study the majority (63.8%) of fallers were women. For fallers of both genders, central obesity was found to be associated with falls (OR=1.56, 95% CI 1.07-2.26) and multivariate logistic regression analysis found that

central obesity was a significant factor associated with falls (adjusted OR=1.67, 95% CI 1.02-2.72). Waist circumference is an essential diagnostic criterion of the MetS and supports the study by Liao et al. that MetS is a risk factor for falls.

Prevalence of Autonomic Neuropathy is Increased in Patients with the Mets

Pilot data from 61 participants enrolled in the ongoing INMED study shows a trend that supports previously published research that there is an increased incidence of autonomic neuropathy seen in patients with the MetS (39, 40, 68). In 61 participants with IGR enrolled in the INMED study the overwhelming majority of subjects; 50 (82%), meet criteria for the MetS. This preliminary data does not have enough power to detect differences between the two groups of participants but there is a trend that those with the MetS have a higher incidence of autonomic neuropathy and have lower scores of tests to evaluate autonomic neuropathy. The E:I ratio is a reproducible measure of cardiac autonomic function. In the 50 participants with MetS 41 (18%) and none (0%) of the 11 participants with IGR had an abnormal E:I ratio. The values of the E:I ratios between the two groups were different: for those with MetS the median ratio was 1.14 (mean was 1.19) and for those with IGR who did not meet criteria for the MetS the median was 1.28 (mean 1.32) (**Fig 2**).

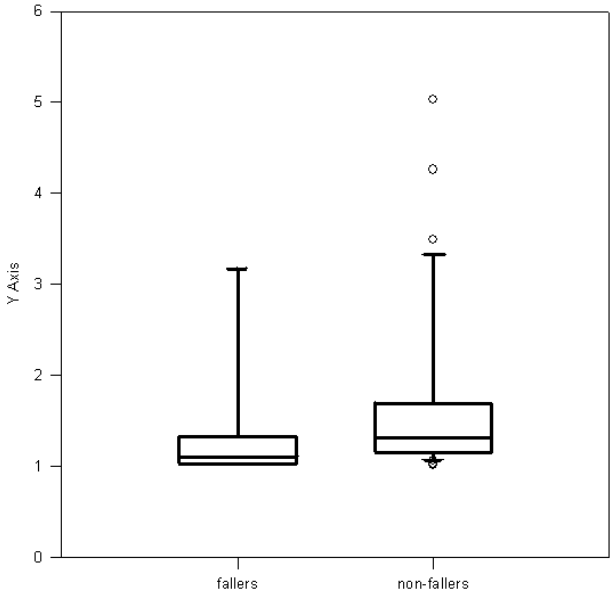
Figure 2:
E:I ratio for patients with the MetS vs those with IGR



A previously published study of 2,092 participants aged 30-80 years sampled from the general population found that the prevalence of cardiac autonomic neuropathy was significantly ($p<0.001$) increased in patients with MetS (68). The prevalence of cardiac autonomic neuropathy was 18.50% in the total sample and 14.54% in those with non-MetS and 24.49% in those with MetS. A univariate analysis found that MetS and resting heart rate are strongly and independently associated with cardiac autonomic neuropathy ($p<0.001$ for both) even after adjusting for potential confounders.

In a study of 180 patients (117 male and 63 female) with type two diabetes under the age of 55 years (mean age 46.62 $\pm$ 6.12 years) 67.8% (122/180) of participants had the MetS and 33.9% (61/180) had at least one abnormal test of cardiac autonomic function. Among the participants with abnormal cardiac autonomic testing there were 53 subjects (86.9%) with MetS and 8 subjects (13.1%) without MetS. Furthermore, in this population of diabetics the prevalence of MetS was significantly higher in the presence of impaired cardiac autonomic function (86.9%, 53 /61) compared to those with normal cardiac autonomic testing (58.0%, 69/119) ($p<0.0001$) (39). The finding that MetS was more strongly associated with cardiac autonomic dysfunction than isolated diabetes suggested that the MetS not only raises that risk of cardiovascular disease in diabetics, but it is associated with cardiac autonomic neuropathy.

Fig. 3: 30:15 ratio in fallers vs. non-fallers



Autonomic Dysfunction is Associated with Risk of Falls

9 out of 44 participants in the INMED study reported a history of at least one fall (20.45%). Between the fallers and non-fallers there was a statistically significant difference in the 30:15 max ratio ($p=0.039$). The median 30:15 ratio was 1.10 in the group of fallers and 1.16 in the group of non-fallers (**Fig. 3**). The 30:15 ratio is an assessment of the heart rate response to standing and It is a measure of cardiovagal function. It is

the ratio of the R-R interval at 30th beat after standing to the 15th beat after standing. Normally there is an increase in heart rate upon standing that is followed by relative bradycardia. In patients with cardiac autonomic neuropathy the increase in heart rate is blunted. The 30:15 ratio specifically measures sympathetic function. This may play an important role in fall risk due to the fact that sympathetic innervation is responsible for autonomic control of blood pressure. The presence of preferential sympathetic dysfunction could predispose these individuals to orthostatic hypotension, which is a risk factor for falls.

The Survey of Autonomic Symptoms (SAS) is a questionnaire designed to assess symptoms of peripheral autonomic function and determines both the number of positive symptoms as well as the frequency of the symptoms and determines scores for each (32). Of the participants in the INMED study who reported a history of falls the median SAS symptom score was 5 compared to a median score of 3.5 in those who did not report a history of falls (**Fig. 4**). The median SAS total impact score (TIS) in fallers compared to non-fallers was 14 and 9 respectively (**Fig. 5**).

Fig. 4: SAS symptom score in fallers vs non-fallers

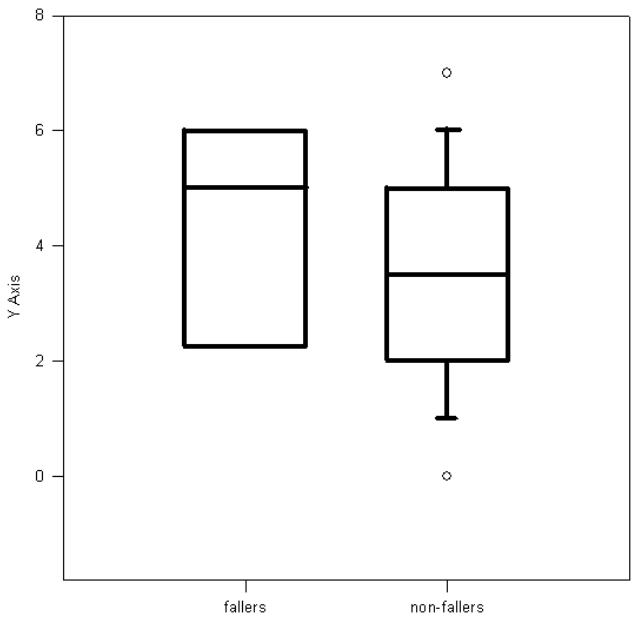
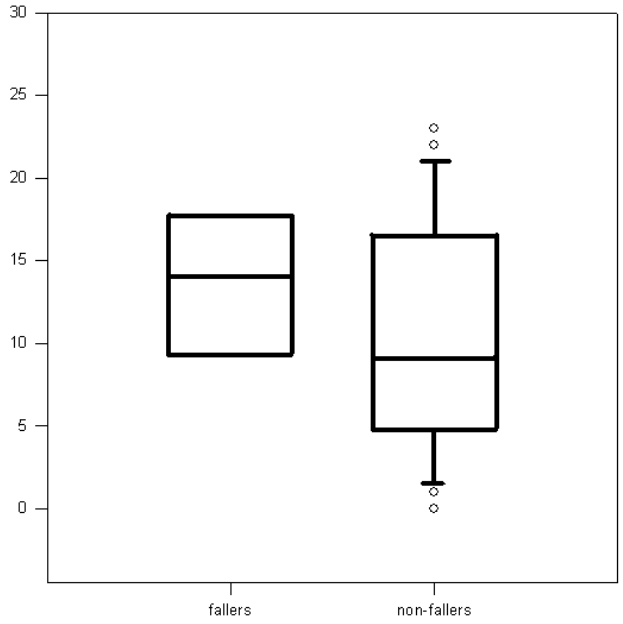


