"Management of Antipsychotic Medication Associated Obesity - 2"

Study Protocol and Statistical Analysis Plan

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2. Research Plan (vers. 02-10-2014)
Merit Review for Rehab R&D
LOI No.
Research Plan: Management of Antipsychotic Medication Associated Obesity 2
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I. Specific Aims:

A. Introduction: This proposal is a resubmission and extension of our currently funded VA Merit Review entitled *Management of Antipsychotic Medication Associated Obesity or MAMAO* (1, 2). To our knowledge, this research is unique in that it represents the longest term intervention to date in patients with severe mental illness and antipsychotic medication associated obesity. 225 veterans were screened and over 120 randomized to either a multi-modal lifestyle intervention termed Lifestyle Balance Program versus usual psychiatric care at the Greater Los Angeles VA Healthcare System. The Lifestyle Balance Program included planned and scheduled psychoeducation, exercise, dietary changes and counseling with caregivers. The Program was adapted in part from the federally-funded Diabetes Prevention Program. A preliminary data analysis was performed using a mixed model analysis of the current patient cohort revealed significantly greater weight management outcomes for those subjects randomized to the Lifestyle Balance Program. N=46 participants completed 6 or more months of the protocol, 22 of whom completed 1 year. For those subjects who completed one year of the protocol a mean difference in weight gain of 11.8 lbs. between the treatment groups was found, favoring the subjects in the Lifestyle Balance Program. Subjects in the Lifestyle Balance Program lost an average of 6.6 pounds while those in the usual care condition gained an average of 5.2 pounds ($F(1,935) = 25.1$, $p<0.001$). This encouraging result is more than double the 5.5 lbs. group difference that we predicted in the original proposal.

Given the success of this program thus far we propose testing this program in a multi-site study at four VA medical centers in the Greater Los Angeles VA Healthcare System (West Los Angeles, Sepulveda, Long Beach VA Medical Centers and the Downtown Outpatient Clinic). Dissemination of this intervention is in line with current VA and national priorities. These priorities include:

1) Weight control is an imperative in Wellness Programs that comprise an integral component in VACO-mandated PRRCs (Psychosocial Rehabilitation and Recovery Centers).
2) VACO mandated national dissemination of skills training principles and techniques for use in PRRC's, approaches that are basic to the current application.
3) Both the FDA and the VA inspector general recommended that the VA actively develop ways to both monitor and control antipsychotic medication-associated metabolic side effects.
4) A comprehensive weight loss program for severely mentally ill veterans is consistent with the recommendations that emerged from the President's New Freedom Commission on Mental Health, the Surgeon General's Report on Mental Health; the Surgeon General's Report: Toward a National Plan on Overweight and Obesity and the Illness Management and Recovery recommendations from the US Substance Abuse and Mental Health Administration.
5) The VACO, NIMH, and NAMI priorities for recovery from schizophrenia and related mental disabilities. Recovery is reached for even the most severely disordered persons when optimal treatments and natural supports enable these individuals to lead meaningful lives with hope, empowerment, self-responsibility and community integration. Recovery and illness self-management include maintaining weight control, avoiding the metabolic syndrome, taking responsibility for reliable and informed use of appropriate medications and having symptoms reduced below the level that they intrude on everyday functioning so individuals can participate in work, education, recreation, friendships, cordial family relations and independent living.
6) An emphasis on spiritually-driven methods in holistic modes of psychiatric treatment that will be incorporated into the DSM V diagnostic system currently under development by the American Psychiatric Association.

The aims of this research program are to 1) reverse obesity in patients with severe mental illness who take antipsychotic medications and 2) begin to disseminate the program to non-research mental health settings such as Psychosocial Rehabilitation and Recovery Centers (PRRCs). It is crucial to the VA mission to develop an accessible and effective program tailored to veterans with severe mental illness (SMI) given the significant morbidity and treatment challenges in this population. Though the existing MOVE! program is recommended for weight loss for all veterans, many patients with SMI are unable to participate for a variety of reasons. Thus, this program addresses a gap in current care. The program in this proposal is similar to MOVE!, but is

specifically designed to meet the needs and treatment challenges of veterans with SMI, and particularly antipsychotic medication associated obesity, over a longer treatment period. Because patients with SMI must take antipsychotics their entire lives, we must be constantly vigilant and monitor their weight and other metabolic parameters as now mandated by the FDA and Inspector General for the VA.

