INMED

Improving Neuropathy and Mobility in People With Early Diabetes (INMED)

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LIST OF ABBREVIATIONS

6MW - Six minute walk	IDS - Intervention Development Study
ADA – American Diabetes Association	IENFD - intraepidermal nerve fiber density
AAHSS – Ann Arbor Human Studies Subcommittee	IFG – impaired fasting glucose
AE – adverse event	IGR – impaired glucose regulation
BMI - body mass index	IGT – impaired glucose tolerance
	IGTN – Impaired Glucose Tolerance and Neuropathy Study
CASS - Composite Autonomic Scoring Scale	ISI - insulin sensitivity index
CAT – cardiac autonomic testing	LDL - low-density lipoprotein
CBT - Combined Balance Training	LME – linear mixed model
DCCT - Diabetes Control and Complications Trial Research Group	MDNS – Michigan diabetic neuropathy score
DPP – Diabetes Prevention Program Trial	NCS – nerve conduction studies
EDIC - Epidemiology of Diabetes and Complications Trial	NCV – nerve conduction velocities
FBG – fasting blood glucose	OGTT – oral glucose tolerance test
FDPS - Finnish Diabetes Prevention Study	PA – physical activity
FFAs - free fatty acids	PNS - peripheral nervous system
GAM – generalized additive models	QSART –sudomotor axon reflex test
GCRC – General Clinical Research Center	RCT - randomized controlled trial
GEN - gender	SAE – serious adverse event
GIC – global impression of change	SAS – survey of autonomic symptoms
GLM – generalized linear model	SC – Standard care
GLMM – generalized linear mixed model	SDMC - Safety and Data Monitoring Committee
GRP – group variable	TDPA - Tailored Diet and Physical Activity
h – hour	T2DM - Type 2 diabetes mellitus
HOMA - Homeostasis model assessment	TREs - trunk repositioning errors
HPDT – heat pain detection threshold	UMIRB – University of Maryland Institutional Review Board

NARRATIVE DESCRIPTION

A. RATIONALE AND OBJECTIVES OF THE RESEARCH

(1) Problem Statement

Diabetic Veterans suffer disproportionately from disabilities related to neuropathy and impaired balance control. We recently completed an NIH-sponsored natural history trial to characterize the association between impaired glucose regulation (IGR) and neuropathy (The Impaired Glucose Tolerance Causes Neuropathy Study - IGTN). Initial findings from that study and others suggest that IGR is associated with a painful distal neuropathy with nerve fiber loss (1). For the purpose of this proposal, IGR includes patients with early type 2 diabetes mellitus (T2DM - within 2 years of diagnosis), impaired glucose tolerance (IGT), and impaired fasting glucose (IFG) based on standardized criteria for the diagnosis of T2DM (2). Our other pilot data also suggests impairment in postural control, specifically, standing balance, in these IGR patients, when compared to controls (3).

The IGTN study examined the metabolic profile, characteristics, and progression of neuropathy in participants with IGT. Participants all had IGT and neuropathy at enrollment, received general dietary and physical activity (PA) advice similar to the Diabetes Prevention Program Trial (DPP) "lifestyle intervention" group (4). This advice was not individually tailored and there was less intensive monitoring than the DPP study, but had similar goals (reduce weight by 7% and increase physical activity (PA) to 150 min/week). Our initial data from the study suggest that participants who lost weight and/or increased PA with concomitant improvement in metabolic control not only had reduced progression of neuropathy based on Intraepidermal Nerve Fiber Density (IENFD) from a 3 mm skin punch biopsy, but were able to regrow their epidermal nerve fibers and reduce neuropathy progression and self report measures (see Work Accomplished). Their mobility function (six minute walk distance – (6MW)) also improved. However, this natural history study, unlike the current proposal, was not designed as a randomized controlled trial to test the effect of exercise on mobility, physical activity, and neuropathy progression which are the endpoints for the current study.

Accordingly, in this proposed study, we will determine if an individually tailored diet and PA enhancement program (TDPA), as compared to standard care controls (SC), can improve mobility (six minute walk, 6MW), physical activity (PA), and neuropathy measured using the IENFD. To our knowledge, no randomized controlled intervention trial has been directed toward actually reducing the progression of peripheral neuropathy, as well as determining the effect of this reduction on key factors such as mobility function and PA. The study will be performed at two sites – the Baltimore VAMC/University of Maryland and the Ann Arbor VAMC/University of Michigan and will leverage the strengths of both institutions (senior VA investigators and GRECC Directors at both sites) to increase the diversity and size of the participant recruitment sources and resources available to the study.

While other interventions, for example glucose-regulating medications, may affect mobility and neuropathy progression in patients with IGT, these approaches are costly and fail to address intrinsic problems in the patient's lifestyle. At present we do not know if a lifestyle intervention as proposed in this study will be effective, because such an intervention has never been tested in a randomized study. This is a fundamental question that needs to be answered. In this study we will use a home-based program that can be used within the community and therefore can be used by the majority of patients with IGR.

This study is novel and timely in that it will: 1) test the efficacy of a TDPA protocol in preventing the progression of neuropathy and improving mobility function and PA in participants with IGR; and 2) explore if these processes are associated with changes in metabolic state of the trial participant.

(2) Endpoints and Hypotheses

Endpoints and hypotheses are prioritized according to their importance in the present proposal as the key endpoints (primary and then secondary) and those of lesser importance (tertiary and exploratory/mechanistic).

Endpoints	6 month	12 month

Primary	6 minute walk (6MW)	
Secondary	Physical activity (PA)	IENFD
Tertiary		6MW, PA

Primary Hypothesis (6MW at 6 months): Compared to IGR participants advised to follow the current standard care recommendations on diet and PA (Standard Care or "SC"), IGR participants undergoing TDPA enhancement program will show greater improvement in the 6 Minute Walk (6MW) at 6 months.

Secondary Hypothesis 1 (PA at 6 months): At 6 months and compared to SC, TDPA participants will show greater improvement in self-reported PA *and Actigraph measured exercise.*
Overview and rationale for primary hypothesis and secondary hypothesis 1: SC participants will receive general dietary and exercise advice at enrollment consistent with the recommendation from the DPP and IGTN study of reduction of 7% of baseline weight and 150 minutes of exercise per week. TDPA participants will receive: 1) a dietary consultation at enrollment tailored to their specific dietary requirements in which the goal will be to decrease their baseline weight by at least 7%, followed by weekly (for 2 weeks), and then monthly telephone or email (provided the subject agrees to email contact) follow up by a dietician coupled with mailings of standardized dietary instruments; and 2) a home-based PA and balance program that involves receiving a tailored behavior change (intervention) including behavioral counseling, goal setting, and personal mailings/email/telephone calls. **A 6 month time point has been chosen for the endpoints, 6MW and PA, because data from the DPP and IGTN study indicate that the greatest change in mean weight reduction occurs at the 6 month follow up and, from the IGTN study that the greatest improvement in 6MW occurs at 6 months.**

Secondary Hypothesis 2 (IEFND at 12 months): At 12 months and compared to SC, TDPA participants will show better maintenance of IEFND.
Overview and rationale for secondary hypothesis 2: The second secondary endpoint measure at 12 months will be the change in IENFD. **The 12 month time point is chosen for the IENFD because 1) data on which to base the statistical analysis is only available at the 12 month follow up in the IGTN study 2) nerve regeneration may not be reliably measurable at 6 months 3) participants may refuse a six month skin biopsy because of the time taken to heal the baseline biopsy.**

Tertiary hypothesis (Maintenance of 6MW and PA at 12 months): At 12 months compared to 6 months, and compared to SC, TDPA participants will show greater sustained improvement in 6MW and self-reported PA.
Overview and rationale for tertiary hypothesis: This hypothesis will test the critical issue of whether participants can adhere to the protocol and sustain any improvement.

Exploratory/mechanistic hypothesis: Improvement in measures of neuropathy (nerve conduction studies (NCS), Michigan Diabetic neuropathy Score (MDNS), IENFD), mobility function and PA will correlate strongly with each other and with improvement in specific measures of metabolic function and weight loss.
Overview and rationale for exploratory/mechanistic hypothesis: Measures of metabolic control will include 1) blood measures such as glucose and insulin control (see section 2). Important covariates that will also be analyzed include other measures of neuropathy progression (exam, questionnaire, and electrophysiological) and other mobility function measures.

(3) Specific Objectives of the Project

Specific Aims are to determine, in participants with IGR:

1) Specific Aim 1: To determine the effect, over a 12 month period, of a Tailored Diet and Physical Activity (TDPA) enhancement program on a) mobility function (6 MW); b) self-reported PA (CHAMPS questionnaire); and c) neuropathy progression (IEFND).
2) Specific Aim 2: To determine the relationships between measures of: a) neuropathy progression, b) mobility function; c) PA; and d) other metabolic parameters and weight loss.

The timetable for achievement of the project goals is shown in the Methodology. **Study of long term improvements (beyond one year) in each of the parameters listed above is not feasible given the time constraints of the present study.**

(4) Current Status

T2DM affects nearly 20 million people in the United States, while pre-diabetes or IGR affects a considerably larger but unknown population group. Up to 20% of veterans are diabetic and are significantly more impaired if they have neuropathy (5). At the current time there is no effective therapy to completely prevent, or reverse the complication of diabetic neuropathy and this represents a considerable challenge to Veterans health.

Impaired Glucose Regulation (IGR)

IGR, as used in this study, includes patients with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and early T2DM. Definitions for individual groups are based on fasting venous glucose, or venous glucose values following a 75 gram oral load. Glucose values are as defined (mg/dl): IFG – fasting $\geq$100 mg/dl, IGT- fasting <126, 2 h 140-199, or T2DM - fasting glucose $\geq$126, 2 h $\geq$200 based on the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2). Investigations of the natural history of IGT reveal a dynamic and reversible state. The DPP study randomized 3,244 patients with IGT to treatment with placebo, metformin, or intensive diet and exercise counseling. Nearly 30% of 1,082 subjects receiving placebo progressed from IGT to T2DM >3 years, but during this same period 25% reverted to postprandial normoglycemia (4). Similar results are seen in other studies (6;7). Overall, most patients progress toward greater glycemic dysregulation, but this progress appears to be slow. Unmonitored patients probably experience many years of occult insulin resistance and postprandial hyperglycemia before developing typical symptoms of diabetes. Thus, although blood glucose values are used to define IFG, IGT, or T2DM in fact these definitions are artificial because they fail to recognize that IGR is a dynamic surrogate marker for an underlying metabolic disturbance and the glucose level fluctuates depending on changes in insulin resistance. Participants in this study will be required to have current evidence of IGR. Moreover, despite the potential dynamism of IGR, we believe that the frequent testing for IGR (twice at entry, and once each at 6 and 12 months) allows us to enroll appropriate participants, track the intervention effects, and then explore the relationships between IGR and other intervention effects.

IGR and Neuropathy

Neuropathy is a common complication of T2DM occurring over time in more than half of patients (8;9). NCS demonstrate that neuropathy is already present in 10-18% of patients at the time of diabetes diagnosis (10;11), suggesting that peripheral nerve injury occurs at early stages of disease and with milder glycemic dysregulation. Neuropathy occurring early in diabetes is usually characterized by symmetrical sensory symptoms including pain, and autonomic dysfunction (1;12-16). In a survey of 669 patients with early diabetic neuropathy, sensory symptoms were present in more than 60%, impotence in nearly 40%, other autonomic involvement in 33%, but evidence of motor involvement in only 12% (17). In large prospective series, 81% of neuropathy patients with IGT had exclusively sensory complaints, and 92% recognized neuropathic pain as a dominant symptom of their neuropathy (1;15;18). IGT neuropathy is thus phenotypically similar to early diabetic neuropathy. These findings suggest prominent, but not exclusive, involvement of small rather than large nerve fibers.

Prospective screening of patients, with otherwise “idiopathic” neuropathy using 2 hour oral glucose tolerance test (OGTT), shows that 30-50% of these patients have IGT using the 1997

American Diabetes Association (ADA) criteria (1;13;19). This is significantly higher than the prevalence of IGT in the age-matched general population (20). Similarly, neuropathy occurs in 26% of patients with diabetes, 11.2% with IGT, and 3.9% of age-matched normal controls (21).

Improved glycemic control and nerve function

The DCCT showed that diabetic subjects with intensive glycemic control were 64% less likely to develop clinically confirmed neuropathy over a 5 year follow-up than diabetics receiving routine care (22;23). Intensive therapy is significantly more effective in preventing progression to abnormal nerve conduction studies in patients with early diabetes associated with no retinopathy, than in patients with known microvascular injury (24). While intensive drug intervention may be appropriate in type 1 diabetic complications and advanced T2DM, this approach is unlikely to be suitable for early or pre-diabetes where medications are both costly and may in themselves induce serious complications including hypoglycemia. A better approach would be to intervene to arrest the processes that will ultimately lead to the functional disability associated with neuropathy. This proposal will use a TDPA approach to treat patients at the earliest definable stage of hyperglycemia, when metabolic neuropathic injury is at its earliest stages. Interestingly, recent evidence indicates that a dietary and exercise life intervention in IGT delays the onset of diabetes (4;25;26) and also may prevent certain complications (18) (see Appendix). Furthermore, the intervention effect did not vary according to race, gender, or ethnic group (4). Although controversy surrounds the most optimal form of dietary intervention, most studies agree that dietary intervention is beneficial and should be tailored to the needs of the individual patient (reviewed in (27)). In the multicenter IGTN study, uniform dietary and exercise advice was offered to all participants with IGT and not as an intensive tailored intervention, thus its effect would fall between the “placebo group” and the “lifestyle intervention” group in the DPP study (4).