Fig. 5: SAS TIS in fallers vs. non-fallers



The aspect of autonomic neuropathy that has received the most attention with regards to fall risk is orthostatic hypotension. The decline in BP seen upon assuming an upright posture can result in decreased cerebral perfusion with impaired consciousness, dizziness, and an increased risk of falling. This theoretical relationship between orthostatic hypotension and falls has been examined and a direct association between orthostatic hypotension and future falls has been identified (69-71).

Heitterachi et al. examined 70 adults (14 men and 62 women, mean age of 76.5 $\pm$ 5.9 years) who were independent-living residents of two retirement villages and measured BP during an upright tilt. The subjects were then followed for a year to determine the incidence of falls. There were 36 participants (51%) who reported at least one fall during the one year follow-up. There was no significant difference between the heart rate response upon tilting between the fallers and non-fallers. However, they did find that the participants who fell had significantly greater decreases in systolic BP when tilted compared to those who did not fall ($p<0.05$). Immediately after the tilt the mean systolic BP of the non-fallers was unchanged compared to pre-tilt measurements (-0.5 $\pm$ 17.9 mmHg) but for the fallers it decreased (-6.3 $\pm$ 21.2 mmHg). During the three minutes after the tilt the mean systolic BP of the non-fallers rose above baseline (5.7 $\pm$ 17.6 mmHg) but that of the fallers was still reduced (-3.6 $\pm$ 16.8 mmHg). After three minutes 8 of the 36 fallers (22%) had BP decreases of at least 20 mmHg compared to only 2 of the 34 non-fallers (6%). The decrease in BP seen at three minutes represented a 70% increased risk of falling (RR=1.71, 95% CI 1.14-2.59). Interestingly, symptoms of dizziness during the tilting were uncommon and were not associated with BP or heart rate changes or the incidence of falls (70).

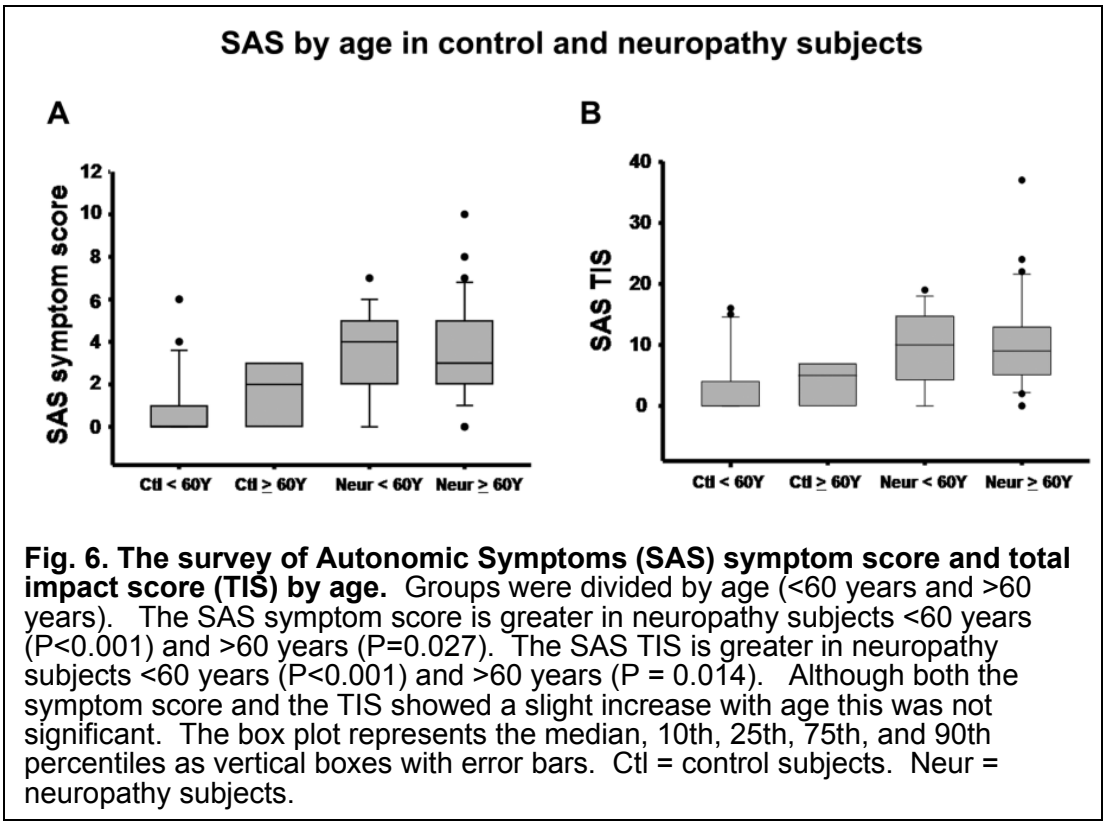


Fig. 6. The survey of Autonomic Symptoms (SAS) symptom score and total impact score (TIS) by age. Groups were divided by age (<60 years and >60 years). The SAS symptom score is greater in neuropathy subjects <60 years (P<0.001) and >60 years (P=0.027). The SAS TIS is greater in neuropathy subjects <60 years (P<0.001) and >60 years (P = 0.014). Although both the symptom score and the TIS showed a slight increase with age this was not significant. The box plot represents the median, 10th, 25th, 75th, and 90th percentiles as vertical boxes with error bars. Ctl = control subjects. Neur = neuropathy subjects.