B. Short Term Objectives: The primary objective of this prospective, multi-site randomized, parallel group research proposal is to evaluate the effectiveness of a multi-modal intervention to combat antipsychotic associated obesity, and to prevent and monitor diabetes and other metabolic side effects of atypical antipsychotics in SMI patients. Specifically, we wish to test the effectiveness of a lifestyle intervention program targeting healthy lifestyles in four different VA settings. We will determine if the classes, individual coaching, along with a prescribed diet and exercise regimen improve patients' metabolic profiles, cardiovascular risk factor status, and overall mental health compared to usual psychiatric treatment. Further, this program will provide the opportunity to increase our ability to identify which veterans (based upon diagnostic, medication, and psychosocial status) are most likely to benefit from this behavioral weight loss intervention.

C. Long Term Objectives: 1) To decrease the long term risks associated with obesity such as coronary artery disease and diabetes in the SMI population. 2) To promote recovery, improve mental health, quality of life, and treatment adherence, and to decrease utilization of hospital resources by improving the overall medical and psychiatric condition of these patients. 3) To create a user-friendly intervention program that is easy to disseminate and implement and can be provided by any motivated health care provider in any mental health setting. 4) Finally, we wish to network with other mental health providers and create an educational website that will allow us to disseminate the program further outside of our 4 sites. Specifically, we think this will be helpful to ultimately disseminate this manualized long term weight loss program to other mental health programs such as PRRCs that are being established by the Uniformed Services Package throughout the country (3).

D. Hypotheses

1. Primary Hypotheses:

a) Veterans with SMI at four different sites with antipsychotic associated obesity who participate in the 12-month multi-modal, MOVE-like, intervention that includes classes of the Lifestyle Balance Program, and individualized lifestyle balance coaching, will gain more knowledge (i.e., greater change scores on before/after survey test instrument) about general health issues (e.g., nutrition, importance of exercise, etc.) than a control group receiving "usual psychiatric care."

b) Subjects randomized to active treatment in the 12-month, Lifestyle Balance Program will make more objective lifestyle changes (as measured by exit interviews, food and exercise diaries, fidelity assessments) than those in the usual psychiatric care group.

c) Subjects who participate in the 12-month multi-modal Lifestyle Balance Program will achieve better cardiovascular (e.g., sustained weight loss, better glucose tolerance, improved lipid profiles) and mental health (e.g., improvements in recovery from mental illness, improvement in biopsychosocial/spiritual wellness [measured by the WHO-QOL BREF and the BPSS], general measures of psychopathology, subjective quality of life, etc) outcomes than the control group.

2. Secondary Hypotheses:

a) Negative and cognitive symptoms. We hypothesize that negative symptoms and cognitive impairment (measured by BPRS subscales) will correlate negatively with weight loss. Motivation (measured by the URICA) and illness insight (measured by the SAIQ) will be positively correlated with weight loss.

b) Treatment adherence. SMI veterans involved in the Lifestyle Balance Program will have better adherence to psychiatric treatment than the "usual care" group as measured by a treatment adherence questionnaire, percent of antipsychotic medication refills and percent of appointments attended.

c) Ongoing informed consent. Consent is to be an ongoing process and we hypothesize that SMI veterans involved with the program will continue to give informed consent to participate. This will be demonstrated by subjects' performance on the informed consent quiz at 0, 6, and 12 months of participation.