Endpoint measures of neuropathy

Although electrophysiological neuropathy endpoints are both sensitive and specific diagnostic measures, the most sensitive measure is skin biopsy with measurement of IENFD (16;28;29). The IGTN Study showed that there is a regrowth of nerve fibers both distally in the leg as well as proximally in the thigh in participants enrolled in a diet and exercise program (see Work Accomplished). This is a novel and critically important finding. There is further support for this finding: the DCCT study showed that improved glycemic control is associated with a reduction in progression of neuropathy (22;24), and diabetic mice with spontaneous resolution of their diabetes also have epidermal reinnervation (30). However, no previous trial examining complications associated with diabetes has shown an association between improved glycemic control with a diet and exercise program and regeneration of nerve fibers. In the IGTN study, the diet and exercise program was introduced using broad DPP guidelines (4) and was not designed as a specific intervention. Follow up was more intense than the DPP diet and PA “placebo” group, but less intense than the DPP “lifestyle intervention” group. The current proposal will examine an important unanswered question: whether TDPA will significantly improve IENFD compared to an SC group.

IENFD was the most sensitive measure of neuropathy (severity diminished in 80%)(31). IENFD directly measures small fiber integrity, the same population of nerve fibers primarily involved in IGTN. Unlike the sural sensory amplitude on NCS, IENFD has excellent test retest reliability with variability of less than 10% and intraclass correlation coefficients of greater than 90% (32). IENFD correlated well with both biochemical and other clinical measures of neuropathy: specifically, at baseline there was a strong correlation with the severity of OGTT, the peroneal compound muscle action potential amplitude, and the sural sensory amplitude.

Choice of biopsy site is important. While 24% of subjects in the IGTN study had absent epidermal nerve fibers distally, all had preserved fibers at the proximal site, making it possible to measure a change in IENFD in each subject. Once there is loss of the dermal plexus, the likelihood of epidermal reinnervation is remote. IGTN subjects with absent distal IENFD did not improve at 1 year if there was loss of the dermal plexus as well (see Work Accomplished). While biopsy of the distal site provided useful correlative data with other neuropathy measures, it was less useful in measuring improvement. In the IGTN study, as in other studies, the biopsy

procedure was well tolerated without significant side effects, and patient compliance with repeat biopsy was high (29;31). In conclusion, IENFD is a sensitive and valid surrogate measure of the mixed, but predominantly small fiber, neuropathy typical of IGTN.

In this study, in addition to the IENFD, a clinical measure of neuropathy severity, the MDNS will also be used to monitor neuropathy progression. The MDNS and NCS have been used in most studies of diabetic neuropathy outcome. Both these measures have been well validated in numerous studies including the Epidemiology of Diabetes and Complications Trial (EDIC) and IGTN study (MDNS) and the EDIC, IGTN and Rochester Diabetic Neuropathy Study (NCS) (18;33-36). In the recent IGTN study, there was at least 1 abnormality of the NCS in nearly 60% of participants, and while they are not as sensitive as the IENFD, NCS performed better than quantitative sensory testing which will no longer be performed. Although the MDNS and NCS are not as sensitive as the IENFD in diagnosis of early neuropathy and would require a much larger study if used as primary or secondary endpoints, they are still very well-validated measures and for this reason will be used in this study to monitor neuropathy progression.

T2DM and functional mobility impairment

There is a particularly strong incentive to prevent IGR and related complications from advancing to T2DM in regards to mobility impairment. Diabetes is associated with disability in nearly every task that has been studied (37). Its strong association with mobility limitations (37), is not always recognized, even though diabetes-related disability occurs in up to 2/3 of older adults with diabetes (38). In older adults, T2DM is strongly and independently associated with slow walking speed, lower physical performance scores (including measures of walking speed) (39), impairments in reported mobility functioning (e.g. walking several blocks), and difficulty with IADL and ADL tasks (37;40). However, the physiological impairments that underlie the effects of diabetes on mobility functioning and disability are not completely understood.

Mobility impaired older adults with diabetes have cardiac and peripheral vascular disease, decreased activity levels, and peripheral neuropathy associated with balance and gait impairment (39). Also contributing to their mobility impairment are high prevalences of obesity, vision problems, and comorbidities unrelated to diabetes such as osteoarthritis. Despite the fact that mobility impairment/disability is a major clinical outcome of diabetes, there is virtually no research on the ability of diabetes management to prevent, treat, or prevent progression of mobility disability. Most research deals with the ability of management to prevent vascular complications and manage hyperglycemia (41;42), but it is not clear whether these interventions will also prevent or manage mobility impairment. Exercise, and enhancing PA in particular, is the most likely treatment modality to prevent or improve mobility impairment in older diabetics.

Mobility impairment and the effect of exercise in T2DM

Surprisingly, in older adults with T2DM, randomized controlled trials (RCT) of exercise interventions are few. One recent report demonstrated that moderate intensity resistive training in older adults with T2DM improved mobility performance (43). Generally, exercise in older diabetes patients (usually “young old” with mean ages in the 60’s) has been studied for its effect on metabolic outcomes, including glycemic control (44), insulin sensitivity (45;46), lipids (47), blood pressure (47) and body composition (47). In unselected older adults with chronic diseases, exercise interventions have been shown to improve balance, and aerobic performance, and changes in these physiological parameters are associated with functional improvement and decreased decline (48). Although people with diabetes have been among those included in such exercise interventional studies, they have been few in number, and no such study has specifically targeted T2DM. Clearly, peripheral neuropathy in diabetes (49) leads to balance impairment. Exercise interventions to improve balance in people with diabetes and peripheral neuropathy may improve functional performance (50).

Characteristics of a practical exercise intervention in older adults

Supervised home exercise is the most practical approach in the present study given the wide geographical distribution of participants and the subsequent inability to run a center-based group program. Nelson et al (51) reported a 6 month RCT of a supervised home-based,

exercise intervention (balance and general PA) where intervention participants demonstrated 82% compliance and improvements in balance and mobility scores. A number of other studies have found that supervised, home-based physical activity programs are effective for promoting PA in older adults (52-54).

Many people, including older adults and those with diabetes, find it difficult to change their lifestyle and to adhere to an exercise program. Many older adults comply with exercise for 3-6 months, but then adherence drops off (55). Designing an exercise intervention to promote adherence is critical if the intervention is to achieve the goals of the present study. Adherence is enhanced if the participant perceives the activities to be meaningful and enjoyable, if the program is individualized and if the program features consistent training personnel (56;57). Setting goals and keeping a record of activity performed may also enhance compliance (58). Similar adherence interventions appear to work for both center- and home-based exercise interventions. For home-based programs in particular, it is important for participants to have consistent monitoring and support (58;59). Personalized mailings and frequent telephone contacts have been found to be effective strategies in PA adherence for a one year home-based PA program for older adults (60). All of these features are proposed in the present program.

A successful exercise intervention should lead to general enhanced activity levels, which may be better achieved by combining both a formal exercise program and an increased amount and intensity of usual activities, a combination not often used in published trials (59). Although the benefits of exercise are taught in diabetes self-management education, such knowledge combined with an exercise prescription from the physician may not lead to increased activity levels in older adults with diabetes. Behavioral counseling by primary care providers alone has had mixed results in maintaining longterm PA behavior (61). Provider-directed interventions to provide exercise counseling to primary care patients have shown modest short-term benefit (62;63) or failed to show an increase in patient activity levels (64). Thus, a more directed and tailored program such as proposed may provide better compliance and longer term benefit.

Other potential benefits of exercise-related mobility improvement

The impact of exercise on quality of life has been extensively studied and remains controversial. A recent meta-analysis of cardiac rehabilitation, for example, found significant effects on mortality, but none on quality of life (65). A recent small study of aerobic exercise training in middle-aged diabetics did not show improvement in quality of life (66). A recent review concluded that exercise does seem to be related to improved quality of life, but the relationship is complex and mediated or modified by many variables (67). The exploratory/mechanistic hypothesis proposed in the present study is thus important to explore these complex relationships.

Components of effective PA interventions

Increasing self-efficacy through individually tailored health media messages via the telephone and mail (60) and incorporating community resources (68) have been shown to be effective behavior change mechanisms. Studies using many personal contacts as well as interventions tailored to the target audience have had the most impact on PA behavior (69). Larger effect sizes have been found for interventions that, for example, focus exclusively on activity behavior, include self-monitoring, use intense contact between the interventionists and participants; and target patient populations (70). This study will include each of these components. Few studies have included tailored behavior change PA adoption and maintenance interventions for community dwelling adults with T2DM. The goal of this proposal is to test an intervention that uses individually tailored health behavior change strategies aimed at increasing PA and improving functional mobility performance among individuals with IGR.

Diet, PA, and IGT

Combined diet and PA interventions for adults (middle-aged into their 70's) with IGT have been shown to be effective (4;26;71). Specifically, 6-month interventions combining diet and physical activity behavioral counseling (by a dietician and a physical therapist, respectively) show significant improvements in fat intake, vigorous PA, body mass index, and insulin

sensitivity compared to usual care controls (71). These combined diet and PA interventions similar to this proposed study are effective in demonstrating improvements in risk factors associated with the development of diabetes.

(5) Significance of Research

The proposed research will determine whether a specially designed exercise intervention can positively affect two critical adverse outcomes associated with diabetes, peripheral neuropathy and mobility impairment, in a growing population group, early and borderline diabetics. It will investigate a key hypothesized mechanism of diabetes-related disability, peripheral nerve damage, and: 1) whether reductions in this damage can be made with diet and PA enhancement; and 2) whether these reductions associate with improvements in mobility function.

The proposed intervention is practical. It is designed with features, suggested by the literature, to promote adherence and retention. The exercise regimen proposed is meaningful because it is related to daily functional activities and individualized to address individual preferences. A single trainer will work with the TDPA group and maintain regular contact with them during the home program. The TDPA group will set goals and maintain activity logs, which will be validated. The intervention is also community-based and inexpensive, and uses no special equipment. Therefore, it can be easily replicated and very accessible. Finally, 12-month follow-up will identify whether any proposed changes in nerve function, mobility function and PA persist.

The proposed intervention is an excellent model of the type of community-based intervention that could be coordinated with primary care via a disease management program or a diabetes care coordinator. We have planned and piloted our intervention. However, ultimately the intervention we hope to test is highly adaptable to a disease management program coordinated with primary care practice settings. It would be a reasonable program to implement over a several year period, with yearly or bi-yearly training sessions alternating with a monitored home activities program. Our planned surveillance may suggest how long the effect lasts, and when a “booster” involving center training might be needed.

Finally, this proposal represents a unique collaboration of two research teams at two centers, examining how pathoanatomic changes may respond to an intervention, and how these changes ultimately relate to intervention-induced functional improvement. The focus is on a critical problem, diabetes-induced neuropathy, in an early stage and a practical intervention to address this problem. To our knowledge, this is the first randomized controlled trial directed toward reversing peripheral neuropathy, as well as to determining the relationship of this reduction to key factors such as mobility function and PA.

(6) Relevance of the Proposed Work to the VA Care Mission

T2DM is a growing problem among all older adults, particularly veterans (72;73) and disproportionately affects several minority Veterans populations. Among Veterans with diabetes, 87% are in poor physical health, and are significantly more impaired if they have neuropathy (5). At the current time, there is no effective therapy to completely prevent, or reverse diabetic neuropathy. Nationally representative data has demonstrated that over 75% of older diabetics will have mobility impairment (38;74) and virtually all will have subclinical or clinical comorbidities (75). The prevalence of mobility impairment may be even higher in older veterans with diabetes, where data suggests that over 85% have functional limitations (5).

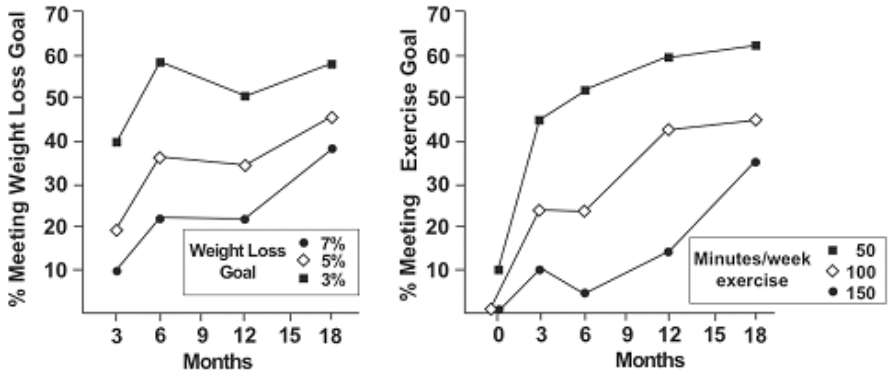
The proposed research is thus highly relevant to the VA patient care mission. An intervention that can prevent and/or treat mobility disability will potentially have major effects on health outcomes important to all older adults with diabetes, including prevention of catastrophic diabetes complications, maintenance of personal independence, improved quality of life and in the long run, decreased costs for medical and personal care. This practical intervention targets people who will most benefit, and is designed to decrease neuropathy progression, improve mobility, increase long-term PA levels, and enhance compliance. The intervention will be replicable and able to reach the large number of older adults with diabetes. This project applies state-of-the-art translational technology and interventional techniques to improve function and investigate mechanisms in a VA-relevant at-risk population. Our intervention is a practical

exercise and diet intervention that provides an excellent model appropriate for use within the integrated VA Health System.