Clinical Autonomic Abnormalities in Subjects with IGR Neuropathy

In order to establish the frequency and range of autonomic symptoms in subjects with IGR, the SAS was administered to a total of 93 subjects. There were 38 women (mean age = 59.37 ± 1.34 years) and 25 men (mean age = 59.20 ± 1.63 years) with neuropathy. Of these subjects, 94% had IGT or IFG, and 6% had early DM2. In the control group, there were 18 women (mean age = 56.94 ± 2.86) and 12 men (mean age = 49.25 ± 1.78 years). Mean ages were not different between men and women with neuropathy and control women, but the mean age of control men was less than control women (P<0.01). Despite the lower mean male control age, there was no difference between gender and age for the SAS symptom score or TIS in either controls or neuropathy subjects (**Fig. 6**). However, there was a difference between groups for both the SAS symptom score (P<0.0001; 95% confidence intervals [CI] are control: 0.58 to 1.69; neuropathy: 2.99 to 4.14) and the Total Impact Score (TIS) (P<0.0001; 95% CI are control: 1.51 to 5.0207; neuropathy: 8.11 to 11.92) between control and neuropathy subjects (**Fig. 6**). **Thus, subjects with neuropathy have abnormal SAS scores and increased autonomic symptoms.**

There was also no association between the SAS symptom score or TIS and the weight, height, or body mass index of the subject. The SAS showed strong associations with the autonomic symptom profile (ASP) total score for all domains, and the secretomotor, vasomotor, and orthostatic intolerance ASP domains. There was a weaker association between the SAS and the ASP bladder dysfunction and diarrhea domains. There was no association between the SAS and the ASP erectile dysfunction, gastric paresis and other domains. Importantly, an increased SAS symptom score or TIS was associated with a reduced forearm or foot sweat volume on the quantitative sudomotor axon reflex tests (QSART) and also with a reduced 30:15 ratio, thus validating the SAS against abnormal autonomic function.

The most common symptoms reported by subjects with neuropathy, “Do you have a dry mouth or dry eyes?” and “Are your feet colder than the rest of your body?” have similar frequencies in both men and women. **This data clearly indicates that there is a significance difference in the frequency and severity of autonomic symptoms between control and neuropathy subjects**. Furthermore, the SAS has power to distinguish between control subjects and those with peripheral neuropathy. The SAS symptom

Table 1. Association Between Nerve Conduction Studies or Intraepidermal Nerve Fiber Density and SAS

Item	SAS No. of Symptoms	SAS TIS
Sural SNAP	NS	NS (0.051)
Peroneal conduction velocity	NS	NS
Sum Score (Sural and Peroneal abnormalities)	NS	NS
IENFD	P<0.0001	P<0.001

NS = not significant

score and TIS are not affected by age, gender, body mass index, weight, or height. This indicates that the SAS would perform well across subject groups in a clinical trial or epidemiological study and would be less likely to be affected by common confounding variables. Furthermore, there was a very strong association between the SAS and the intraepidermal nerve fiber density (IENFD), which is a sensitive and reliable measure of loss of small unmyelinated nerve fibers that includes sudomotor fibers (**Table 1**).

The neuropathy characteristically seen in patients with MetS is similar to that seen in IGT. Both are characteristically painful, predominantly small fiber neuropathies with autonomic involvement. Our preliminary work has shown that the SAS is a validated measure of autonomic symptoms n IGT. In the proposed study the SAS will be one of the tools used to detect the presence of symptoms of autonomic neuropathy in potential study participants. In addition one of the aims of the proposed study is to determine if the SAS can be used to detect the presence of increased fall risk in participants with MetS by determining if there is a correlation between the SAS symptom score and/or SAS TIS score and performance on the FSST.

RESEARCH DESIGN AND METHODS

The proposed study is a single blinded, randomized study to determine if a targeted balance exercise program improves fall risk in patients with MetS and autonomic neuropathy. Subjects will be defined for entry as having the MetS and autonomic neuropathy but will not be required to have a history of falls. Fall risk will be determined in the study. Following baseline testing participants will be randomized to either a balance exercise program or standard care. Participants in the balance exercise program will be seen weekly to promote program adherence. Standard care participants receive information about fall safety and [will be seen weekly for health education classes] but do not receive tailored exercise instructions.

Participants

Participants aged [50 to 70 years] will be entered based on the presence of MetS and autonomic neuropathy. MetS is defined based on criteria published by the International Diabetes Federation (45). **Subjects must have both MetS and autonomic neuropathy as determined by the study physicians.**
A) MetS will be defined based on the 2006 International Diabetes Federation definition (45): Study participants must have central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity specific values for other groups or if BMI is > 30kg/m^2 central obesity can be assumed and waist circumference does not need to be measured) plus any two of the following four factors: (1) raised triglyceride level (≥ 150 mg/dL) or specific treatment for this lipid abnormality,(2) reduced HDL cholesterol (< 40 mg/dL in males and < 50 mg/dL in females) or specific treatment for this lipid abnormality, (3) raised BP (systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg) or treatment of previously diagnosed hypertension, or (4) raised fasting plasma glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes.
B) Autonomic peripheral neuropathy will be defined according to the Toronto Diabetic Neuropathy Expert Group criteria (72, 73): Based on these criteria, subjects will be entered into the study if they have (1) increased symptoms of autonomic neuropathy based on an increase in the number of symptoms (>3) or impact score (>7) on the validated SAS (32) or (2) at least two abnormalities on autonomic testing. The autonomic testing includes: (1) heart rate variability (E:I ratio and heart-rate range-HRR), (2) Valsalva ratio, (3) Valsalva beat to beat BP variation, (4) 30:15 ratio, and (5) tilt table testing. Normal values for each test are established.

Inclusion criteria:

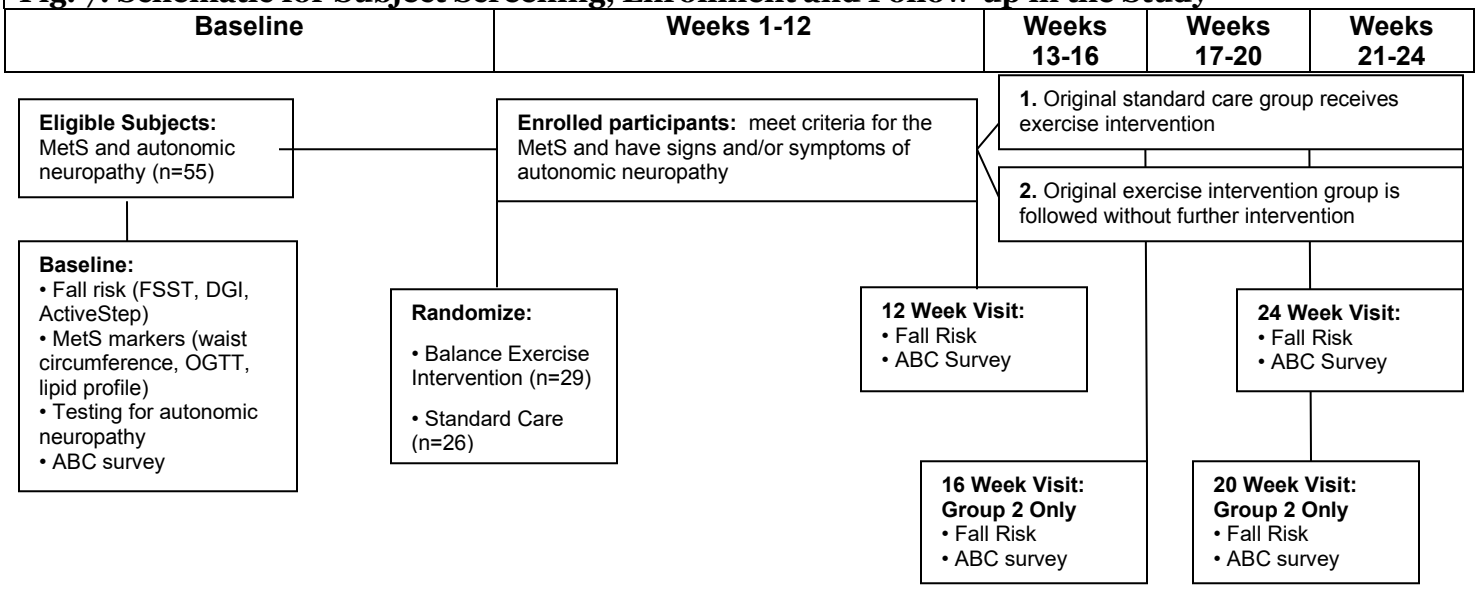
(1) MetS at the time of screening based on the International Diabetes Federation definition (45). This definition includes patients with central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, ≥ 90 cm for South Asian men and ≥ 80 cm for South Asian women; use South Asian recommendations for South and Central American and use European data for Sub-Saharan Africans and Eastern Mediterranean and Middle East populations) plus any two of the following four factors: raised triglyceride level (≥ 150 mg/dL) or specific treatment for this lipid abnormality, reduced HDL cholesterol (< 40 mg/dL in males and < 50 mg/dL in females) or specific treatment for this lipid abnormality, raised BP (systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg) or treatment of previously diagnosed hypertension, or raised fasting plasma glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes. (2) No risk factors for other causes for neuropathy (determined by a medical history, family history, history of medications, occupational history, history of exposure to toxins (including significant alcohol use), physical and neurological examinations, and laboratory studies). (3) Autonomic neuropathy as defined by the Toronto Diabetic Neuropathy Expert Group 2010/11 consensus criteria (72, 73) (4) [Age 50 to 70 years] inclusive at the time of