II. Background and Significance

A. Overview of Obesity in the SMI Population: [Definitions: "Obesity" is defined as a body mass index of $\geq$ 30. "Overweight" is defined as a body mass index of $\geq$ 25. Body mass index (BMI) is a ratio of person's weight in kg divided by their height in meters squared. Severe mental illness (SMI) includes schizophrenia, bipolar disorder, severe recurrent depression, obsessive-compulsive disorder, and panic disorder] Obesity is a severe public health problem in the United States that shortens our lives due to its association with a number of diseases, including diabetes, cardiovascular illness, and several forms of cancer

(4). Obesity is "outweighing" smoking as the number one modifiable risk factor for cardiovascular disease and death in this country. Obesity is an even greater problem for patients with SMI. The SMI have a higher all-cause mortality rate than the normal population with suicide and cardiovascular disease accounting for the lion's share of the early deaths (5-7). Given a smoking prevalence sometimes exceeding 75% it is not surprising that cardiovascular disease remains the leading cause of premature deaths.

Within the Veteran's Healthcare System, the cost of obesity and its associated morbidity including diabetes and cardiovascular disease was $5.3 billion in 2003. The cost of the treatment of SMI was approximately $3 billion (vaww.arc.med.va.gov). In a recent publication, Banerjea and colleagues examined the healthcare costs to the VA and Medicare of co-morbid diabetes and mental illness. Fiscal expenditures in 200 for people with the two problems combined along with substance abuse were $19,801 compared to $6,185 for diabetics with no mental illness (8). Across 400,000 charts reviewed, this is staggering and does not even take into account indirect costs of these combined illnesses. The prevalence of obesity is estimated to be 60% among veterans. The VA Inspector General's report reflected that of all charts reviewed, 80% of patients taking second generation antipsychotic medications or SGAs were obese (9). While the cause of the obesity epidemic can in part be traced to our evolutionary roots, much of the increasing incidence of obesity stems from our increasingly sedentary lifestyles and the steady inflation of portion size – particularly those of fast foods (10). Clearly, patients with SMI share many of these risk factors and have others specific to their psychiatric conditions and their sequelae. For example, inadequate financial resources contribute, where rates of obesity are inversely correlated with socioeconomic status, due to limitations in adopting healthier but more expensive diets. In the inpatient and residential care setting, inactivity is encouraged and patients have little control over diets that often exceed caloric requirements. Further, the cognitive handicaps associated with SMI can render a person less responsive to warnings about the health consequences of poor diets.

B. Overview of Antipsychotic Medications: Antipsychotic medications have proven to be the most effective treatment for severe mental illness; however, these medications have their own liabilities. The focus of this project is to develop a strategy to combat medication associated weight gain, the most problematic side effect of the newer antipsychotic medications. The threat posed by iatrogenic weight gain for patients with schizophrenia includes medical sequelae of obesity such as increased cardiovascular disease risk, the added stigma of obesity, and the exacerbation of mental illness through nonadherence with pharmacologic treatment due to the weight gain (11). Nonadherence to treatment is a major cause of relapse and rehospitalization and has been estimated to increase relapse rates by five-fold (12). It is estimated that the rate of nonadherence is around 50%, and, although there are no data from controlled studies on the subject, weight gain can contribute to nonadherence in schizophrenia patients treated with atypical antipsychotics (11, 13). The prejudice, disrespect, and frankly biased treatment severely overweight persons receive from society at large only adds to the alienation, helplessness, and frustration of the mental illness itself.

Advances in the medication treatment of psychotic disorders over the last two decades have brought about the development of a new class of antipsychotic agents. These second generation antipsychotic medications (SGAs) such as clozapine (CLOZ), olanzapine (OLZ), quetiapine (QUE), risperidone (RIS), ziprasidone (ZIP), and aripiprazole (ARI) offer significant advantages over first generation antipsychotic (FGAs) medications such as haloperidol (HAL), fluphenazine (FLU), chlorpromazine (CPZ) due to their more favorable extrapyramidal side effect (EPS) profiles. FGAs caused short and long-term disability from neurological side effects including drug induced Parkinsonism, dystonic reactions, and potentially irreversible choreoathetoid movement, tardive dyskinesia (TD). The SGAs have minimal neurological sequelae but do have side effects that are clinically significant. In particular, most of these medications have significant effects on weight gain, impaired glucose tolerance, and changes in lipid profiles. When considered with the alarmingly high rate of smoking in this population, obesity and its related complications clearly exposes this group to a markedly enhanced risk of coronary artery disease and premature death. SGA associated weight gain is perhaps the most serious common side effect of this new class of agents threatening to dwarf the seriousness of TD from the FGAs. The purpose of this merit review program is to continue the testing and fine-tuning of a behavioral weight loss program that will be tailored to the special needs of patients with severe mental illness (SMI).