B. BACKGROUND AND WORK ACCOMPLISHED

Metabolic and neuropathy characteristics of IGTN study

We have completed a four year, NINDS funded pilot natural history study designed to: 1) Characterize the clinical, electrodiagnostic, and histological features of neuropathy associated with IGT; 2) Define the progression of neuropathy associated with IGT; 3) validate clinical scales, NCS, IENFD, as progression measures specific to early neuropathy. IGTN subjects were 35-75 years old, and had both IGT as defined by ADA guidelines and a polyneuropathy demonstrated by appropriate symptoms and physical exam findings, and confirmed by an abnormality of at least one of the following: NCS or quantitative sudomotor axon reflex test (QSART). Common alternative causes of neuropathy were ruled out for all subjects. Clinical exam scales, electrodiagnostic testing and IENFD were performed at baseline and then annually. Participants were advised to reduce baseline weight by 7% and exercise for 150 mins per week. The bionutritionist saw the participant every 6 months and could contact them by telephone or email every 3 months depending on the participant's needs. The study enrolled 67 subjects, 61% were women and the mean age was 57 (range 38-75 years). In general, baseline characteristics of this cohort reflect typical features of the metabolic syndrome. The average body mass index (BMI) is 32.7 (obesity is defined as BMI > 30). Prior to enrollment, participants were inactive, reporting an average of just 12 minutes of recreational exercise weekly, however after enrollment they were able to comply with the diet and exercise protocol (Fig 1) although most of the improvement in weight occurred within the first 6-12 months (Fig. 2). In the IGTN study, the diet and exercise advice was given to all participants as standard care, was not intended as a specific intervention, and did not include a balance component. Thus, the IGTN study failed to answer certain critical questions that a comparison intervention study will help to clarify. **At the end of the current proposal we should be able to determine if an intensive home-based diet and exercise program can improve walking and PA, and reverse neuropathy in subjects with IGR. The study will also determine if there is a rational and sustained metabolic basis for this improvement in neuropathy and functional state. The main outcome variables will be 1) the 6MW, 2) the IENFD, and 3) PA.**

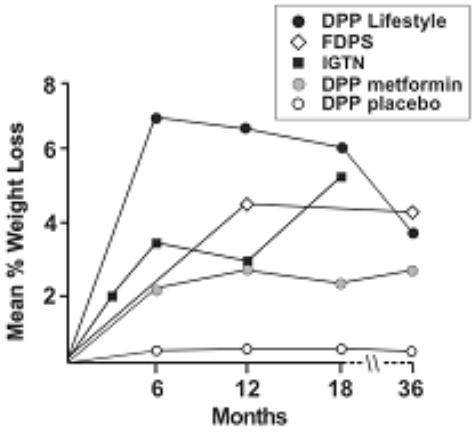


The preliminary data presented in Work Accomplished support the concept that somatic and autonomic neuropathy in participants with IGT may improve concurrent with the improved metabolic control associated with diet and exercise. The current proposal will use the expertise gained from the IGTN study to examine the TDPA intervention.

Fig. 1. IGTN subjects have complied with the diet and exercise program. Subjects were asked to lose 7% body weight and increase weekly exercise to 150 minutes per week. The graphs show the percent of participants meeting each goal level.

The DPP and Finnish Diabetes Prevention Study (FDPS) provide benchmarks for compliance with individualized diet and exercise regimens in subjects with IGT. These studies

used intensive counseling schedules to motivate compliance. Although these intensive intervention studies resulted in rapid weight reduction, most of the reduction occurred within the first 12 months, thus supporting the duration of the current proposal.



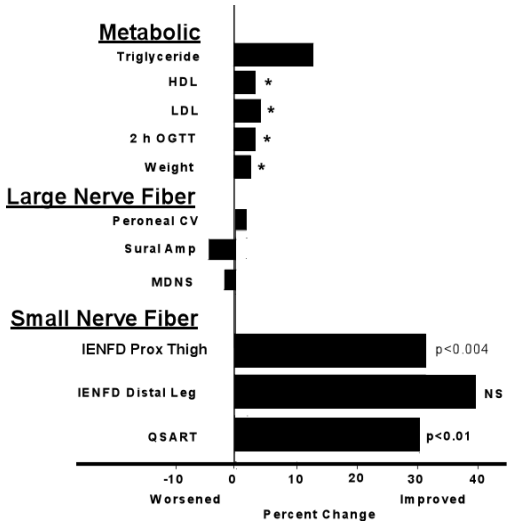
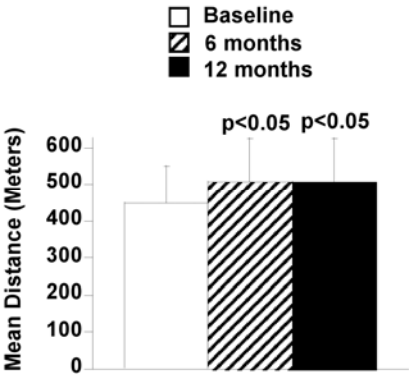


Fig. 2. Change in weight with diet and exercise is dependent on the intensity of the protocol. Subjects in the placebo arm of the DPP study show no change in mean % weight loss. The SC group in the current proposal would be close to this group. In contrast, the DPP lifestyle group and FDPS had a more intense diet and exercise protocol and a greater mean % weight loss. IGTN subjects where the diet and exercise protocol were less intensely monitored than the DPP "lifestyle group", but more than the DPP "placebo" group, fall between these two groups.



Improvement in metabolic control with diet and exercise is assocated with improvement in clinical, electrophysiological, and pathological measures of neuropathy

The improvements in metabolic function were associated with a trend toward improvement in neuropathy (Fig. 3-right). The greatest improvement was in the IENFD and QSART, measures of small nerve fiber function, whereas there was less change in NCS and other measures of large nerve fiber function. This supports the concept that small fibers are the first to recover in IGT associated neuropathy and that it may take longer than 1 year for large fiber function to change. Small fiber and sensory subscores of the MDNS show the same change. In Fig. 3, changes on the right indicate improvement and left worsening. * = p<0.05. IENFD was measured from 3-mm skin biopsies at the distal leg and proximal thigh at baseline and after 1 year in subjects with IGT (See Appendix). Each received diet and exercise counseling as a standard of care. NCS, QSART, and the MDNS were performed, and a visual analog pain scale was completed. Baseline distal IENFD was 0.9+1.2 fibers/mm and proximal IENFD was 4.8+2.3 fibers/mm. Baseline distal IENFD correlated with fasting glucose (0.001) and OGTT (0.01). After 1 year of treatment, there was a 0.3+1.1-fiber/mm (30%) improvement in distal IENFD and a 1.4+2.3-fiber/mm (70%) improvement in proximal IENFD (0.004). There was a greater improvement in the proximal thigh because many participants had no distal skin fibers, but all had proximal fibers, thus proximal IENFD may be a better measure of early nerve regeneration. Proximal IENFD was used to power the IENFD endpoint in the current proposal. The change in proximal IENFD correlated with a change in sural sensory amplitude (0.03).

This data represents a mean of the whole natural history cohort and cannot separate out those participants who showed the greatest improvement in weight loss and exercise capacity. The current proposal will address this question.

Improvement in IGTN six minute walk (6MW)

Participants in the IGTN study on a diet and exercise program showed an improvement in their 6MW values at 6 and 12 months compared to baseline (p<0.05 for both timepoints). The results represent data for all subjects irrespective of level of PA or diet control. Improvement in the

6MW was greatest at 6 months, thus the current study was powered at 6 months, although the improvement was sustained to at least 12 months.

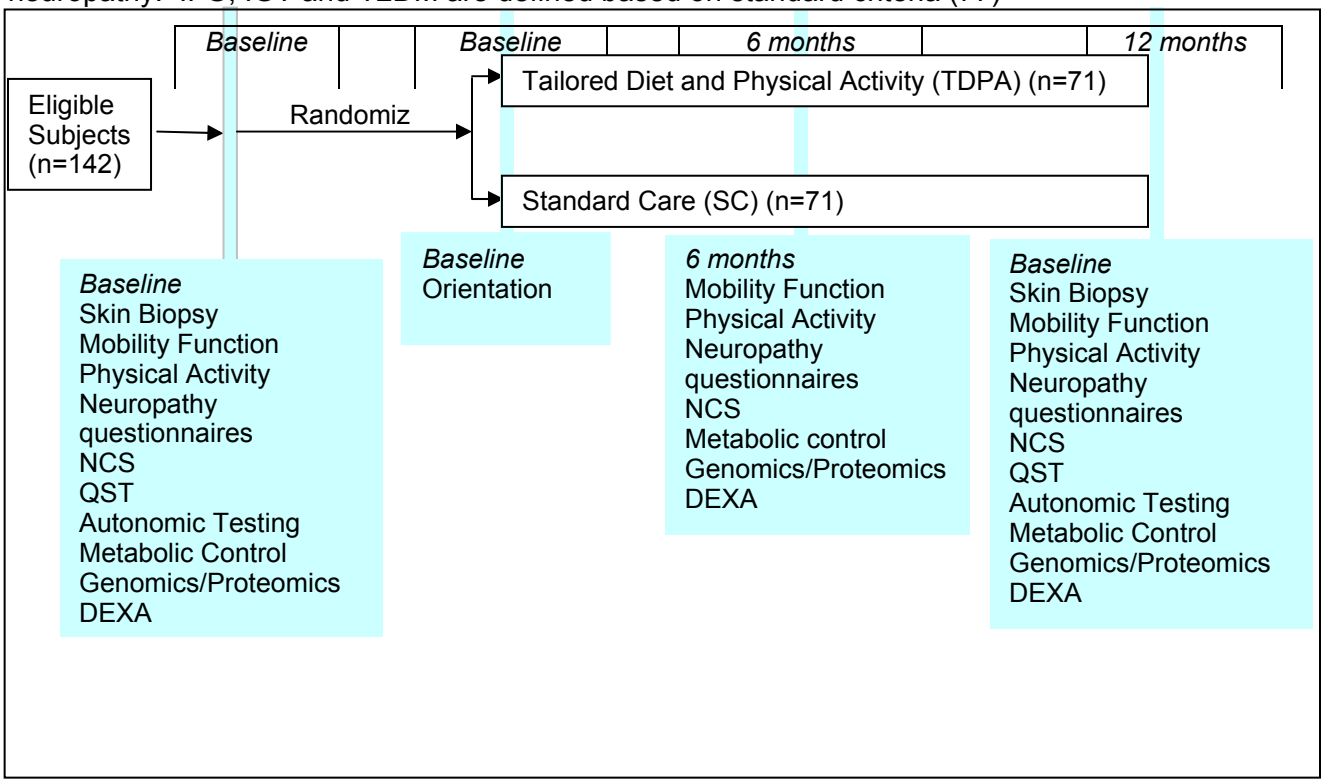
Fig. 4. Improvement in 6MW in participants on a diet and exercise program in the IGTN study. Results were based on 40 paired observations. The 6MW procedure was standardized for all participants.

IGR-related Neuropathy and Impairment in Standing Balance
Our pilot data suggest that compared to healthy age- and gender-matched controls, patients with IGR-related symptoms of neuropathy (n=8 in each group, mean age 60) have a two-fold decline in measures of standing balance, namely in Unipedal Stance Time and in trunk repositioning errors (TREs) despite no difference in other measures of balance and walking such as the Timed Up and Go. TREs are a new measure of trunk postion sense that is presumably dependent on distal leg sensation and ankle strength (76) Work completed in this study is in press (3).

C. WORK PROPOSED

(1) Methodology

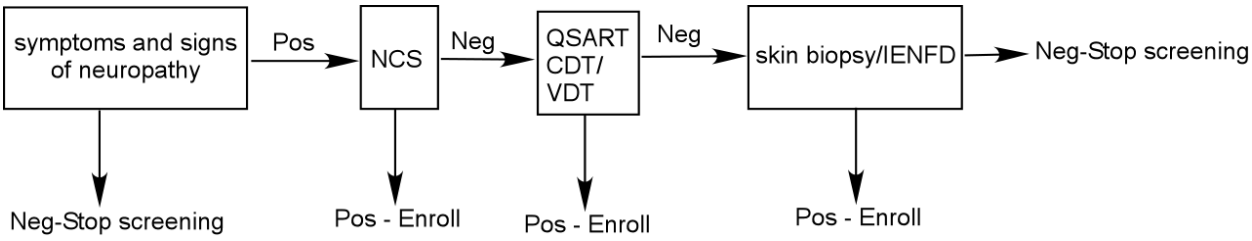
In this single blinded study, following baseline testing, participants are randomized to either TDPA or SC. TDPA participants receive initial orientation in diet and a home-based lifestyle physical activity enhancement program with an intensive walking focus and a supplemental balance program. They are then regularly contacted by phone, email or mailings to promote program adherence. SC participants are also followed on a regular basis by phone or email but receive no tailored instruction in diet and exercise and thus receive only generic health education support. Participants return for 6-month and 12-month testing that repeats the baseline test.
Participants: Participants aged 30 to 75 will be entered based on the presence of IGR and neuropathy. IFG, IGT and T2DM are defined based on standard criteria (77)



Neuropathy Study Schedule

	Screening	Enrollment	Randomization	6 months	12 months
			Tailored diet and physical activity or standard of care		
Informed consent	R				
Blood tests to rule out other causes of neuropathy (if not previously performed)	R				
Metabolic blood tets (HBA1c/lipids etc)	R			R	R
Blood for DNA/protein studies	R			R	R
Physical and neuro exam, height, weight, waist circ.	R			R	R
Nerve Conduction Study	R			R	R
Autonomic Testing	R				R
QST	R				R
Skin biopsy	R				R
DEXA scan		R		R	R
hCG prior (females of child bearing potential only)		R		R	R
Michigan Diabetic Neuropathy Score/neuropathy exams	R			R	R
2 hour OGTT	R			R	R
Questionnaires	R			R	R
6 minute walk		R		R	R
comfortable gait speed		R		R	R
unipedal stance time		R		R	R
TREs (voluntary trunk control)		R		R	R
CHAMPS		R		R	R
Actigraph (TDPA and SC)		R		R	R
Three day food record (TDPA)			prior to nutrition phonecalls		
Activity log (TDPA)			weekly for 12 months		
NeuroQOL/SF12	R				R

Neuropathy Flow Chart:



Selection of subjects: Subjects must have both peripheral neuropathy and IGR as determined by the study physicians.
A) Peripheral neuropathy will be defined as the presence of both neuropathic symptoms and physical examination signs of peripheral neuropathy in addition to an abnormality of one of four confirmatory tests: NCS, QSART, QST (CDT/VDT) and IENFD. Normal values for each test are established. Subjects will be screened for other causes of neuropathy. These tests will include CBC, electrolytes, creatinine, urea, liver function tests, serum vitamin B12, folate, anti-nuclear antibody, ESR, thyroid stimulating hormone and serum protein electrophoresis and immunofixation testing. Patients with minor abnormalities of these tests can be enrolled in the study provided that the abnormalities are not clinically significant, or the subject is being treated for the abnormal condition, is stable on treatment, and the treatment has not resulted in any significant improvement in the neuropathy e.g. abnormal TSH in a patient with treated hypothyroidism, abnormal B12 treated with adequate B12 replacement and there is no improvement in neuropathy. This is because minor abnormalities of laboratory tests are common and may be irrelevant to the neuropathy.