screening. (5) Medically stable at the time of enrollment. (6) Able to participate in a standing balance exercise program without constant standby monitoring. (7) Women of childbearing potential must be using an acceptable method of contraception to prevent pregnancy when they are enrolled in the study and must agree to continue to practice an acceptable method of contraception for the duration of their participation in the study. (8) Willing to accept assignment to either training group. (9) Willing and able to participate in the assigned intervention program.

Exclusion criteria:
(1) Pregnant women, prisoners, institutionalized subjects and other at risk subjects will not be included in this study. (2) Etiology of neuropathy (including significant alcohol use) other than MetS based on careful clinical and laboratory evaluation by the physician. (3) History of severe medical conditions likely to shorten lifespan or alter ability to participate in the trial, for example advanced current ischemic heart disease (e.g., angina or congestive heart failure), other significant abnormalities of cardiac function, permanent residual lower extremity weakness or loss of balance resulting from a stroke, severe obstructive or restrictive pulmonary disease, or current cancer treatment, renal failure requiring dialysis, severe ongoing peripheral vascular disease. (4) Severe autonomic neuropathy with significant autonomic abnormalities such as postural orthostasis that restricts daily function and the ability to participate in the study interventions. (5) An inability to understand or cooperate with the procedures of the trial or refusal to sign the informed consent. (6) Unable to answer questions correctly on the Evaluation to Sign Consent (ESC) tool. (7) Significant other neurologic, rheumatological, neuromuscular, or other extremity conditions that limit safe exercise or weight bearing.

Screening, Enrollment, and Randomization

Fig. 7: Schematic for Subject Screening, Enrollment and Follow-up in the Study



Screening

At screening the potential study participants will be evaluated for MetS and autonomic neuropathy. Subjects may be enrolled if they have MetS as defined under the participants and an abnormal SAS or two abnormal autonomic function tests as defined under participants. Blood samples to confirm the presence of MetS will be drawn (2hr OGTT, lipid profile). *If the screening fasting glucose is ≥ 126 (subject is diabetic), then for safety, the rest of the OGTT will be deferred.* SAS and autonomic studies will determine if autonomic neuropathy is present (required for enrollment). Randomization assignments will be provided by the study statistician once the subject has completed the screening visit.

During screening or at anytime during enrollment in the study, if participants are found to have under or untreated hypertension or hyperlipidemia the abnormal results of clinical tests will be sent to the participant's primary care physicians for further evaluation.

Randomization Scheme

Randomization will occur at the time of enrollment. Participants will have an equal chance of being assigned to either study group. Due to concerns regarding recruitment we do not feel that only including

individuals with a history of falls in the study sample would be practical. On the other hand only including those without a history of falls may decrease the sensitivity of the study. Therefore, a stratified randomization will be utilized to achieve between group comparability in terms of the numbers of fallers and nonfallers in each group. This will be especially important due to the relatively small total sample size. Within each stratum a blocked randomization strategy will be used to ensure an equal number of participants in each group during the course of randomization. Because the trial is not double blind the blocking factor will be varied between 2 and 4 as recruitment continues so that the blocking factor remains unpredictable to study staff. Blocked randomization can increase the power of a study but will require appropriate statistical analysis since simple randomization will not be used.

Table 2. Testing Scheme for Subjects Screened and Enrolled in the Study

	Screening	Enrollment	12 weeks	24 weeks
hCG (females of child bearing potential only)	X			
Physical and neurologic examination	X		X	X
Waist Circumference	X		X	X
BP measurement			X	X
Metabolic blood tests (OGTT, lipids)	X		X	X
Autonomic studies and SAS questionnaire	X		X	X
FSST & DGI		X	X	X
ABC Survey		X	X	X

Sample Size Calculation

The FSST was chosen as the primary efficacy measure because it has been demonstrated to be a reliable and valid clinical test of fall risk. Importantly, it has been shown to have a higher sensitivity and specificity than the Timed Up and Go test, the Step Test and the Functional Reach Test for identifying differences between groups of older adults; non-fallers, non-multiple fallers, and multiple fallers (14). In normal controls the FSST has been shown to have a standard deviation of 2.34 seconds (74). A minimal detectable change has not been established in a population of elderly adults who are at risk for falls. However, in other populations of patients with neurological disorders that had a similar age and mean score at baseline the minimal detectable change estimate for the FSST was 4.6 seconds (75).

Table 3. Number of Subjects Required for a Range of Mean Differences in FSST

Smallest detectable mean difference in FSST (SD=2.34)	Number of subjects per group	Actual Power
1.0	87	0.800
1.5	40	0.808
2.0	23	0.809
3.0	11	0.816
4.0	7	0.835
Sample size per group required for to detect a specified mean difference in FSST at 12 weeks based on a two sample t test, power=0.8, significance level=0.05		

Based on the FSST, the required sample size to detect a difference of 2.0 seconds is 23 participants per group. Based on results from similar intervention studies, the drop-out rate is up to 25% (14, 76). Allowing for a 10% drop-out rate in the standard care group, we will need to recruit 26 participants into the standard care group and 29 participants into the balance exercise group for a total of 55 participants.

Statistical Analyses

The two treatment groups will be compared using baseline demographic variables (age and gender) and relevant prognostic covariants (history of falls, BMI, abdominal circumference, fasting glucose, BP, lipids, SAS score, and baseline values of primary endpoints). These variables will be tested for baseline comparability using a univariate analysis. The variables will also be examined by stratified analysis to

determine if any of them are potential effect modifiers or confounders. [The unadjusted associations between covariates and the primary outcome variable will first be examined. The covariates that are found to have statistically significant associations with both the exposure and the outcome variables will be examined by stratified analysis to determine if they are potential confounders. All covariates will be examined by stratified analysis to determine if they are potential effect modifiers. If there are potential effect modifiers, interaction terms will be included in the logistic regression model. If the interaction terms are found to be significant in the model, indicating that there is effect modification, then the final analysis will be stratified].