C. Evidence of SGA Associated Weight Gain, Diabetes and Dyslipidemias: The PI has been at the vanguard of the field in increasing physicians' awareness of side effects of the novel antipsychotic agents (e.g., weight gain, diabetes, metabolic syndrome, and dyslipidemias) and has demonstrated the benefit of behavioral interventions on SGA associated weight gain (11, 14). In a retrospective analysis of 99 patients' charts we found that simple behavioral weight loss strategies that we routinely employ in our clinical care of patients, such as weighing patients at their visits, asking patients to keep a food and exercise diary, and encouraging

exercise and healthy diets, resulted in modest changes in average weight lost. The first case reports of diabetes associated with SGAs as well as compelling evidence that glucose and lipids were deleteriously affected by SGAs were reported by the PI (15-17). A monitoring program for following the metabolic side effects of antipsychotic medications that was designed in this laboratory was adopted by the American Diabetes and American Psychiatric Association and published in Diabetes Care in 2004 (18). The PI has been an advocate of physical monitoring of patients on antipsychotic medications for over a decade and has been involved in multiple publications in addition to the ADA/APA consensus statement on this topic (19, 20).

Our initial observations have been confirmed by head to head comparisons amongst the medications. Head to head comparison data amongst the SGAs indicates that the hierarchy of weight gain liability is (CLOZ>OLZ>QUE>RIS>ZIP=ARI) (21). These results have been supported by consensus statements and the largest, national study comparing all antipsychotic medications (21). Numerous studies have now demonstrated that the SGAs have increased liability for the metabolic syndrome, diabetes and dyslipidemias (19, 22). Taken together, research shows that the coronary artery disease risk factors for patients taking certain antipsychotic medications clearly increase (21). The Office of the Inspector General (OIG) has determined that metabolic monitoring needs improvement. Also, the referrals of patients at risk for weight gain who take SGAs to MOVE! programs or other weight loss interventions are also suboptimal. Thus, the need for a behavioral weight loss intervention specifically designed for those with SMI is vital to detect, monitor, and reverse weight gain in order to increase the lifespan as well as quality of life.

D. Treatment of Iatrogenic Weight Gain and Obesity in Psychotic Patients: Because the literature thus far suggests that some of the SGAs cause somewhat less weight gain than others—one suggested strategy is to attempt weight loss by simply switching patients from CLOZ or OLZ (SGAs associated with the most weight gain) to ARI, ZIP, RIS or QUE (11, 23). While there is some evidence that RIS is useful in treatment refractory patients, (i.e., patients who take CLOZ) (11) no such data exists yet for QUE although Reinstein's work is somewhat promising (24). The problem is that one cannot assume equal antipsychotic efficacy in every patient for each antipsychotic medication. Indeed, CLOZ is reserved for the most refractory patients and no other medication to date has proven as effective in such patients. Thus, switching medication for weight loss purposes alone must be done with great caution due to the risk of psychotic exacerbation, rehospitalization, and even death. Ideally, clinicians will try to choose the medications that are most favorable and least harmful in terms of weight gain, but we are often limited by formulary and other financial restrictions.