B) IGR will be defined based on the ADA diagnostic guidelines following an OGTT (see inclusion criteria)(2). Study candidates must have had one abnormal hemoglobin A1C value, fasting glucose value, or glucose on OGTT prior to screening to confirm that IGR is definitely present.

Inclusion criteria (further detailed in Human Studies):

1) IGR at the time of screening or within three months of screening. This definition includes patients with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and early diabetes. Patients can be included if they have an increased risk for diabetes with a HBA1C > 5.7% (using a method certified by the National Glycohemoglobin Standardization Program), or they have diabetes with a HBA1C > 6.5%, or an abnormal fasting venous glucose, or abnormal venous glucose values following a 75 gram oral load. Glucose values are as defined (mg/dl): IFG fasting greater than 100 mg/dl, IGT- fasting less than 126, 2 h 140-199, or diabetes - fasting glucose > 126, 2 h > 200 based on the Standards for Medical Care in Diabetes 2010 by the American Diabetes Associaition (77).
2) IGR diagnosed within 2 years of enrollment.
3) The HbA1c may be normal, but must be <8%.
4) If diabetic subjects are on medication, they should be stable on medication for at least 3 months prior to entering the study. Addition or change in antidiabetic medications after enrollment does not affect participation or group assignment.
5) 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, physical and neurological examinations, and laboratory studies).
6) Clinical signs or symptoms of neuropathy as determined by the treating neurologists history and physical exam, PLUS an abnormality of one of the following: NCS, QSART, QST, or IENFD.
7) Age greater than 30 years and less than 75 years at time of screening.
8) Medically stable at the time of enrollment.
9) Able to participate in standing exercise program without constant standby monitoring.
10) 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.
11) Patient must agree to taking an alternative medication to coumadin when undergoing a skin biopsy.
12) Willing to complete weekly self-report questionnaires.
13) Willing to accept assignment to either training group.
14) Willing and able to increase activity level and exercise independently at home.

Exclusion criteria:

1) Pregnant women, prisoners, institutionalized subjects and other At risk subjects will not be included in this study.
2) Hx of diabetes > 2 years or taking insulin.
3) Etiology of sensorimotor neuropathy other than IGR based on careful clinical and laboratory evaluation.
4) 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), 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.
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.

Patients with IFG or IGT should not be receiving anti-diabetic treatment based on current standard of care recommendations. However, some early diabetic participants may be taking an oral hypoglycemic medication. These subjects will be included in the study provided they are on stable medication dosing and their HbA1c is stable.

Screening, enrollment and allocation procedures:

At screening, clinical neuropathic examination (MDNS), and electrophysiological studies will be performed to determine the presence of neuropathy (required for enrollment). In participants where these tests are normal but the participant has symptoms of neuropathy, a skin biopsy for IENFD will be performed to determine enrollment eligibility. To minimize the number of blood draws for the participant, all blood samples will be taken at screening instead of enrollment (e.g. lipid profile), although measurements will only be made if the participant is enrolled. SC and TDPA intervention timelines are described in detail in the specific intervention sections (see also Human Subjects-Appendix). Allocation assignments will be provided by the study statistician once the subject has completed the screening visit. ENROLLMENT CAN OCCUR ON THE SAME DAY AS SCREENING AND WILL OCCUR WITHIN 30 DAYS OF SCREENING.

Minimization Screen:

Participants will be allocated to TDPA or SC groups according to a minimization scheme. Minimization maintains balance in group distributions of a number of key variables by assigning subjects to either TDPA or SC group based on: age strata (30-40, 41-50, 51-60, 61-75), gender (male vs female), and BMI (less than 30, 30-40, >40). Since the number of stratification cells generated by these factors is large, the use of minimization techniques for subject assignment is especially suitable (78). Minimization stipulates that the next subject to enter the trial is assigned to a group with a probability greater than 0.5 in favor of the treatment that minimizes group imbalance on a particular variable. This minimization of strata imbalance between the training and control groups also reduces confounding of the outcome with prognostic factors, similar to stratified randomization. Operationally, after completing baseline testing, minimization strata for each participant are entered into a computer program which then generates the group assignment for that participant. We have used minimization in a number of controlled exercise studies and it appears to be a reasonable alternative to randomization when key confounders must be controlled and a relatively small sample is anticipated for recruitment.

Sample size calculation: We consider three outcomes: 1) Primary endpoint: 6MW at 6 months. 2) Secondary endpoint: IENFD at 12 months 3) Secondary endpoint: PA at 6 months.

Sample size will be based on the previous data from our IGTN natural history study and relevant pilot data from our ongoing Rehab R&D-funded Merit Review T2DM exercise study. An assumption is that the IGTN study represents a more intense intervention than SC and that the difference between the TDPA and the SC will be at least as large as the difference between baseline and the 6 or 12 months endpoints of IGTN (see below). The table below uses the IGTN baseline-endpoint data to compute an adjusted standard deviation (i.e. the SD can be reduced by taking into account the contribution of each individual's baseline in explaining the overall variation). For the T2DM study, PA (from CHAMPS scores) is available at baseline (Mean ± SD 1350.5 ± 946.5) and at 10 weeks of a physical activity enhancement intervention for our pilot group (10 week delta=over 600). At present, we do not have sufficient 6 or 12 month data for PA in T2DM, but we anticipate that the initial PA benefit may be sustained. The expected sample size required is noted for two-sided alpha=0.05 and with power of 80%.

Study	Variable	SD of the outcome adjusted for baseline	Desired TDPA-SC difference	Effect size for adjusted outcome	Sample size per group
IGTN	6MW	97	50	0.51	64
IGTN	IENFD	2.2	1.0	0.45	53
T2DM	PA	1000	500	0.50	64

Thus, the sample size estimate needed for the primary hypothesis efficacy measure (6MW) will be 64 per group for a total of 128 needed in the study. In the T2DM CHAMPS PA data, using baseline information and assuming a delta of 500 and standard deviation of 1000, with 64 subjects per group we can detect an effect size of 0.5. Based on reliable data from the current IGTN study, we know that the actual 1 year dropout for enrolled subjects is 4%, so that the number of subjects to be enrolled is 133. We estimate a more liberal 10% dropout rate from

baseline to the 12 month endpoint, thereby requiring randomization at baseline of 142 in order to guarantee recruiting the necessary 128 participants.

The sample size estimate needed for the secondary hypothesis efficacy measure (IENFD) will be 53 per group for a total of 106 needed in the study. Using the 10% dropout rate from baseline to the 12 month endpoint, 117 would be required for randomization, well within the 142 planned to satisfy the requirements for 6MW noted above.

The SC is closer to the "placebo" group in the DPP study (4) because the IGTN cohort received more dietary support than is proposed for the SC group, and the TDPA group is closer to the "lifestyle intervention" in the DPP study because participants receive greater diet and PA intervention than in the IGTN study. Thus the expected improvement of the SC group is likely to be less than that noted in the IGTN group. Given the proposed sample size, the study power is likely to be further enhanced.

Recruitment:

Recruitment numbers are indicated above. This requires that we recruit 6-7 patients/month for 21 months. The recruitment catchment area to the University of Maryland and the Baltimore VAMC is from Maryland, Virginia, and southern Pennsylvania, however, most participants will be recruited from Baltimore City, Baltimore County, Howard, Carroll, Frederick, and Harford counties. Dr. Russell is Head of the Neuromuscular Division at the University of Maryland. The division sees approximately 3000 patients with neuropathy at the Baltimore VAMC and University every year. Approximately 2000 of these patients will have diabetic, IGR associated, or undermined "small fiber neuropathy". A database held by the division includes over 250 patients with IGR and neuropathy. At the University of Michigan/Ann Arbor VAMC recruitment based on the IGTN study is primarily from Michigan and Eastern Ohio. Many of these patients are referred to two of the large referral centers in Michigan, the Ann Arbor Veterans Affairs Medical Center and the University of Michigan. These hospitals are further fed by referrals from over 3,000 primary care physicians, VAMCs, and other hospitals within Michigan that refer directly to these medical centers. In Michigan, through the Neuropathy Center (see consultant letter from Dr. Ann Little), a database has been developed to list subjects with neuropathy. Based on current data, there are approximately 100-150 patients entered per year into the database with a diagnosis of polyneuropathy and IGR (including IFG, IGT, and early T2DM). Most of these patients would be eligible for entry into the current study. Furthermore, there is no expected competition for participants. This is the only center in the area recruiting participants with IGR and neuropathy, and furthermore the current NIH funded natural history study terminated in 7/2006 and participants are eligible to enter the current study. There are currently 67 participants entered into the IGTN natural history study and those completing the natural history study in 7/2006 would also be eligible for enrollment in the current study. We have decided to include participants with IFG, IGT, and early T2DM (within 2 years of diagnosis) to increase the pool of potential participants and because subjects can rapidly change from one glucose status to another but still have IGR and metabolic syndrome as discussed in the Current Status. In the IGTN study, approximately 25% of potential participants fail screening under the IGT glucose criteria despite having a recent previous OGTT consistent with IGT. These subjects all have glucose values consistent with either IFG or T2DM and would be eligible for recruitment in this current proposal, and thus we will further enhance recruitment. We will also recruit subjects using mass faxing of trial information to primary care physicians, neurologists, and diabetologists in the greater Baltimore metropolitan area and the Washtenaw county area. 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.

HEIGHT AND WEIGHT

Morphometric Measurements:

1) Height: The floor should be hard, even and uncarpeted. Respondents should remove shoes, but keep socks on. Ask participant to stand against doorway/wall with feet together and flat on the floor, and having heels, hips and shoulders directly against the wall. Height is measured in centimeters from top of head to the floor.

2) Weight: Participants weight will be measured in kilograms using a scale. Place scale on a regular flat surface, preferably without any carpeting or rugs. Participant should be in stocking feet or barefoot, wearing light indoor clothes with pockets emptied. Place scale so that participant is facing and within arms reach of a wall. Participants can use the wall to balance themselves as they get on/off the scale. Push the on button and weight for 0.0 to appear. Stand beside patient as they mount the scale and assist as needed. Record weight after 5 seconds and assist participant off scale.
3) Waist and hip measurements: Waist and hip circumferences are 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. Hip circumference is measured by positioning tape measure at the level of the great trochanter or approximately four inches down from the waistline (widest point over the buttocks). Measurements are taken twice and the average of each site is recorded.

Measures of Neuropathy Progression: These include the IENFD, NCS, and MDNS. Further information for specific tests and clinical recording forms are included in the Appendix. A brief description of each test is included below. Adverse effects from any of the procedures are discussed in Human Subjects (see Appendix):

1) Intraepidermal Nerve Fiber Density (IENFD): Three 3 mm skin punch biopsies will be performed at the left thigh and calf using 1-2% lidocaine local anesthetic at enrollment and 12 months. The punch biopsies samples are fixed and the change in IENFD is compared against the baseline value in the same participant. This change is dependent on the baseline IENFD and is not affected by age or gender (18;79;80). Thus, these variables are not expected to affect the endpoint analysis.

2) **Cutaneous Innervation Laboratory Data Integrity and Quality Control Procedures:** Each punch biopsy specimen is given a unique number and placed in a -20 deg freezer. Each step in the processing, including quality control data and precise location of each punch biopsy and section are recorded in a secure on-line password protected database. This database is backed up nightly. Intraepidermal nerve fiber density measurements are performed using established criteria (81). **See Appendix for specific counting methodology (81)**. For each study, approximately 5% of samples are randomly selected for blinded recount to ensure adequate test retest reliability. The laboratory has demonstrated excellent intra and inter observer reliability, with intraclass correlation coefficients of greater than 95% and relative intra-trial variability of approximately 10% (32). Additionally, the laboratory participates in a multicenter quality control program in cooperation the laboratories at Johns Hopkins University, Rochester University and the Cleveland Clinic. Quarterly, one laboratory sends sections to another for independent analysis.
3) Nerve Conduction Studies (NCS): will be used to measure neuropathy progression (see Current Status, Endpoint Measures of Neuropathy for rational). NCS will be performed on the left side with the lower limb maintained at 32°C and the upper limb at 33°C (82). The amplitudes of the sural sensory, peroneal motor, tibial motor, radial sensory, and ulnar sensory and motor nerves and their respective distal and long latencies, and conduction velocities are obtained. Data will be used from individual measurements and using a mega score of combined variables. The electrophysiology personnel at both sites have been trained by Dr. Russell and nerve conduction results from Ann Arbor will be faxed to Batimore for reading by Dr. Russell's group. This will ensure reliability and uniformity of electrodiagnostic studies.
4) Michigan Diabetic Neuropathy Score (MDNS): will be used to measure neuropathy progression (see Current Status, Endpoint Measures of Neuropathy for rational). MDNS provides a quantitative neurological assessment of sensation, strength and reflexes in the extremities, with emphasis on the hands and feet. This instrument is currently in use in the EDIC Trial (33;34). The MDNS has been administered to over 8,000 patients (83;84). A final score is obtained for analysis. This will be compared with the early neuropathy score (ENS), total neuropathy score (TNS), neuropathy impairment score in the lower extremities (NIS-LE), Utah early neuropathy score (UENS) and the Toronto

5) 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 is recorded at 4 sites: the forearm, proximal leg, distal leg and foot. Results are converted to percentiles and then to standard normal deviates.
6) Quantitative Sensory Test (QST): The CASE IV sensory testing system is used as described (87;88). The following sensory changes are measured: 1) CDT a measure of small fiber function and 2) VDT, a measure of large fiber function. All measurements are done on the dorsum of the hand or foot. The sensory thresholds are converted to standard normal deviates relative to matched normal subjects.
7) 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.
8) COMPASS: This is a comprehensive survey of autonomic symptoms developed by Dr. Phillip Low at the Mayo clinic. It divides autonomic symptoms into categories of autonomic dysfunction to characterize the overall clinical dysautomic syndrome. Scores are provided for individual components and a total score.
9) Composite Autonomic Scoring Scale (CASS): A composite score of autonomic function will be used to assess progression of autonomic neuropathy. The 10 point CASS score was developed by Low et al and provides a total score and also autonomic subcomponents.
10) Cardiac Autonomic Neuropathy (CAN): Patients will be asked to abstain from caffeine and medications known to affect autonomic function the day of testing. Three tests will be performed in the VAMC Electrodiagnostic laboratory: 1) Expiration:inspiration ratio (E:I) ratio. 2) The Valsalva maneuver 3) 30:15 ratio which is a measure of the heart rate response at the 15th compared to the 30th beat. Each test provides a continuous variable as a measure of change.