An intention to treat analysis will be used. Descriptive statistics will be used to assess the distribution of the FSST. Bivariate analysis including Chi-square and t-tests to compare the categorical and continuous variables will be performed. Mean and standard deviation for the FSST at each time point will be computed and analysis of variance will be used to compare the means of the two treatment groups, controlling for baseline characteristics. The main hypothesis is that the participants in the balance exercise program will show a greater improvement in the FSST at 12 weeks compared to baseline than the participants in the standard care group.

Table 4. Hypothesis Testing Plan

Endpoints	**Baseline**	**12 weeks**
Primary	FSST	FSST
Secondary	Instrumented DGI (time spent in double support)	Instrumented DGI (time spent in double support)
Tertiary	ABC scale	ABC scale
Exploratory 1	ActiveStep (recovery steps)	ActiveStep (recovery steps)
Exploratory 3	Autonomic testing	

[**Primary hypothesis** – the change in FSST from baseline to 12 weeks will be compared between the standard care and exercise intervention groups to determine if there is a significantly significant difference between the two groups. (covariates included in the model will include outcome at baseline, gender, age, race, and intervention group)

Secondary hypothesis – the change in the DGI score and time spent in double support on the instrumented DGI from baseline to 12 weeks will be compared between the standard care and exercise intervention groups to determine if there is a statistically significant difference between the two groups.

Tertiary hypothesis – the change in the score on the ABC scale from baseline to 12 weeks will be compared between the standard care and exercise intervention groups to determine if there is a statistically significant difference between the two groups.

Exploratory hypothesis 1 – the change in the number of recovery steps taken on the ActiveStep from baseline to 12 weeks will be compared between the standard care and exercise intervention groups to determine if there is a statistically significant difference between the two groups.

Exploratory hypothesis 2 – the individual results of autonomic testing (30:15 ratio, valsalva ratio, E:I ratio, blood pressure response to valsava and tilt table testing) as well as the cardiovagal and adrenergic subscores on the CASS will be compared between those with and without a history of falls at baseline to determine if there is a statistically significant difference between the two groups.

Upon enrollment participants will be randomized using a stratified randomization to achieve group comparability in term of the number of fallers and nonfallers in each group. Due to the fact that randomization will be stratified the analysis will also be stratified and the adjusted analysis will include not only the covariates that are found to be different between the groups, but also those stratified during randomization (4)].

A secondary analysis to examine the individuals that received the full dose of the intervention compared with those that only receive some of them will be done with the understanding that per protocol analyses are not as trustworthy as intention to treat analysis and will not be the preferred analysis (77). [In an attempt to examine the effects of the number of sessions attended we will to add a model that includes the number of sessions attended to the exploratory analyses].

Recruitment

There is a specific weekly neuromuscular clinic at the Baltimore VA as well as daily neurology clinics. Approximately 15-20 veterans with MetS are seen each week. We will also recruit subjects through the Baltimore GRECC utilizing subjects referred to the MOVE program and through the GRECC recruitment core. Further strategies that we have used are web advertising through clinical trials.gov, VA and University of

Maryland websites, and mass faxing of trial information to primary care physicians and neurologists in the greater Baltimore metropolitan area.

Within the division of Neuromuscular Medicine a total of 841 patients were seen in 2010 with "diabetic and other axonal neuropathies" were seen in the outpatient neurology clinic at the University of Maryland. An additional 315 patients with neuropathy were seen. Within the neuromuscular division, the Peripheral Neuropathy Center has an established database of patients with neuropathy. In addition, there is a biweekly dedicated neuromuscular clinic at the Baltimore VA Medical Center that sees approximately 800 patients a year.

There is a wide recruitment catchment area to the University of Maryland, Baltimore and the Baltimore VAMC. However, most participants will be recruited from Baltimore City, Baltimore County, Howard, Carroll, Frederick, and Harford counties. Dr. Zilliox is a member and Dr. Russell is Head of the Neuromuscular Division of Neurology at the University of Maryland. In **Fig. 8** we provide an example of the type of community outreach that already exists for the Neuromuscular Division. The patient outreach includes local patient groups located throughout the state, a series of neurology and primary care practices that regularly refer patients to the neuromuscular program, and regional community hospitals throughout the state. This network receives research and clinical information from the neuromuscular program and faculty from the program are involved in community outreach to the various regional medical centers that form part of the UMMS network and other regional hospitals not listed on the map.

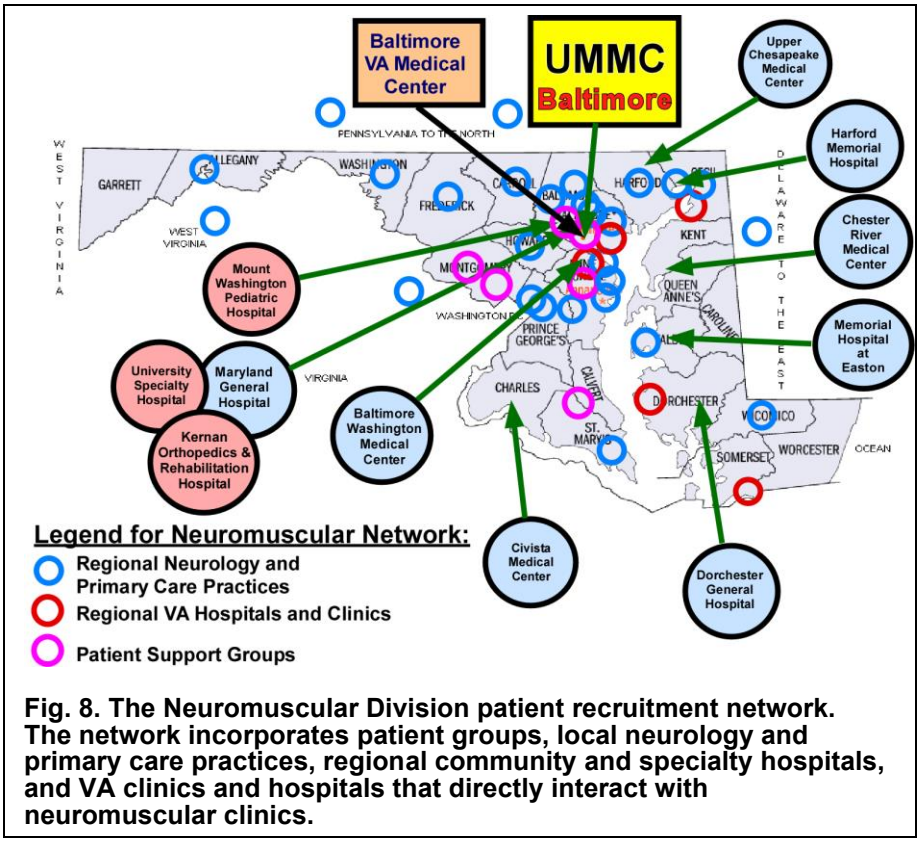


Fig. 8. The Neuromuscular Division patient recruitment network. The network incorporates patient groups, local neurology and primary care practices, regional community and specialty hospitals, and VA clinics and hospitals that directly interact with neuromuscular clinics.