Unfortunately, the adjunctive medication options for treatment of obesity that exist in the non-psychiatric population are virtually contraindicated in patients with SMI. Medications that can result in weight loss such as psychostimulants can exacerbate psychotic symptoms. There have been few studies of administering weight loss agents to psychotic patients. Amantadine, fenfluramine, and chlorphentermine have been used with moderate success (25-28). Orlistat is an inhibitor of gastric and pancreatic lipases that decrease dietary fat absorption, resulting in lowering of body weight and plasma cholesterol (29). Orlistat is difficult to administer, requires three times a day dosing, and vitamin supplementation, thus may be difficult to use in psychiatric populations. A new anticonvulsant, topiramate, that was tested but was not effective as a mood stabilizer in bipolar disorder, causes a decrease in appetite and weight loss. It has not been systematically studied as primarily a weight loss agent but has demonstrated weight loss in patients with epilepsy and bipolar disorders. Topiramate may get an FDA indication for binge eating disorder (30, 31). Sibutramine is FDA indicated for weight loss in obesity but not proven safe yet in the treatment of patients with psychosis (32). Sibutramine is a serotonin and norepinephrine reuptake inhibitor that was originally developed as an antidepressant, but was instead approved by the FDA as a treatment for obesity (33-36). Sibutramine demonstrated some efficacy in 37 patients taking olanzapine who were suffering from the side effect of weight gain (37). The combined effect of sibutramine and behavioral modification over 12 weeks was positive.

Current medical practice lists most psychiatric illnesses as contraindications to bariatric surgery. At our VA, there is concern that patients with psychotic illnesses are not cooperative enough with special instructions and dietary restrictions that follow the surgery, and thus they will run into serious complications. Thus, at our VA, bariatric surgery is not an option. One study that was recently published suggested that it is possible to perform this surgery in such patients so perhaps this prejudice will eventually be lifted (38). If we can elaborate a behavioral intervention that psychotic patients can understand and follow, perhaps some of our surgical colleagues will reconsider their ban on this effective treatment for obesity.

E. Behavioral Treatments for Weight Loss in Psychotic Patients: Despite the dangers of obesity and the negative impact it has on patients' quality of life and long-term health, little effort has been put forth into helping this disabled population with behavioral weight loss strategies. Often patients with psychosis are viewed as impaired in their thinking and ability to reason, but many are capable of learning materials,

particularly if educational materials are presented in a multi-modal and repetitive manner. Informal reports about SMI patients attending the relatively new MOVE! program at our VA suggest that often these patients are disruptive, have difficulty concentrating in the classes, and are poorly adherent to the program. Because of the special learning needs and accommodations some SMI patients' need, it is imperative that a modified MOVE! program be available with trained professionals who can deal with the special needs of this population. Though the recovery model would suggest that all SMI patients should be able to avail themselves to the non-psychiatric MOVE! program, the reality is that a subset cannot or will not. Therefore, psychiatric care centers, such as the newly developing PRRCs, would be an ideal place to implement a MOVE! program aligned with the special cognitive and psychiatric challenges presented by a segment of the SMI population. Based on an anecdotal survey of our PRRC patients, 50% reported that they would not avail themselves to either MOVE! classes or to the research program that we offered. We therefore integrated both individualized and group MOVE! like classes into our PRRC.

Social skills training is a vital component to the treatment of schizophrenia (39-41). A natural extension of educational programs to aid with the treatment of schizophrenia is to also include education about other aspects of health, particularly lifestyle balance to combat obesity. The Lifestyle Balance Program classes that were developed for the nationally funded Diabetes Prevention Program (DPP), as part of behavioral strategy to thwart diabetes in patients at risk have been utilized in our study. These manualized classes can be provided by "lifestyle balance coaches" and are a combination of education, motivation, and skills training to help people eat properly and exercise (42). The class materials are available on the Internet at http://www.bsc.gwu.edu/dpp/lifestyle/dpp_part.html. If successful in this population, this publicly available information will be easy to disseminate to other clinicians and patients.