Measures of nutrition compliance: The Three-Day Food Record is used to self-record daily food intake and physical activity over 3 days (2 weekdays and 1 weekend day) (89). It will be completed prior to each nutrition contact. The dietician will provide nutrition counseling based on the participant's food record results. Participants will also monitor and report their weight during the counseling sessions with the dietician. Other nutrition instruments used by the dietician are included in the Appendix.

Measures of mobility function: All tests are based on published protocols and have been used extensively in Dr. Alexander's previous work. Pilot data (see Work Accomplished) show differences in balance between IGT and controls, and improvement in six minute walk in the observational study among those who underwent diet and PA interventions.

1) Balance:

a) Unipedal stance time.

Unipedal stance time is particularly important in predicting both peripheral neuropathy (90) and as a risk factor for falls (at <30 sec; (91)) and fall-related injury (at <5 sec; (92). The participant raises each leg for a practice trial, followed by two trials up to 30 seconds. Best score between both legs is used.

PROTOCOL:

Equipment: Stopwatch
Description: This test will consist of four trials, 2 on each leg, with a maximum time of 30 seconds per trial. The tester is allowed to help the subject get into position. Timing begins once the subject is standing independently. The examiner stands to the side and slightly behind the subject to provide balance assistance as needed. The subject must complete the activity with

arms crossed over chest. The foot off the floor must be approximately two inches from both the weight-bearing leg and the floor. The non stance leg must not be allowed to contact the stance leg for support. The subject will be allowed one practice trial per leg, prior to beginning the test trials. The test is begun with the preferred foot and both test trials are completed before proceeding to the opposite foot. The trial will end if the subject reaches 30 seconds, uncrosses their arms, touches the floor with non weight-bearing leg, moves their head, arms, trunk and/or non-stance leg excessively, or loses their balance.
Instructions to subject: "I would like you to stand on one leg for as long as you can. I would like you to keep your arms crossed and lift your foot a few inches off the ground."
Scoring: Timing begins when the subject has assumed unipedal stance with arms crossed and ends when 30 seconds has elapsed or an error has occurred.

b) Maximum step length.
This is the maximum distance the participant is able to step with one leg while keeping the other foot stationary (staying within the box and weight shifting forward, lifting heel of stance foot, but not moving the toe) and returning to the initial position in one step.

PROTOCOL:

Equipment: a directional floor grid 60 inches in length in each direction with 2 12"x 6" starting boxes positioned at the intersection of the zero marks. (See appendix)
Directions: This test consists of maximal stepping in the forward direction with the left lower extremity, 2 trials. The subject will be allowed to practice the activity preceding the first test trial. The subject must complete the activity with arms crossed over chest and hands placed on opposite shoulders.
Instructions to subject: "Please stand in the box. During this activity you will be asked to step as far as you can forward with your left leg. When you step, I want you step as far out as you can, however, you must be able to return in one step. Also, I want you to keep your hands crossed over your chest during the stepping. (Demonstrate stepping procedure. Allow subject to practice, provide verbal cueing to correct any performance errors.)
Now I want you to step as far forward as you can with your left leg and return to the start position. Step forward and return. And a second time, step forward and return.
Scoring: Record length of step in inches, to nearest inch, for each directional trial, for each leg. The reading is taken from the most anterior edge of the subject's shoe for the forward and backward directions and the most medial edge of the shoe in the lateral directions. A trial is repeated if the subject evidences one of the following errors:

1) Loss of balance
2) Failure to return to initial starting position
3) Multiple steps either to step out or step back
4) Failure to keep arms crossed
5. Movement of the stance foot out of the starting box

TREs. Given the contribution of trunk control to avoiding falls, we developed a measure of voluntary trunk control and position sense, TREs, which is strongly correlated with clinical measures of standing balance and, as in many of these balance tests, relates more to levels of distal rather than proximal leg strength (76;93). With an inclinometer placed on the T4 spinous process, the participant leans forward approximately 30 degrees and then is asked to reproduce the angle under three conditions, eyes open, eyes closed, and eyes open while standing on foam. The difference between the initial and the reproduced angle is the TRE, although the actual score used is the average of three trials performed in randomized blocks (over the three conditions, for a total of nine trials).
The task measures the length of time a subject can stand on one foot.

PROTOCOL:

Assess trunk repositioning sense as a measure of trunk control.
Equipment: Pro-360 digital inclinometer, foam.

Description: Subjects tested in standing (testing done with eyes open and closed, on firm and compliant surfaces), and while stepping forward at 80% of Max. Step Length (MSL)
TRE Instructions:
1. Subject bends trunk forward to ~30º and holds for a count of 3. (record angle)
2. Subject returns to upright position.
3. Subject is asked to reproduce the trunk angle, holds for a count of 3. (record angle)
   The difference between the 2 angles is the trunk repositioning error (TRE).
4. Repeat 5 times, best and worst scores discarded, TRE=mean of remaining 3 scores.

TRE with STEPPING Instructions:
1. Subject steps forward at ~80% of MSL simultaneously flexing the trunk to >30º (arms folded across chest, holds for count of 3). (record angle).
2. Subject returns to upright position.
3. Subject is asked to reproduce the trunk angle while stepping, holds for a count of 3. (record angle). The difference between the 2 angles is the TRE.
4. Repeat 5 times, best and worst scores discarded, TRE=mean of remaining 3 scores.

2) Walking:

a) **Six minute walk (6MW):** was originally validated as a measure of functional outcome in patients with cardiopulmonary disease, but in fact correlates well with age, comfortable gait speed and balance measures, and has been used as a measure of improvement in rehabilitation and exercise programs. The participant is instructed to cover as much ground as possible in six minutes. The examiner records the time using a stopwatch. b) Comfortable gait speed predicts disease activity, mobility- and ADL-disability, institutionalization and mortality. Two trials of walking 10 feet (3 meters) are performed and the fastest of two trials are used for the data analysis. These tests are extensively reviewed in Alexander 2005 (94).

PROTOCOL:

Equipment: Measured 50 foot walking course and stop watch.
Directions: Subject will walk for a total of 6 minutes. Subjects are allowed to stop and rest if necessary, but time will run continuously. The subject should walk at a pace in which they could talk with you if you asked them (not extremely short of breath) and attempt to maintain a constant pace throughout the walk. The subject should wear their customary footwear and may use an assistive device if necessary (document on the testing form). The subject must use the same device for all future tests. No verbal encouragement is provided by the tester.
Instructions to subject: "This task requires you to walk as far as you can in 6 minutes. You may stop and rest at any time during the 6 minutes, but I will ask you to resume walking after each rest, until the 6 minutes has elapsed. I would like you to walk at a comfortable pace that will not make you short of breath and to try to keep your pace constant
Scoring: The distance the subject walks in 6 minutes will be recorded. A running time will be also taken at each lap so that speed variations during the walk may be noted.

b) **Comfortable gait speed:**The task measures the time it takes a subject to walk a 6-m course at a normal, comfortable pace.

PROTOCOL:

Equipment: Stopwatch, tape, and tape measure. An unobstructed 6-m marked course is marked off, with at least 1-m of clearance at each end to allow for normal pacing.
Description: Subject begins test standing one meter behind the line. Subject performs the test in usual footwear and may use a walking aid if so desired. A practice trial is performed, followed by a timed trial. Examiner walks to the side and slightly behind the participant, being careful not to pace the subject.
Instructions to subject: "This is our walking course. When I say 'go,' I would like you to walk to the other end of the course at your usual speed, just as if you were walking down the street.

Walk past the tape at the other end before you stop. I will walk with you. If you use a cane or other walking aid and would feel more comfortable with it, you may use it."
Scoring: Timing begins as the subject walks across the first line and ends when the participant's toe crosses the end line. Note whether an assistive device is utilized to perform the task.

Self report measures

1) Self-reported PA (CHAMPS): PA will be measured by the CHAMPS questionnaire, which was specifically designed for use in evaluating intervention-induced changes in a broad range of self-selected physical activities, similar to that proposed in the present study (95). This questionnaire was validated using an intervention to improve self-selected physical activities, in a group of older adult participants (mean age 76) with significant health problems (54), and in diverse populations older than age 40 years (96). Two measures will be used in the analyses, first, calories expended for all activities and then calories expended performing activities of moderate intensity or greater, the latter a measure of more aerobically challenging activity. Furthermore, PA compliance will be confirmed using a actigraph measurement
2) Neuropathy Specific Quality of Life Instrument (NeuroQoL) and SF12: The NeuroQoL is a recently introduced patient-specific, neuropathy-centered instrument to evaluate quality of life in participants with diabetic neuropathy (97) and consists of 6 domains consisting of 43 items with subscores and a total weighted score. The NeuroQoL will be used to monitor changes in quality of life between the SC and TDPA groups. The SF12 is a short form version of the SF36 and shows a high degree of correlation with the SF36 used widely as a QOL measure.
3) Subject and examiner indication of the subjects group assignment. Both the subject and the examiner will indicate whether they think the subject isin the TDPA or the SC group

Measured physical activity

One key indicator of exercise compliance is an objectively measured level of physical activity. Each participant will wear an Actigraph (Computer Science and Applications, Inc. Shalimar, FI) for 7 days each at the 3 data collection timepoints (3 weeks total): baseline, 6 months and 12 months to corroborate their PA as self-reported on the CHAMPS questionnaire. The Actigraph is a small uniaxial accelerometer that is one of the most widely used and reliable devices to measure PA (98) is sensitive to PA improvements due to behavioral interventions in T2DM (99). We considered using a pedometer to measure PA compliance but this population may have impairment in their gait, therefore step length may vary making the pedometer a less reliable source of validation. The Actigraph has the benefit of assessing activity counts independent of step length or gait impairment. Mean daily total counts on the Actiwatch will be analyzed and correlated with self-reported activity logs and CHAMPS assessment data.

Blood Tests

1) OGTT and insulin: the OGTT will be done between 0700h and 1100h after a 12 h fast. Subjects will be encouraged to increase their carbohydrate load for 72h prior to the fast to increase test sensitivity. After fasting, subjects will be given a 75 g glucose load. A fasting venous glucose and glucose at 0 (obtained twice to confirm a stable baseline value), 60, 90 (1.5 h) and 120 minutes (2 h) after the 75 g glucose load will be obtained. The fasting and 2 h glucose values will be primarily used for statistic association with the endpoint measures as these correlated best with diabetic complications (18). IFG, IGT, and T2DM are published (2). Insulin will be drawn at 0 (obtained twice to confirm a stable baseline value) and 1.5 hours during the 2 h OGTT to measure insulin sensitivity using the oral glucose insulin sensitivity (OGIS) mathematical model (100).
2) Lipids: total cholesterol, HDL, HDL ratio, LDL, triglycerides, and free fatty acids.
3) Procedure for blood processing for RNA, DNA, and protein: 10mls of whole blood will be collected in each of the following tubes: PAXgene Blood DNA Tube, one PAXgene Blood RNA Tube, 2 Green-top-Heparin blood collection tubes for a total of 60 mls of whole blood. Tubes should be immediately inverted several times to prevent clotting. Blood will then be shipped on wet ice to processing lab at the Baltimore VA. Samples will be labeled with an identification number, date, and visit type. Upon arrival, Paxgene tubes will be frozen at -

70°C pending nucleic acid processing. RNA tubes will be stable up to 6 months post freeze. DNA tubes will be stable indefinitely. Heparizined collection tubes must be processed for protein immediately. To process whole blood for protein, tubes must be centrifuged at ~900g at room temperature for 15 mins. Serum will separate from cells and will be collected and stored at -70°C until protein processed. The red blood cells will then be lysed using Qiagen's QIAamp procedure which uses a hypotonic buffer for selective lysis of erythrocytes. The remaining leukocyte pellet will then be frozen at -70°C pending processing. To process protein, Agilent Technologies Human 14 Multiple Affintiy Removal Spin Cartridges will be used.

DEXA scan
Participants will undergo a total body dual energy x-ray absorptiometry (DEXA) (Hologic QDR1000/W, software version 6.2OD; Waltham, MA) to assess fat free mass and fat mass according to standard GCRC protocols.

Intervention Protocol

TDPA group:

1) TDPA Exercise Component:
For the Tailored Diet and Physical Activity (TDPA) intervention group, the training protocol consists of a graduated walking program, with additional focus on specific balance exercises. During the 1.5 hour orientation period, the home balance exercises and walking program will be introduced and the appropriate level of balance challenge and walking intensity will be established.

The walking program will utilize the guide "The Exercise and Your Heart: A Guide to Physical Activity" program sponsored and developed by the National Heart, Lung and Blood Institute and the American Heart Association. Along with the walking program, the guide includes additional content such as Benefits and Barriers to physical activity (PA), Keys to Success, and Pacing Yourself. The guide will be supplemented with materials from the PBS America Walks website www.pbs.org/americaswalking/index.html .