Another resource available to us for recruiting minority subjects is the Community Engagement Research Resource at the University of Maryland. This resource is able to recruit underrepresented minorities for clinical and translational research. African Americans have comprised 35% of our research volunteers over the past 5 years. The University of Maryland Medical Center serves central Maryland (Baltimore City and Baltimore, Carroll, Howard, and Harford counties), a catchment area of a million individuals of which 64% of Baltimore City's 630,000 residents and 29% of all residents are African Americans. The Department of Informatics and Biostatistics Resource is using the COMmunity Partners Advancing Science System (COMPASS) to recruit subjects for clinical research and establish a volunteer registry. COMPASS provides UM researchers with a search-and-discovery tool to identify potential study participants. These methods have been successful in current and previous trials the PI is conducting. In combination, we are confident that the recruitment goals can be met.

Measurements in subjects:

Measures of Fall Risk:

1) Four Square Step Test (FSST): The FSST involves the participant stepping over four canes that are laid on the ground at 90° angles to each other. A cross is formed on the floor by the four canes (90cm long) resting flat on the floor. The participant stands in one of the squares (square 1) formed by the canes facing forward. They are then instructed to step as quickly as possible into each square in a specified sequence; rotating clockwise around the "plus sign" by moving forward to the right, backward, and to the left. They then reverse their direction and move in a counterclockwise direction (14). The score is recorded as the time taken to complete the sequence. Two FSSTs are completed and the best time is taken as the score.

A cutoff score of greater than 15 seconds on the FSST has been identified to categorize subjects as multiple fallers. This cutoff score has a positive predictive value of 86% and a negative predictive value of 94% in a population of community dwelling older adults. The FSST was found to have a higher combined sensitivity and specificity then the Timed Up and Go test, Step Test, and Functional Reach Test in this patient population (14).

The FSST measures proactive dynamic standing balance and the ability to rapidly change directions while stepping, which involves altering the body center of mass-base of support relationship by appropriately matching the stepping limb motion to movement of the whole body to maintain balance. In the planned intervention program one of the proposed mechanisms underlying the change that we expect to see is an improvement in dynamic and reactive balance control with more efficient weight-shift during protective stepping. The FSST has been validated against the Timed Up and Go test, the Step Test, and the Functional Reach test in a population of community dwelling adults (14). Compared to the three other tests of balance, the FSST demonstrated significantly better performance scores for the healthy control and the nonmultiple faller groups. In fact, using a cutoff score of at least 15 seconds, the FSST was found to have a sensitivity of 85% and a positive predictive value of 86% in a population of community dwelling adults over age 65 years. It has also been shown to have excellent test-retest and inter-rater reliability (ICC = .99 and .98 respectively) (14). However, the minimal detectable change and minimally clinically important difference in the FSST have not been established. In terms of sensitivity to change, a recent study demonstrated a significant improvement in the FSST ($p=0.041$) after 5 weeks of treadmill training in patients attending an outpatient gait rehabilitation program (78). The FSST also improved significantly after 6 months (6%, $p<0.05$) of a community based multimodal exercise program (79). In a study of ambulant stroke patients over a 4 week period of outpatient rehabilitation there was a moderate change (ES 0.33) in the FSST (80).

2) Dynamic Gait Index (DGI): [An instrumented DGI will be performed and gait variables of time in single or double support as well as step length and width and gait velocity will be measured.] The clinical DGI will also be performed. The DGI is a measure of functional balance during walking and its score has been shown to be responsive to change after interventions in older adults with impaired balance. However, the DGI score has not been found to be predictive of falls in two studies of community dwelling older adults (15, 81). The DGI had a lower sensitivity (59%) than the FSST when used to identify fallers vs. non-fallers in community dwelling adults over age 65 years (15). To our knowledge the sensitivity of the DGI and the FSST to detect a change in function has not been compared. However, the FSST has been found to have a good correlation with the DGI in people with vestibular disorders and ambulant people with multiple sclerosis (75, 82). In terms of the ability of the DGI to detect change, a 2012 study of community dwelling older adults found that the DGI had poor responsiveness (ES=0.27) after a 16 week exercise trial (18).

As a novel and more quantitative measurement we propose performing the level walking items of the DGI on an instrumented gait mat (GaitRite). This would allow for examination of the temporal and spatial characteristics of gait during performance of the DGI and the findings could potentially be used to provide novel insights on individual items, [such as time in single or double support as well as step length and width and gait velocity,] that potentially may be more revealing in identifying balance and gait deficits than just a timed performance score. The rating criterion for the DGI involves observational quantification of functional gait performance and deviations may be missed. However, the gait mat performs this analysis in an objective, detailed, and reproducible manner.

3) ActiveStep: The ActiveStep treadmill system is another sophisticated tool that is used to assess balance performance and fall risk. [Specifically we will examine the presence of recovery steps after a balance challenge.] This assessment tool is different than the FSST and DGI in that it quantifies reactive balance control. Rapid changes in the movement of the treadmill belt, either from rest or during ongoing gait, produce large postural disturbances that require rapid compensatory responses in order to maintain balance and prevent a fall.

Measures of Obesity:

1) **Height:** Height is measured in centimeters from top of head to the floor.
2) **Weight:** Participants weight will be measured in kilograms.
3) **Waist measurements:** Waist circumference is measured using a measuring tape over one layer of clothing. Waist circumference measurements are made halfway between the lower border of the ribs, and the iliac crest in a horizontal plane. Measurements are taken twice and the average of each site is recorded.

Measures of Metabolic Function:

1) OGTT: The OGTT will be done between 0700h and 1100h after a 12 h fast and will be performed at baseline, 3, 9 and 15 months. Subjects will be encouraged to increase their carbohydrate load for 72h prior to the fast to increase test sensitivity. After fasting, separate baseline samples will be obtained to ensure reproducibility of the fasting samples. Subjects will then be given a 75 g glucose load (Trutol 75, Custom Laboratories, Baltimore, MD). A fasting venous glucose and glucose at 2 h after the 75 g glucose load will be obtained.

2) Lipids: Fasting total cholesterol, HDL, HDL ratio, LDL, and triglycerides will be performed at baseline, 3, 9 and 15 months. Abnormal lipid levels are part of the diagnostic criteria for MetS and hypertriglyceridemia has been associated with the presence of severity of neuropathy (72, 83).

Measures of Blood Pressure:

1) Blood Pressure: Participant will sit with their back supported and their feet flat on the floor. The elbow will be at the level of the heart with the arm supported on a flat surface. Two measurements will be recorded and averaged.