Behavioral interventions such as calorie restriction, exercise, and behavior modification are key elements to successful, sustained weight loss. Three behavior modification techniques will be key elements in the Lifestyle Balance Program: (1) motivational interviewing and (2) contingency contracting, and (3) social skills training provided by the Lifestyle Balance coaches. These will be described in the Methods section below. In fact, behavioral interventions have been used successfully to prevent diabetes and demonstrated efficacy equal to the anti-diabetic medication metformin (43). Behavioral interventions may be an excellent option for the SMI population given the relative risks of any of the above strategies discussed — switching antipsychotics to a potentially ineffective one, adding medications with additional toxicities and propensities to worsen psychiatric symptoms, and finally surgery that is risky in patients whom surgeons feel will not benefit from such intervention. Most publications on weight loss in the SMI population to date are neither controlled nor large, but offer some hope that behavioral strategies can be of assistance to patients with psychotic disorders. In one small 14-week study, (N=14) patients achieved, on average, 10 pounds of weight loss when given behavioral interventions (classes and a contingency model—rewards for weight lost) compared to a control group (44). Retrospective analysis of simple interventions we have offered in clinic suggest behavioral interventions such as simply weighing patients, meeting with a nutritionist, maintaining a food diary, and encouraging exercise were fairly successful in RIS and OLZ treated subjects, although these strategies seemed to have little effect in CLOZ treated subjects (11).

A recent retrospective analysis concurs that combined behavioral interventions may be critical to managing antipsychotic drug-induced weight gain (45). Others are testing outpatient interventions such as Weight Watchers (46), dietary pharmacological manipulations (47), and intensive classes (48) that are encouraging. Vreeland and colleagues developed a multimodal approach that was successfully implemented in 31 patients in a day treatment program compared to concurrently treated, but not randomized "usual care" patients (49). Within group differences in hemoglobin A1C, BMI and weight were observed at the end of the yearlong program. The lack of randomization and proper control make the data difficult to interpret, however, the within-group changes on metabolic parameters are encouraging. Another group utilizing a modified version of the Diabetes Prevention Program (the same educational materials we are using) among SMI patients reported success in a pilot study demonstrating weight loss ranging from 1 to 20 pounds (50).

F. Dietary Considerations: Controversy exists over type of diet to recommend to patients who suffer from obesity and no research has explored particular dietary interventions alone in patients with psychotic illnesses. Although it is tempting to try to control the diets of the patients who will participate in the study, we want to approximate real world care, and plan to work individually with each patient and caregiver to initiate a calorie restricting diet they can implement easily. Food diaries will help us focus in on trouble eating behaviors. The choice in this study is to follow the dietary guidelines recommended in the diabetes prevention program. The DPP study focused initially on reducing total fat rather than calories (42). This allowed study participants to reduce calories while at the same time emphasizing healthy eating. After several weeks in the program, the

concept of calorie balance and the need to reduce caloric intake as well as fat was taught to study participants. It is crucial to educate our patients about making healthier choices at fast food restaurants and convenience stores (10), which provide food at a low cost, but in large portions high in both fat and carbohydrates. In addition, psychiatric patients often consume excess calories from soft drinks, in part due dry mouth, a common medication side effect. In a recent survey that we administered to inpatients, most reported not preparing their own meals, so that even when eating at home, many patients are not controlling what they eat. Many ate out at fast food restaurants. For the sake of practicality, we believe in advocating a diet that modestly reduces dietary fat, carbohydrates from refined sources, and daily caloric intake, while also using an exercise program to supplement weight loss. We plan to follow the dietary recommendations utilized in the diabetes prevention program and seek to achieve 7% weight loss in our patients. The DPP also allows for the use of meal substitutions such as Slimfast products for patients who cannot control the food prepared for them and are having difficulty reaching their weight goal. We have found this to be particularly helpful for certain patients and a case series report is in preparation from our laboratory about this.