The TDPA walking program is a graded exercise program with a target goal of 30 minutes of moderate intensity walking 5 days a week and is consistent with the American College of Sports Medicine recommendation to achieve exercise related health benefits. It will consist of a warm up, a brisk walking period, and a cool down. Participants will be instructed to begin walking at a slow pace for 5 minutes (warm up), increase intensity to a brisk walk (RPE 11-15) for the prescribed duration and finally walk more slowly for 5 minutes (cool down). The warm up and cool down will remain the same throughout the program but the duration and intensity spent in a brisk walk will increase each week and will be tailored to each participant's individual fitness level. The interventionist will prescribe walking at a level tolerated by the participant initially and increase the duration, frequency, and intensity over time until the participant is at the desired levels. The Kick-Off Your Walking Quiz (see TDPA form 1) will be utilized to determine the correct initial program level for each participant. Participants receiving a score of 4 points will begin at LEVEL 1 (TDPA form 2) , scores of 5-7 points will begin at LEVEL 2, (TDPA form 3) scores of 8-10 points will begin at LEVEL 3 (TDPA form 4) , and scores of 11-12 will begin at LEVEL 4 (TDPA form 5).

The balance program will focus on proximal and distal lower extremity strength, lower extremity proprioception, and static and dynamic balance skills (TDPA form 6). Participants will be taught 6 exercises and asked to perform them 5-7 days a week. These exercises will be progressed every 6 weeks (see TDPA form 7) to gradually increase the balance challenge and strengthening effect.

During the TDPA orientation session, participants will learn to monitor their walking intensity using the Borg Rate of Perceived Exertion scale (TDPA form 8) and practice the balance exercises with the opportunity for clarification and correction from the interventionist. Following

the orientation session, counseling will be conducted to assess exercise progress, identify strategies to overcome barriers, and discuss changes in medications and health status. Phone or email consultation will occur weekly for the first 3 months following enrollment, transitioning to biweekly calls during months 4-6, and monthly contact in months 7-12 to promote individual exercise and physical activity goals.

2) TDPA Behavioral Component:

TDPA participants will also receive tailored lifestyle behavioral change instruction during this orientation period to facilitate home program adherence and promote lifestyle activity. For a well-balanced PA program that will promote PA maintenance, participants will be encouraged to add lifestyle PA activities. These activities will include tasks that are meaningful and include current activities, such as increasing the time spent, distance or intensity in: walking hallways, housework activities, climbing/descending stairs, low-intensity leisure activities (e.g. gardening), community activities (e.g. volunteer work), errands (e.g. grocery shopping) and moderate-intensity recreational sports (e.g. tennis, golf). Thus, participants will perform balance exercises, participate in a walking program, and include lifestyle PA. During the first four weeks, participants will be instructed to perform PA for a minimum of 90 minutes per week (a combination of walking, balance exercises, and lifestyle PA), at a suggested rate of perceived exertion of 11-13. At eight weeks, participants will be encouraged to perform PA a minimum of 120 minutes per week at a suggested rate of perceived exertion of 12-13. At twelve weeks, participants will increase their PA to a minimum of 150 minutes per week. At sixteen weeks participants will increase their total PA to a minimum of 180 minutes per week at a suggested rate of perceived exertion of 13 and will be expected to maintain or increase this level for the remainder of the study. This graduated approach and use of the Borg rate of perceived exertion scale allows participants to slowly increase PA to limit injuries and promote behavior change over time thereby meeting the American College of Sports Medicine and Center for Disease Control and Prevention's Physical Activity Guidelines for Adults (101). Each week the participant will fill out a short log of typical activities performed in the past 7 days and will return it in a self-addressed, stamped envelope. The activity logs will be used to assess PA adherence, lifestyle activity (balance exercise, and, walking), allowing the interventionist to structure the components of the total physical activity program to best meet the needs of each individual participant.

The TDPA program includes a tailored behavior change component to facilitate the adoption of long-term PA behavior. The goal is to increase the intervention participants' PA levels and maintain those levels across time (12 months). TDPA participants receive 60 minutes of tailored lifestyle behavioral change instruction during the orientation period, followed by behavioral support via telephone calls or email weekly for the first three months (months 0-3), biweekly for 3 months (months 4-6), and monthly for the remaining 6 months (months 7-12) to reinforce behavioral strategies such as relapse prevention, goal setting, overcoming barriers (e.g. weather, increasing self-efficacy, and self-monitoring of PA. Monthly mailings throughout the 12 month intervention are used to reinforce and adapt the program as needed, as we have done in our pilot studies.

To promote an individualized (tailored) PA program and identify preferences for tailoring, participants will complete a questionnaire at baseline (See Appendix) that includes theoretical items noted to impact PA behavior. Findings support that older adults intend to perform PA if they: (perceive benefits of PA (outcome expectancies) and perceive confidence to perform PA in spite of barriers (self efficacy) (102) and confidence to walk (self-efficacy for walking).

Responses from the questionnaire will be used for behavioral counseling, telephone calls, email and mailings. A library of tailored messages and strategies has been developed for each combination of responses (e.g. low benefit/low self-efficacy, high barriers/low self-efficacy). Each participant's program will be tailored based on: 1) personal psychosocial determinants (self-efficacy, benefits, barriers); 2) PA preferences; 3) available community resources; and 4) health and environmental factors. Examples of the theory-based tailored behavior strategies are presented in the following table.

Example of Tailored Behavior Change Based on Assessment Data:

Behavior/Problem Examples	Goal of Intervention	Tailored Intervention (BC=Behavioral Counseling; TS=Tip Sheets; CR=Community Resources; RP=Relapse Prevention; TC=Telephone Call
Benefit low/Self-efficacy low: Believes walking will not improve peripheral neuropathy symptoms so lacks confidence and limits walking	Enhance walking for leisure Increase confidence that walking will improve peripheral neuropathy symptoms such as pain	BC/TS: 1) Discuss/provide benefits of regular PA on peripheral neuropathy; 2) Discuss specific strategies to begin walking program such as walk 15 minutes first day and increase by 5 min. each day; 3) Check peripheral neuropathy symptoms (pain) level before and after walking; 4) Set realistic walking goals; 5) Provide positive reinforcement that PA will help to maintain health and independence CR/TS: Provide list of resources for walking in participant's community (e.g. recreation center, high school track, shopping mall) RP: 1) If social with friends/family, encourage participant to include this person in walking ; 2) Schedule walking into daily routine; 3) Discuss barriers and strategies to manage them TC: 1) Assess progress toward goals; 2) Discuss potential barriers and strategies to overcome them; 3) Provide positive reinforcement for working toward goals; 4)Renegotiate goals

Following the questionnaire assessment and as part of the orientation period, participants will meet with the interventionist for behavioral counseling which will include goal setting, problem-solving to overcome barriers (e.g. lack of time), identifying resources (e.g. people), increasing self-efficacy, and reviewing strategies for relapse prevention. Tip Sheets (tailored written messages) will be mailed to the participants' homes monthly; these will be developed from the responses from the baseline and 6 month assessments, and will address increasing self-efficacy, overcoming barriers, and increasing knowledge of benefits of PA. Personalized messages have been found to be an effective behavior change strategy as they are read more thoroughly, recalled better, and are more likely to be acted upon than the standardized written PA information typically available at physician offices. Telephone calls or email will be conducted to assess progress in achieving PA goals, renegotiation of goals if necessary, identify strategies to overcome barriers, and discuss changes in medications and health status. Frequent follow-up calls and mailed tailored messages have been highly effective for PA behavior change89.

3) TDPA Nutrition Component:

In the TDPA group, the dietary protocol will be based on the Bouchard 3 day dietary instrument and will include individual tailored dietary instruction with the goal of reducing baseline weight by at least 7%. During the 2 hour orientation appointment, the nutritionist will perform a one-on-one dietary consult with the subject and establish a nutritional plan. The dietary consult will assess the individual participant's diet at enrollment and develop a specific plan for that individual (weight loss >7% baseline weight). This will include developing a calorie-restricted diet, addressing the distribution of energy yielding macronutrients, and will also develop a long term plan to improve the quality of the participant's diet so as to achieve a safe but consistent negative balance. For each individual participant, the basal metabolic rate and total energy expenditures will be determined based on PA assessment using Harris Benedict equations and criteria developed by the Food and Nutrition Board of the Institute of Medicine (103). Based on this information and BMI, the nutritionist will provide individual information on the calorie reduction to provide steady weight loss. The dietician may meet with the subject again one month after the initial consult and may also meet as needed with the subject during the 12 month intervention depending on the needs of the subject, compliance with the protocol, and the decision of the dietician and TDPA interventionist. The initial consultation session will be followed up with counseling 1 and 2 weeks after enrollment by the TDPA interventionist and then monthly 30 minute telephone or email assessments and behavioral counseling to promote

individual dietary goals. The dietician will meet with the subject, at the 6 month return visit and at the 12 month visit.

TDPA Intervention Summary
This program consists of several components that have been shown to improve exercise compliance, and, in our preliminary data, to be feasible in physically impaired older adults. These include: personalized program emphasizing activities that are meaningful to or preferred by participants; consistent contact between the participants and research staff; and monitoring of activity levels by log, Actigraph (an accelerometer worn at the waist that measures physical activity). Participants will place PA goal sheets, Tip Sheets, exercise pictures and instructions, behavior change materials, and balance program information in a project-provided binder for reference at home.

Participants that are failing to meet their established dietary and PA goals as assessed by the TDPA interventionist during telephone interviews or email at 1, 2, or 3 months will be asked to meet face-to face with the assessor to re-establish dietary and PA goals.

Intervention-Protocol - SC group:

The SC group will be told following their DEXA appointment that they should reduce their baseline weight by 7% and exercise for at least 150 minutes/week. There will be no tailored, directed program. These participants will attend a total of 90 minutes of health education classes (no behavior change component) during the orientation period and receive general health related telephone calls or emails weekly during the first 3 months, biweekly during the next 3 months (months 4-6) and monthly for the remaining 6 months (months 7-12) and monthly health related mailings throughout the intervention (12 months). The time allocated to these health activities in the SC group is the same as the TDPA, in order to control for a possible attention and monitoring effect.

Data management
The technician 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. Co-Investigator Dr. Galecki will participate in the design of these protocols, choice of software platforms, computer data organization and structures, merging data sets, and data transport.
Independent Safety and Data Monitoring Committee (SDMC)
This study will use a lifestyle intervention and it is not predicted from the current IGTN study that a standing independent SDMC will be required. If necessary, a plan for convening a SDMC is described in Human Studies (see Appendix).
General analytic plan
Comparability of treatment groups will be performed using the baseline demographic variables (i.e. age, gender, BMI) and relevant prognostic covariants (e.g., HbA1c, autonomic symptoms, and baseline values of primary endpoints). The demographic and prognostic values will be presented by treatment group as means and standard deviations for continuous variables, and analysis of variance will be used to compare the means of the two treatment groups, controlling for baseline. Baseline characteristics will be compared between the study groups. Standard two group comparison methods will be used, such as two sample t-tests for normally distributed variables. Measures of central tendency (means) and variability (standard deviations, ranges) will be estimated. Initial data analyses will allow us to explore the distributions of outcomes studied, may lead to transformation of the dependent variable, and may help identify outlying measures not detected earlier in the data cleaning process.
1) Model check and alternative analysis plans: Model fits will be checked for individual and systematic departures of the observed and fitted values using informal (e.g. inspection of residuals) and formal methods (e.g. based on score tests for extra parameters (104;105). The influence of individual outliers will be evaluated by comparing models with and without outlying values. Outcome variables will be transformed when we cannot fit a parametric model. In our

preliminary data, assumption of normality is reasonable for most outcome variables, including those which are log transformed. Non-parametric analyses e.g. Generalized Additive Models (GAM), (106), or Friedman two-way analysis of variance (105), will be utilized when we cannot fit a parametric model. Outcome measures will be adjusted for baseline by including baseline values as a covariate into the model. As another option, a baseline measure becomes another dependent variable in the repeated measures model and appropriate contrasts will be constructed to adjust for baseline. In computations, SAS PROC MIXED (107), SAS PROC GENMOD, and PROC GAM in SPLUS will be used.
2) Incomplete data: The regression techniques e.g. linear mixed effects, allow for data missing-at-random (108), i.e. the missing values do not depend upon values of the observed outcome measures. The difference in post-intervention distribution of group characteristics, not observed in study groups right after randomization, may indicate bias due to missing values (informative drop-out). For example, some subjects discontinue the intervention due to intervention-related factors. If we suspect such a bias, we will compare data from subjects with completed outcome measures, with data from subjects lost to follow-up. If necessary, careful imputation and/or modeling of missing values will be considered (108).
3) Retention bias and dropouts: In order to understand the factors associated with successful completion of the study, those who are able to complete testing at various points in the timeline will be compared with those who are unable to complete the interventions and tests. Data will include reasons for ineligibility after screening (including medical conditions and functional status); reasons for inability to participate (e.g. too much time commitment); and task performance (e.g. 6MW) in those who do not complete the interventions.
4) Compliance issues: Subjects will be monitored for training-related injuries, onset of new medical conditions, the introduction of supplemental exercise programs (such as physical therapy), or any other potential reasons for protocol interruption or failure of compliance. Some subjects will not follow the intervention protocol (e.g. they refuse to participate in the intervention program, non-compliance). Effort will be made to minimize the number of participants who do not follow up the protocol. Those participants who discontinue treatment will still be encouraged to participate in subsequent assessments. All patients will be kept in the study as randomized regardless of failure of compliance using an intention-to-treat analysis. A dose-response relationship in compliance and performance change will also be examined, i.e. that subjects with higher self-reported physical activity on their logs will be expected to have greater improvement in 6MW. To ensure that there is compliance with activity, actigraphs will be used in participants to determine compliance with protocols and accuracy of the activity logs.
5) Strategies for multiple inferences: The analysis involves several hypotheses tests, thereby requiring a strategy to control the alpha level. We will give higher priority to the primary hypothesis so that the outcomes of tests of mechanism hypotheses will not be given the same strength of interpretation. Overall significance levels will be controlled using the probabilistic inequalities (e.g. Bonferroni or Sidak's methods), adjusted confidence limits (e.g. Tukey), methods based on resampling (109) or other appropriate multiple comparison adjustment methods (7).