Measures of Autonomic Function:

1) **Cardiac Autonomic Neuropathy (CAN):** Patients will be asked to abstain from caffeine and medications known to affect autonomic function for at least 24 hours prior to testing. The following tests will be performed: (1) the E:I ratio which compares the ratio of the averaged stable R-R interval during expiration to inspiration (2) HRR provides a measure of changes in the heart rate during expiration compared to inspiration (3) The valsalva maneuver with valsalva ratio and beat to beat BP measurement. The ratio provides a measure of the change in heart rate and BP during the valsalva maneuver. The beat to beat BP variation allows measurement of baroreflex responses (32, 84, 85). Each test provides a continuous variable as a measure of change.
2) **Quantitative Sudomotor Axon Reflex Test (QSART):** is based upon the axon reflex sweat response mediated by the postganglionic sympathetic sudomotor axons that are activated by acetylcholine (85, 86). The stimulus is a constant electrical current applied for five minutes and then the sweat response is recorded for a subsequent five minutes. The total sweat volume and the sweat onset latency are recorded at 4 sites: the forearm, proximal leg, distal leg and foot. Results are converted to percentiles and then to standard normal deviate.
3) **Tilt Table Testing:** A 70 degree 5 minute upright tilt will be performed on each subject as previously described (32, 84, 85). The tilt table provides a measurement of baroreflex sensitivity and orthostatic response that is important in understanding autonomic balance in subjects with autonomic neuropathy. Heart rate and beat to BP variation will be monitored during the complete study. Any orthostatic symptoms will be recorded during the study. At the end of the study, the patient will be returned to the supine position.
4) **Composite Autonomic Scoring Scale (CASS):** A composite score of autonomic function will be used to assess autonomic neuropathy. The 10 point CASS score assesses the following: QSART, orthostatic BP, heart rate response to tilt, heart rate response to deep breathing, the valsalva ratio, and beat-to-beat BP measurements during phases II and IV of the Valsalva maneuver, tilt, and deep breathing (87, 88). The CASS provides a total score and also autonomic subcomponents. One of these subcomponents requires measurement of the tilt table response.
5) **Survey of Autonomic Symptoms (SAS):** This is a questionnaire designed to assess symptoms of peripheral autonomic function and determines both the number of positive symptoms as well as the frequency of the symptoms and determines scores for each. The scale has been validated in patients with diabetic neuropathy against other autonomic scales and autonomic testing (32).

<u>Intervention Programs</u>

Once they have been enrolled in the study, participants will be randomized to either a balance exercise program or receive standard care. Both groups will receive education regarding falls and falls prevention and will be contacted on a weekly basis from members of the study staff. However, participants in the balance exercise program will be instructed in a personalized balance exercise program.

[All participants will attend weekly sessions at the Baltimore VA annex. Participants in the intervention program will attend weekly group training sessions and those in the control group will attend weekly group health education classes. In order to avoid drop-out from the study, all participants will also keep an exercise log of home activity and they will be contacted by phone if they do not attend a weekly group session.

Furthermore participants will be reimbursed for parking for each weekly visit and an additional $25 for the screening, enrollment, and the 12 and 24 week visits. This is important because many Veterans in Baltimore have limited income and the cost of travel and parking is a potential limitation to subject participation.

Upon completion of the initial 12 week intervention period the participants who had been randomized to the control group will be offered the exercise intervention for an additional 12 weeks (enrolled in the study for a total of 24 weeks). Due to concern regarding an unknown washout period those participants initially randomized to the intervention program cannot serve as their own controls but they will be followed without further intervention and reassessed at 4 week intervals (weeks 16, 20, 24) to gain additional information about what the length of the washout period might be.]

Balance exercise program

Subjects in the balance exercise program will participate in a three month exercise program designed to improve balance. Balance exercises will be performed three times per week in a home-based training program and participants will also attend a weekly group training session at which time participants will be instructed on the proper performance of the exercises and how to progress the exercises if appropriate. If a participant is unable to attend one of the weekly group sessions they will be contacted by phone and will continue the exercises performed in the previous week.

The balance program will consist of 12 exercises designed to challenge balance during stepping and walking. These exercises will include the activities listed in **Table 5**. Participants will complete up to 10 steps for each exercise and repeat the sequence of 12 exercises in two to three blocks up to a maximum of 30 minutes total. The number of steps to begin the program will be determined at baseline and progression will be tailored to the specific individual. A trainer will instruct the participant as to how to perform each of these exercises.

Table 5: Balance Training Program Exercises

Exercise	Repetitions (Maximum)
Side stepping to the left	10 steps
Side stepping to the right	10 steps
Backward stepping	10 steps
Forward stepping	10 steps
Alternating toe touch to box	5 touches per side
Tandem walking forward	10 steps
Tandem walking backward	10 steps
Walking on toes [1]	10 steps
Walking on heels [1]	10 steps
Walking with longer steps [1]	10 steps
Walking with shorter steps [1]	10 steps
Walking with wider steps [1]	10 steps

Progression of the balance exercise program will depend on the individual participant's ability to complete 3 sets of 10 repetitions of a particular exercise using smooth, controlled movements. At the weekly group session the trainer will determine if a participant should progress a particular exercise and will instruct the participant on how to progress. The participant will continue these exercises as instructed at home for the next week. Once a participant can complete 3 sets of a given exercise they will be given personalized instructions to progress the exercise. All participants will initially perform the exercises with hold support that will be progressed by instructing them to gradually reduce their reliance on external support. Once they can demonstrate that they can safely perform 3 sets of the exercise with minimal support the exercise will be progressed to be performed without support (**Table 6**). For the side and forward/backward stepping the participants will be instructed to take narrower steps and to vary the pace of the steps or to perform the exercise with their eyes closed. The side stepping exercises can also be made more challenging by using cross-over steps forward and backward in addition to direct lateral side steps. The alternating toe touches will be advanced by increasing the speed of the movements, varying the width of the base of support, and by instructing the participants to simultaneously move their arms by lifting light hand weights. The walking exercises will be progressed by varying step length, width, and speeds, stepping over objects, and using different lighting intensities.

Table 6: Balance Training Program Progression:

Exercise	Level A	Level B	Level C	Level D	Level E	Level F
Side stepping	10 steps Hold support	10 steps No support	10 steps Vary step length	10 steps Vary step speed	10 steps Eyes closed	
Forward/Backward stepping	10 steps Hold support	10 steps No support	10 steps Vary step length	10 steps Vary step speed	10 steps Cross-over steps	
Alternating toe touch to box	5 touches per side Hold support	5 touches per side No support	5 touches per side Increase speed	5 touches per side Vary width of base of support	5 touches per side Simultaneously move arms	5 touches per side Add hand weights
Tandem walking	10 steps Hold support	10 steps No support	10 steps Vary step speed	10 steps Vary light intensity		
Walking on toes/heels	10 steps Hold support	10 steps No support	10 steps Vary step length and width	10 steps Vary step speed	10 steps Vary light intensity	
Walking with varying step lengths and widths	10 steps Hold support	10 steps No support	10 steps Vary step speed	10 steps Step over objects	10 steps Vary light intensity	

The criterion for adequate compliance for a participant is to complete at least 75% of the balance training sessions. Several previously successful community and home based exercise programs were examined to determine what an expected level of compliance would be and how compliant a participant would need to be in order to observe an improvement in fall risk. One report of a multidimensional exercise program in community dwelling older adults showed that while performance on several balance scales improved significantly in both fully and partially (attended less than 75% of therapy sessions) adherent groups, the fully adherent group decreased their fall risk by 33% and the partially adherent group decreased their fall risk by 11% (89). Another study of a 12 week duration group-based exercise intervention that was found to significantly improve balance demonstrated a 78% attendance rate for group exercise sessions and 70% of the intervention participants attended at least three fourths of the sessions (90). In a study of diabetic patients there was a median exercise adherence of 87.5% over a 12 week training period (46) . Interestingly, compared to these trials the “Feet First” trial of lower extremity exercise and walking on balance and fall incidence in diabetic neuropathy patients had only 45% protocol adherence in the intervention group and it was found that the degree of protocol adherence did not affect the trial results (48).

Participants will be given a balance exercise log to record the number of repetitions or steps completed of each exercise for each balance training session. Logs will be monitored and compliance assessed weekly. The goal is for participants to improve their balance and decrease their risk of falling. Balance and mobility will be assessed at base-line and 12 weeks.

Standard Care

The SC group will be assigned an interventionist assessor for the duration of the study. This assessor will meet with the subjects during their orientation meeting and will be provided information about falls and recommendations for fall prevention. There will be no directed program throughout the study. [Participants in the standard care group will also meet in person on a weekly basis for general education class regarding health and fall prevention but will not participate in an exercise class. They will also be asked to keep a log of any exercise that they perform at home. This will attempt to control for the effects of coming into a facility once a week in both the standard care and balance exercise intervention.]

At the completion of the study participants in the standard care group will receive instruction in the balance exercise program so that they may benefit from the program as well.

Intervention Timeline

Initially enrollment will be slow to pilot the intervention program and will aim to enroll one or two participants. The next two waves of patients will include 4 to 6 participants and afterwards each wave will include approximately 8 participants. This will require approximately 48 months to complete the intervention for 55 participants.

Table 7: Intervention Program Timeline:

Group (n)	Months																	
	1-3	4-6	7-9	10-12	13-15	16-18	10-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48	49-51	52-54
1 (1 - 2)		x	x															
2 (4 - 6)				x	x													
3 (4 - 6)						x	x											
4 (8)								x	x									
5 (8)										x	x							
6 (8)												x	x					
7 (8)														x	x			
8 (8)																x	x	
Recruitment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Screening	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Enrollment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Outcome Assessment			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Data management

The database manager utilizes a structured data entry system into a database with range checks on individual items and double keying to ensure accuracy. Data are entered into computers as per standard protocols. Data are cleaned and edited after being transported into a statistical software package. Protocols have been developed to handle missing or out of range values, documentation, file backup and archiving, and confidentiality procedures. The VA statistician, Dr. Zhan, will participate in the design of the protocols, choice of software platforms, computer data organization and structures, merging data sets, and data transport.

Blinding and Unblinding Plan

Only the research assistant and the biostatistician, neither of whom will be responsible for assessment of the outcome measures, will handle the randomization list with subjects' names. The treatment allocation list will be blinded to the investigators who measure the outcome measures. The main study data will be kept in a separate database with only the dummy ID. Unblinding prior to the completion of the study will be granted only for urgent clinical reasons, such as a subject has an urgent medical problem or has developed a serious adverse event, which requires the intervention allocation be made available. Otherwise, unblinding will occur on completion of all the recruitment and study measures. Unblinding is achieved by merging the main database with the treatment allocation list. At completion of the study, the study database will be locked. The statistician will finalize the statistical analysis plan and perform the analysis on the locked database.

The participants in the study will not be blinded to their group assignment since the intervention is an exercise intervention that requires active participation in both group and home exercise programs. However, the individuals performing the pre and post intervention assessments will be different individuals than those who lead the weekly group exercise sessions and are in regular contact with the participants. These assessors will be blinded to the participant's group assignment and will follow standardized protocols to perform and record the participants' performance on the outcome measures. To ensure that potential bias is minimized standardized instructions will be given to the participants and established protocols will be followed for measurement of the FSST (14) and DGI (15, 91). Assessment of the DGI on the GaitRite and the assessments performed on the ActiveStep are computerized measurements that will be automated.

Independent Data and Safety Monitoring Plan (DSMP)

The University of Maryland Institutional Review Board (UMIRB) and the Baltimore VA R&D committee will review the proposed level of risk and monitoring plan. All serious adverse events (SAEs) will be reported to the UMIRB and the VA R&D committee. The IRB will perform an annual review that may include any of the

following: adverse events (AEs), enrollment numbers, procedure reports, raw data, outcomes (primary, secondary), and preliminary analyses.

A data safety monitoring board (DSMB) will meet every six months or more frequently if a safety review is required. The DSMB will perform an unblinded review of adverse events, protocol deviations and changes, and enrollment numbers. Due to concerns regarding repeated testing for significance and given that this is a pilot study; interim analyses for efficacy will not be performed. Reasons for early termination of the trial will include an increased rate of serious adverse events related to the intervention or severe logistical or data quality problems that would make completion of the trial unfeasible.

Potential problems and limitations of the planned protocol

1) Choice of the FSST as the primary efficacy measure: The FSST was chosen as the primary efficacy measure because it has been shown to be a valid and sensitive measure for fall risk in populations of community dwelling older adults with excellent reliability and reproducibility. To our knowledge it has not been established what a clinically meaningful change in the FSST is for this population, but data from other groups of ambulatory patients with neurological disorders has been published (75) and we have powered the proposed study to examine for a smaller detectable mean change.

We considered comparing the proportion of participants with times on the FSST greater than 15 seconds (those at high risk for falls) in both groups at baseline and at 12 weeks, but the sample size required for this analysis was too large to accomplish within the constraints of the CDA-2. At baseline we would expect 30% of participants to be at risk for falls and we would hope to decrease this proportion by 40% in the balance exercise group. This would require a sample size of almost 400 subjects, which is not feasible for this pilot study.

2) We do not know how long of an intervention will be required to demonstrate an improvement in fall risk: It is possible that it can be seen after only a few weeks or it could take longer. The study was designed with a 12 week endpoint based on previously published data from studies of similar balance intervention programs. The FSST and DGI will be assessed at 4 and 8 weeks in addition to the primary endpoint at 12 weeks. This will be done to determine if the balance exercise intervention is effective as early as 4 weeks and if there is improvement over 12 weeks or if the intervention effect plateaus before 12 weeks. Alternatively if the 12 weeks of the balance exercise intervention is associated with an improvement in the FSST but it is not significant than a longer intervention may be required as part of a larger, more comprehensive study.

3) Choice of the balance exercise intervention: The intervention program chosen is a balance exercise program that can be easily taught and safely preformed by the study participants both at home and in a group setting. Previously published work has demonstrated the success of similar programs in reducing fall risk. A program that incorporates a targeted strengthening program as well might be more effective, but this is a potential area for future research.

4) Lack of a true control group: Due to the fact that participants enrolled in the proposed study are at risk for falls it is not ethical to provide them without standard care, which consists of education and guidance regarding falls. In addition at the end of the study those randomized to the control group will receive the same instruction in the balance exercise program as those randomized to the balance exercise group.

5) Effect of age on fall risk: Age and gender have been shown to be risk factors for falls. In this study randomization will not be stratified but these factors will be included as confounding variables in the final analyses. Stratifying by each of these variables would increase the required sample size. The objective of the currently proposed study is to demonstrate if a balance exercise program will improve fall risk in patients with the MetS and autonomic neuropathy. If successful, data obtained will be used to plan a larger study.

6) Participant compliance: We are experienced in providing long-term follow up in diet and physical activity interventions. Given the 12 weeks time period, the incentives provided, the proposed attrition rate, and the intrinsic value provided by the intervention that the proposed plan is feasible.