Hypothesis testing plan

For the purposes of hypothesis testing, specific key primary and secondary variables, based on previous pilot data have been identified.

Endpoints	6 month	12 month
Primary	6 minute walk (6MW)	
Secondary	Physical activity (PA)	IENFD
Tertiary		6MW, PA

Primary Hypothesis (6MW at 6 months): Compared to IGR participants advised to follow the current standard care recommendations on diet and PA (Standard Care or "SC"), IGR participants undergoing TDPA enhancement program will show greater improvement in the 6 Minute Walk (6MW) at 6 months.
Secondary Hypothesis 1 (PA at 6 months): At 6 months and compared to SC, TDPA participants will show greater improvement in self-reported PA.
For the Primary Hypothesis and Secondary hypothesis 1 that address the 6-month 6MW and PA intervention effect, the goal is to determine whether there is a group (TDPA versus SC) difference in 6-month improvement. A regression model will be used to test these hypotheses

controlling for the minimization variables and baseline outcomes (BA=outcome at baseline; GEN=Gender; BMI=Body Mass Index, Age=Age, GRP=intervention group):
Outcome at 6 months= BA+GEN+BMI+AGE+GRP

Secondary Hypothesis 2 (IEFND at 12 months): At 12 months and compared to SC, TDPA participants will show better maintenance of IEFND.
A similar strategy will be used to test for the 12 month intervention effect.
Outcome at 12 months= BA+GEN+BMI+AGE+GRP
The key parameter tested in all of these models is the group variable (GRP). The training efficacy hypotheses will be tested by comparing two nested models with and without GRP. The outcome at baseline and gender, BMI and Age variables are included to adjust the primary outcome for its baseline value. Assuming that residuals from the model fit are normally distributed, the analysis is equivalent to a classical analysis of covariance. For outcomes that do not fit a normal distribution, inverse, logarithmic or power transformations will be performed or generalized linear models (GLM) (110) with Poisson or gamma error will be considered. Since the outcomes are measured on three occasions (baseline, 6 months and 12 months), a model that takes into account repeated measures will be developed in the framework of linear mixed effects models (LME) or generalized linear mixed effects models (GLMM). Models for repeated measures will yield three tests: 1) a test for outcome changes over time of the study (time effect); 2) a test of group differences (an intervention effect); and 3) a test for interaction of intervention effect with time. We are primarily interested in the overall intervention effect. However, a changing intervention effect over time as reflected in an intervention by time interaction is of great interest since it might suggest that the intervention has a greater impact as time progresses.
Additional data analyses
A number of additional key variables will be assessed in order to investigate the maintenance of PA and 6MW improvement and mechanisms underlying the changes in neuropathy progression and mobility function.
Tertiary hypothesis (Maintenance of 6MW and PA at 12 months): At 12 months compared to 6 months, and compared to SC, TDPA participants will show greater sustained improvement in 6MW and self-reported PA.
Exploratory/mechanistic hypothesis: Improvement in measures of neuropathy (NCS, MDNS, IENFD), mobility function and PA will correlate strongly with each other and with improvement in specific measures of metabolic function and weight loss
We will rely on regression models to study multivariate relationships. These hypotheses will be addressed by examining the extent to which change in one of these measures relates to each other when controlling for other factors. Models can utilize outcome measurements at all time points (baseline, 6 months, and 12 months). We can also consider a number of measurements as contributing factors, i.e. covariates. For longitudinal data, models of the following type will be considered: (VS=Variables used in minimization; BA=outcome at Baseline; GRP=intervention group; COV= one or more covariates; TIME= time variable; *=interaction between variables):
Outcome at 6 and 12 months = VS + BA + GRP + COV + GRP*TIME + COV*TIME
The key aspects of this model in the context of our tertiary hypotheses are interactions GRP*TIME and COV*TIME, and the magnitude and significance of these interaction effects provide insight into mechanisms underlying study group differences. The remaining terms are used in the model to reflect study design and adjust for baseline values. The following methods will be considered particularly when analyzing longitudinal data for post-intervention hypotheses: LME models for continuous variables with normally distributed residuals); GLMM (111), and SAS PROC/GLMMIX (112). Both of these methods allow for unbalanced data, time-varying covariates, and structured covariance matrices. For the 12 month outcome, the model can take into account repeated measures and as such will be developed in the framework of LME or GLMM.
These exploratory analyses will not provide a definitive mechanism underlying changes in neuropathy progression, mobility function, or PA but we will be able to determine which variables are more strongly correlated and potentially more physiologically related. Our sample size of 64 per group (which should be achievable because we will recruit more people based on drop-out, as previously discussed) allows

us to detect effects of variables and/or their interactions as low as 5-6% of the variance explained over and above other predictors with alpha=0.05 and power of 80%.

Table 5: Summary of Variables

Variable	Type	Time		
		Baseline	6 months	12 months
Age, Gender, BMI	Minimization variables			
6MW	Dependent (Primary)	X	X	X
IENFD	Dependent (Secondary)	X		X
CHAMPS	Dependent (Secondary)	X	X	X
Measures of progression: MDNS	Covariates	X	X	X
Electrophysiological measures of progression: NCS	Covariates	X	X	X
Metabolic measures: Glucose, Lipids, HgbA1c	Covariates	X	X	X
Mobility function measures: Unipedal stance, TRE, 6MW, and gait speed	Covariates	X	X	X

Rationale regarding potential limitations to planned protocol

1) Use of single combined diet-PA intervention versus factorial design: We considered a four group factorial design, comparing diet only, PA only, combined diet-PA, and usual care. There are a number of problems with this design. Firstly, diet interacts with PA and this likely occurs in a non-additive but multiplicative manner. This interaction may depend on weight loss as well, which results from both diet and possibly PA interventions, further complicating the study interpretation. Secondly, in order for the factorial design to be properly tested, the diet group must not increase PA and the PA group must not diet. This may be theoretically scientifically valid but operationally not practical. While the proposed Standard Care group may or may not change their diet, increase their PA or lose weight, at least we will know the effect of the use of a standard set of recommendations, and, subsequently, the incremental benefits of a tailored combined diet-PA enhancement program. Finally, given the literature supporting the benefits of diet and PA interventions in reducing the progression of IGT (4;26;27), a more valid program to translate into the community should at least attempt elements of each. Often the initial evaluation may include several components, to be determined in later studies in a factorial design. In this case, such a design appears ill-advised and impractical.

2) Center-based group PA program versus home-based program: We are experienced in providing both center-based and home-based programs. Given the wide geographical distribution of the participants, a center-based program, even once per week, is not possible. The home-program is somewhat of a misnomer, in that TDPA participants are encouraged (and provided support) to enhance their PA in whatever manner they would prefer. This could include participation in a local center-based group program at a center of their choice.

3) PA program with an additional walking and balance program: The addition of the walking and balance program in particular is critical to address what we believe to be basic impairments in walking endurance and standing balance in patients with IGR. We understand that this addition will also complicate interpretation of the results, i.e. the effect of a PA program alone will be unclear, although the interpretation is already complicated by addition of a diet component. Future studies may consider deleting this supplement and testing the effect of the PA program alone, although PA programs in general tend to include walking anyway.

4) Lack of a “true” control group: While scientifically valid, a control group with no diet or PA intervention whatsoever is both unrealistic and unethical, given the present guidelines for those with IGR and promulgation of diet and PA suggestions in general. The control group must also receive a control “intervention” (health education follow-up) for the added “attention” provided to the intervention group. It is also likely that the effect of the proposed intervention would have been greater had the control group not participated in any follow-up (as in the usual care scenario), and this should be acknowledged in the interpretation of the study outcome.

5) Compliance with long term biopsy and intervention adherence: We are experienced in providing long-term follow up in diet, exercise, biopsies (IGTN study), and PA interventions. We believe that given the incentives provided, the proposed attrition rate, and the intrinsic value

provided in both intervention groups, the proposed plan is feasible and will likely lead to the expected outcomes.
6) Minimization variables: Use of a minimization technique to allocate participants to experimental groups leads to group equivalence in key variables including age, gender, and BMI. Other variables that might be considered for minimization include a measure of functional status (such as gait speed or neuropathy impairment level) and a measure of diabetes status (such as fasting glucose, HgbA1c, or time since diagnosis of diabetes). We were limited in the number of minimization variables allowed and thus chose what we believed to be the most crucial variables. We will nevertheless include all of these variables in the tertiary and exploratory analyses.
7) Move Program: We carefully considered adapting the nationwide VA Managing Overweight and/or Obesity for Veterans Everywhere Program (MOVE) as the main intervention but favored our tailored behavior change program with which we have extensive experience. Our rationale is that the MOVE program:
i) is primarily focused on diet and weight control and less on PA, the latter a key outcome in the present study.
ii) has less intensive contact with trainers than in TDPA.
iii) is focused on improving aerobic function and strength, whereas TDPA is focused on improving walking and balance, two key deficits in IGT-neuropathy in our pilot data.
iv) advises that the participant reach relatively high RPE (Rated Perceived Exertion) levels (up to 16 out of 20), which may require formal stress testing for safety, thereby requiring physician involvement, while the goal peak recommended TDPA RPE is 13. At week 13 and thereafter, the goal MOVE RPE is 13, the same as TDPA.
v) advises attendance at group diet seminars (at Level 2) whereas TDPA is individualized and home-based.
vi) is based conceptually on stage of readiness and self-efficacy whereas TDPA is based on a broader behavioral model, with the examination of perceived behavioral control (barriers), attitudes toward PA, and social support, as well as self-efficacy. This broader theoretical framework allows the trainers to tailor advice on additional important factors found to influence PA.
vii) is otherwise consistent with the TDPA exercise frequency and duration.

(2) Resources

Neuro-electrodiagnostics Laboratory (Baltimore and Ann Arbor): Both laboratories are equipped to perform nerve conduction and autonomic studies. The Baltimore Laboratory consists of 4 new Teca Synergy electromyography machines. The laboratory is managed by a senior electrophysiology technician. The Ann Arbor VAMC laboratory is staffed by a senior electrophysiology technician trained by Dr. Russell. Dr. Russell will oversee the quality control on the electrodiagnostic studies at both sites.
Mobility and Exercise Testing: In Baltimore, participants will be tested in the GCRC and Human Motor Performance Laboratory (see letter from Dr. Golberg and Forrester), and in Ann Arbor in the clinical center of the VA GRECC and Mobility Research Laboratory.
General Clinical Research Center (GCRC, University of Maryland and University of Michigan): The University of Maryland GCRC provides the following support: (1) exercise physiology unit and consultant exercise physiologist (2) A bioinformatics core for preparation and maintenance of the study database (3) Biostatistical core. The University of Michigan GCRC has a bioelectrical impedance analyzer. Blood tests can be obtained through both GCRCs at reduced costs to the study (see letters from Directors of the GCRC in Maryland and Michigan).
Research Laboratory (Baltimore VA): Dr. Russell has 1250 sq. ft. laboratory space at the Baltimore VA and leased VA space. This modern laboratory space is fully equipped to processing of skin biopsies. All processed biopsies will be sent to Dr. Smith's laboratory for IENFD analysis (see letter of support).
Ancillary support: All offices have locked file cabinets available for study data. Most personal proposed for this project (see budget justification) are already in place and have been working on electrophysiology/neuropathy measures or functional assessment and exercise projects for more than five years using similar assessment and training methodology as described in this

protocol. Because of the team's extensive experience, several study staff are proposed as IPA's. The investigators are all appointed at the VA except for the statistician.

(3) Collaboration: This proposal is a collaborative effort between the Baltimore VAMC (Dr. Russell) and Ann Arbor VAMC (Dr. Alexander). This collaborative effort offers an opportunity for two VAMCs to use the resources of both centers to enhance the proposal. This project is a model example of the melding of two premier VA research centers in applying state-of-the-art translational technology and interventional techniques to improve function and investigate mechanisms in a VA-relevant at-risk population. Please see enclosed Consultant letters of support from Drs. Smith (IENFD consultant), Andrew Goldberg (Baltimore GRECC), Carol Tacket, MD (Director, University of Maryland GCRC), Randall Keyser PhD (Director of the Human Motor Performance Laboratory, Baltimore VAMC), Ann Little (Ann Arbor Neurologist), and John Wiley (Director, University of Michigan GCRC).

HUMAN STUDIES

Risk to Subjects

1) Human Subjects Involvement and Characteristics: Patients with documented IGR will be entered in the study. All patients will have baseline HbA1c measurements between <8%. All participants will have mild neuropathy as described below. A total of 142 participants will be entered in equal proportions between the two groups (SC and TDPA) using a minimization procedure. The scheme will be prepared to achieve equal sample sizes for the two groups, for age, gender, BMI, time from diagnosis of IGR. Persons assessing diet, PA, mobility function and neuropathy progression will be blinded to group assignment.

This research topic is relevant to both women and men, and both will be included as they are recruited, approximately in proportion to their representation among older adults with T2DM. African-Americans will be recruited in proportion to their numbers among patients with T2DM, and if needed, emphasis on recruiting on recruiting African-Americans will assure they are not underrepresented in the study. Other minorities will be recruited based on their percentage in Washtenaw County, the primary recruitment region (3% Asian American, and 2% Hispanic).

Table 6 indicates the distribution of patients in Baltimore County, Maryland where the Baltimore VAMC and the University of Maryland are located and in Washtenaw county where the Ann Arbor VAMC and University of Michigan Hospitals are located. The distribution of Black or African Americans in Baltimore county is twice the national average and in Baltimore is over five times the national average thus increasing recruitment of minorities from this population group. In contrast, the distribution of Asian/Pacific Islander and Native American or Alaskan Native is greater in Washtenaw county than in Baltimore, increasing recruitment of these population group in Michigan. Both site will relatively under recruit Hispanics, although the rate of growth of this group is now among the highest in the nation in the greater Baltimore area. The distribution of patients seen at the Baltimore VAMC and the Ann Arbor VAMC is similar to respective demographics listed below with the exception that the proportion of male to female patients is greater. T2DM is more common in blacks than in the general population, and as much as three times more prevalent in some groups of American Indians (20), thus we predict that we will recruit an increased number of minorities into the study.

Table. 6: Baltimore (Baltimore VAMC and University of Maryland) and Washtenaw County (Ann Arbor VAMC and University of Michigan) Hospital Demographics

MARYLAND/BALTIMORE COUNTY HOSPITAL DEMOGRAPHICS (%s)							
	American Indian / Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic of any race	White, not of Hispanic Origin	Other or Unknown	* TOTAL
Female	0.054	2.11	12.96	1.35	37.48	1.24	55.19 (52)
Male	0.046	1.79	11.04	1.15	32.12	1.06	47.21 (48)
Unknown	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	0.1	3.90	24.0	2.50	69.60	2.30	102.40 (100)
DATA SOURCE: **Baltimore County;** US Census Bureau, Census 2005. & Census 2005 Brief – Overview of Race and Hispanic Origin							

CITY OF BALTIMORE HOSPITAL DEMOGRAPHICS (%s)							
	American Indian / Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic of any race	White, not of Hispanic Origin	Other or Unknown	* TOTAL
Female	0.23	0.93	37.32	1.32	17.37	1.50	58.67 (54)
Male	0.17	0.68	27.88	0.98	12.84	1.10	43.65 (46)
Unknown	0.0	0.00	0.0	0.0	0.0	0.0	0.0
Total	0.4	1.60	65.20	2.30	30.20	2.60	102.32 (100)
DATA SOURCE: **Baltimore Metropolitan Area;** US Census Bureau, Census 2005. & Census 2005 Brief – Overview of Race and Hispanic Origin							

WASHTENAW COUNTY (MICHIGAN) HOSPITAL DEMOGRAPHICS (%s)							
	American Indian / Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	* TOTAL
Female	0.18	3.17	6.15	1.37	38.70	1.81	51.37 (50)
Male	0.18	3.17	6.15	1.37	38.70	1.81	51.37 (50)
Unknown	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	0.36	6.34	12.29	2.74	77.40	3.61	102.74 (100)
DATA SOURCE: **Washtenaw County;** US Census Bureau, Census 2000. & Census 2000 Brief – Overview of Race and Hispanic Origin							

Sources of Materials

The majority of data collected will be directly from the human subject and will include basic demographic data, a patient history, physical examination, NCS. Assessments of PA and mobility function will be performed as indicated in the protocol. Clinical surveys include the MDNS. In addition, we will obtain:

1) 100 mls of blood from subjects to perform biochemical measures of metabolic function, genetic, and proteomic studies at enrollment, at 6 months, and at 12 month follow up visits.
2) Three 3 mm skin punch biopsies will be performed on the left thigh and calf at enrollment and 12 months.

We will also request to corroborate the subject interview with inspection of their medical records that may include information about their number of physician visits and hospitalizations related to T2DM. All HIPAA requirements will be carefully followed.

Potential Risks

The risks to the subjects from participation in this study are low and consist predominantly of any adverse effects consequent to a tailored diet and physical activity program. There are no significant risks to the patient from NCS, which are used in routine clinical practice. Patients may have mild discomfort during the NCS.

In the IGTN study, there were no significant complications from the skin biopsy with the exception of minor bleeding. There is a risk from bleeding in participants taking blood thinning medications such as coumadin. There is a remote risk of skin infection at the site of the skin biopsy, although this did not occur in the IGTN study. In the current IGTN study, use of NSAID has not been a contraindication to performing a biopsy. There is also a risk of keloid formation, delayed healing, or scarring.

There is a risk of worsening clinical angina, arrhythmias, myocardial infarction, and pulmonary symptoms and of possibly provoking death when an exercise program does not involve proper screening and monitoring. Given the known comorbidities and complications associated with T2DM, participants may have a number of symptoms related to the exercise program, such as localized muscle pain, joint pain, or cramping with soreness, sensations of warmth, sweating, fatigue, loss of balance, light-headedness, dizziness, irregular heart beat, chest pain, or shortness of breath. Some of these symptoms may be related to hypoglycemia. These risks are all research risks, given that the training measures, although commonly used, are part of a research paradigm.

Adequacy of Protection from Risks

1) Recruitment and Informed Consent: 128 subjects (64 per subject group) will be recruited. Using the actual 1 year drop out for enrolled subjects from the IGTN study of <4%, the number of subjects to be enrolled is 133 and 142 if we assume a more liberal dropout of 10%. This requires that we recruit 6-7 patients/month for 21 months. A recruitment plan is outlined in the recruitment section of the grant. A flyer has been designed (subject to Human Use approval) to provide information about the program. After showing interest, a potential participant will be contacted by telephone or email by trained study personnel to begin to determine eligibility. An appointment at their convenience will be made and the project will be further explained together with the subjects review of the consent form, which will be signed, if the subject wishes to participate in the study. The consent form will be a written document that is fully in compliance with the requirements of the Veterans Administration Human Studies Committee. The consent will be obtained by the study coordinator or study physician. The nature of the information provided to subjects (which will be included on the consent document, a copy of which will be kept by the subject) will include a description of the background of the study, the relevance and purpose of the study, and a detailed description of the type of procedures that the patient will undergo including any potential risks or discomfort that will be experienced. The potential long-term benefits of any new data derived will also be explained as will any direct utility to the

individual concerned. Confidentiality will be ensured as all data will be kept in a locked cabinet within a locked office. Only named investigators on the Human Studies application will be aware of the patient's identity and clinical details. The patient may withdraw from the study at any time.

2) Protection Against Risk: In order to minimize any potential possibility for risk, 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. Subjects will have the potential side effects explained to them. In order to perform blood samples for metabolic function, a small cannula will be placed into a vein of the arm in order to draw blood samples that involve a small amount of discomfort. We will aim to collect approximately 40 mls of blood (6 teaspoons) at each time point for metabolic studies.

There are no significant risks to the patient from NCS. NCS are used in routine clinical examination. Patients will be warned of mild discomfort during the NCS.

Skin biopsies will not be performed in subjects on anticoagulants or with poor skin condition. To avoid infection post skin biopsy, the procedure is performed under sterile conditions, antiseptic ointment is applied to the biopsy site and bandaged with sterile dressings. Participants are warned to keep the biopsy site dry for 72 h, and to replace the dressings with antiseptic ointment and bandages provided by the study team. **Skin biopsies are performed as a routine clinical procedure at the Maryland and Michigan sites and in over 200 patients have not been associated with any adverse effect.**

The entry criteria for the study exclude potential participants with other significant medical illness such as angina or pulmonary disease, and based on the IGTN study no participant has had a medical reason why they cannot exercise. Potential participants with other conditions such as joint disease, amputations etc. that would limit exercise are excluded from the study.

The protocols for testing and training have been chosen to minimize risk, and we believe that there are no other alternatives that would provide the information we seek while reducing risk further. We have minimized these risks by using careful screening and monitoring, and with careful instructions to our participants. Data (including our own) exists showing that it is safe for older adults with chronic disease and functional impairment to participate in both on-site and home exercise programs.

Safety during testing assessments and training is ensured by a team with considerable experience and expertise. Monitoring of the trainers, physical therapist and exercise physiologist will be under the supervision of Dr. Alexander and Dr. Gretebeck. Participants are supervised during testing by a trained technician, as well as the study coordinator, in addition to the overall physician supervision. Test procedures, including the sampling of blood, DEXA, and functional tests are associated with minimal side effects or risk. Participants will be educated regarding symptoms and signs of hypoglycemia, and check post-exercise pulse. The physical therapist will check glucose levels, heart rate and blood pressure during the orientation sessions. Hypoglycemia, marked by consistent tachycardia or blood pressure elevation or depression may lead to discontinuation in the study. Participants will be instructed to exercise only to the extent that they feel comfortable. The option to discontinue the protocol at any time will be stressed. Subjects are instructed to curtail exercise for a particular day if any muscle or joint pain is encountered. Injuries are evaluated by the physical therapist and/or clinical trials coordinator under physician supervision. Treatment is offered through the subject's private physician (who has already has been contacted to provide permission for the subject's exercise program participation), or VA Clinics. Consistent with our long-term policy, new abnormal test findings and/or change in health status are communicated quickly to the subject's personal physician or nurse practitioner, with agreement from the subject. Subjects with continued pain or intolerance to even the lowest level of exercise may be discontinued from the program. All subjects are encouraged to maintain their usual level of activity and not initiate a new exercise program. Concurrent participation in a personal physician-ordered physical therapy program

will not be allowed.

Safety during the home program is ensured in several ways. Firstly, participants will have undergone screening, assessment and training. Secondly, participants will not perform any exercises on which they are trained. Thirdly, they will be monitored by telephone contact with the physical therapist and exercise physiologist, who will specifically ask about problems participants are experiencing and offer the participant opportunities for questions.

Confidentiality will be maintained to the fullest extent possible. The data will be entered into an access protected electronic database, each subject will be coded and personal identifiers will be removed, and paper copies of all original documents will be maintained in the study binder. Longstanding protocols have been in place, including data coding by subject number, locked in file cabinets, and cross-referenced by a name-number key in another location. Biological specimens will be coded and stored in a locked refrigerator in a locked room as already established for current VAMC studies.

3) Independent Safety and Data Monitoring Committee: This study will use a lifestyle intervention, and it is not predicted from the IGTN study that a standing independent SDMC will be required. All serious adverse events (SAEs) will be reported to the University of Maryland Institutional Review Board (UMIRB), which oversees both University of Maryland and Baltimore VA clinical research studies, or the Ann Arbor Human Studies Subcommittee (AAHSS) at their monthly meetings. If in the opinion of the IRB or the HSS, the number of probably related SAEs is determined to be higher than predicted, then an SDMC will be convened under the direction of Dr. Weiner, the Chair of Neurology at the University of Maryland. The records for the study will be reviewed, and a preliminary data analysis and assessment of frequency of SAEs and AEs will be performed with the assistance of the study statistician, Dr. Andrzej Galecki. A report of the SDMC findings, recommendations, and study requirements will be submitted to the UMIRB, the AAHSS, and the study investigators, and compliance will be overseen by the SDMC, the UMIRB, and the AAHSS.

Potential Benefit of the Proposed Research to the Subject and Others

There may be no or only minimal benefit to the subject from participation in this study. This will be indicated in the informed consent. Early peripheral neuropathy may result in severe neuropathic pain. Potentially the TDPA program may affect the participants response or perception of pain.

The exercise and diet program may improve general health, fitness, and overall well-being. All subjects will receive some instruction regarding exercise and diet, although the benefits may vary in type and amount, which is part of the research question. The screening evaluation may be useful for the participants and if permitted by the participants, to their physicians, due to the thorough evaluation and stress testing.

Importance of the Knowledge to be Gained

Knowledge will help determine if a TDPA program is able to prevent, or ameliorate neuropathy in persons with IGR and improve function and mobility. There is currently no effective treatment for diabetic neuropathy, other than improved glycemia. Thus any improved therapy that helps to prevent one of the most severe and costly complications of diabetes, namely diabetic neuropathy, would provide significant benefit within the population. New knowledge related to the treatment and mechanism of neuropathy outway the small risks from the tests performed and the TDPA intervention.

In summary, important potential benefits exist for the participants, including improved fitness and possible well-being and useful medical information. In addition, extremely useful information with potential to benefit other older adults with diabetes will be obtained. Given the extensive plan to minimize risk, the risk: benefit ratio appears acceptable.

Expertise of the PIs in this Project

Dr. Russell has been a funded, active VA investigator for the past 10 years and has recently been appointed Head of the Neuromuscular Division at the University of Maryland. He recently moved from the University of Michigan where he was an Associate Professor in the Department of Neurology and a member of the GRECC. The University of Maryland and VA together have 12 half day clinics/week dedicated to seeing patients with neuropathy. The Division is staffed by seven neurologists, a nurse practitioner, and eight other support personnel. The Division also has active collaborations with the Diabetes Research and Training Center and the GRECC. Dr. Russell has Merit funding for research in diabetic neuropathy, and for the past 15 years had clinical research interests in the study of diabetic neuropathies and is actively involved in clinical trials of diabetic neuropathy including an NIH funded study to understand the mechanism/s and progression of neuropathy related to impaired glucose tolerance and a trial funded by the Juvenile Diabetes Research Foundation to test therapies to prevent the progression of diabetic neuropathy. Dr. Russell's laboratory has as its research focus understanding the mechanism/s and treatment of diabetic neuropathy. Understanding the pathogenesis of diabetic neuropathy will allow a more a rational design of therapies to ameliorate of reverse this devastating condition.

Dr. Alexander is Director of the Ann Arbor GRECC and Director of the Mobility Research Center at the UM Geriatrics Center. He has completed a number of mobility assessment studies as well as intervention studies in physically impaired older adults and has internationally recognized expertise in mobility performance assessment. His recent interest in measurement of aerobic performance, particularly sub-maximal performance in impaired older adults is of particular benefit to this proposal. Dr. Alexander is PI on a (Medical) Merit Review randomized clinical trial in progress to determine the effect of six months of aerobic, functionally-based exercise on functional outcomes in older adults with congestive heart failure. As co-investigator, he is applying this model to a (Rehab R&D) Merit Review recently funded trial (Caroline Blaum PI) to use the same aerobic paradigm in older adults with Type 2 diabetics. An experienced clinical intervention team of a nurse practitioner, exercise physiologist, physical therapist, and lab technicians are thus already in place. His appointments are as a full-time professor in the UM Department of Internal Medicine/Division of Geriatrics, Acting Director of the VA Ann Arbor Health System GRECC, and Senior Research Professor in the UM Institute of Gerontology.

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