G. Exercise as part of a weight loss program: Correlations made between sedentary lifestyle, an increase in daily energy intake, and obesity among mentally ill patients make change in this part of a patient's lifestyle as important as in the areas of diet and nutrition education. Though some raise concerns about increased appetite due to increased physical activity, many studies have found that while there is a "loose coupling" between exercise and energy intake this effect can be controlled by psychological processes (51, 52). Thus, being involved concurrently in the education program, patients may be more capable of controlling this effect. However, adherence is the most critical factor in a successful exercise regimen.

Some patients may be interested in losing weight, but not able or willing to commit to an intense or time-consuming workout. In such cases, the intervention performed by the DPP may be ideal. Over 1,000 non-schizophrenic, non-diabetic participants, with a mean age of 51 and mean BMI of 34, were assigned for three years to a lifestyle intervention program (42). The goal was to achieve a minimum 7% weight loss by dietary intervention and engaging in at least 150 minutes of physical activity per week at the intensity of brisk walking. By the end of 6 months, 50% of the patients had lost 7% or more of their body weight. 74% had adhered to the goal of 150 minutes of weekly activity by the end of the study and 58% continued to do so at the time of their last visit. Decreases in daily fat and overall caloric intake resulted, and a 58% reduction in the rate of diabetes within the intervention group was found upon follow-up. This level of activity would be easy to implement even on an inpatient unit. A growing body of evidence points to another important side benefit of exercise, it improves mood in patients with mental illness. We will be able to gauge this during this study as well. It is important to note that the diabetes prevention program's lifestyle intervention lasted three years and had remarkable results at preventing the development of diabetes.

Encouragingly, the positive impact of exercise and diet in preventing diabetes has been replicated in two other studies, the Da Qing study (53) that compared diet and exercise to no treatment and The Finnish Diabetes Prevention Study (54, 55) that provided behavioral interventions to prevent diabetes in large groups of patients. A recent naturalistic study by Poulin and colleagues was promising and demonstrated that structured, facility –based exercise programming was helpful for weight control over an 18 month period for patients with antipsychotic associated weight gain (56).

III. Relevance of the Proposed Work to VA Patient Care Mission

Antipsychotic medication associated obesity, diabetes and dyslipidemias are now recognized as important problems to be monitored and reversed if possible by the ADA, APA, FDA, and VA Inspector General. Product labeling of all antipsychotic medications now clearly indicates that they carry the risk of weight gain and that physicians need to evaluate, monitor and intervene as possible for patients taking these medications (18). To prevent and treat antipsychotic medication associated obesity and its medical complications in SMI veterans is an important and difficult task. We wish to teach patients with SMI about lifestyle balance and demonstrate that a behavioral weight loss intervention can be effective in preventing weight gain and/or promoting weight loss. This behavioral program may lead to a decrease in morbidity and mortality in psychotic patients from obesity related disorders such as coronary artery disease and diabetes. Improvements in long-term health outcomes may then be expected to change quality of life, promote treatment adherence and rehabilitative potential, decrease resource utilization program experience and a decrease of negative symptoms. Indeed preliminary data analysis from our first grant already indicates weight loss, a decrease in cardiovascular disease risk factors, and improvement in psychiatric symptoms and quality of life are occurring.

This work has relevance to the VA's care mission in that it is in line with the report and recommendations of the President's New Freedom Act and the Department of VA Office of Inspector General on the management and screening of weight, diabetes and hyperlipidemia in patients taking atypical antipsychotic medications. Also this work is in keeping with the VA's embracement of the MOVE! program, the Recovery Model of mental illness and the Uniformed Services Package that develops PRRCs that are mandated to have a significant "wellness component." (3, 9, 57)

This work has ramifications to the VA patient care mission at multiple levels. The findings of this study can potentially result in an effective, easy to implement behavioral approach to combat the most debilitating and costly side effect of the new antipsychotic medications. The cost to the VA of taking care of patients with psychotic disorders is extremely high. The complication of co-morbid medical conditions such as iatrogenic obesity and its potential health risks, (e.g. diabetes, hypertension, coronary artery disease, etc.) further compound the cost to the veteran, his family, and the healthcare system in general (8). Obese patients utilize more resources, and are more likely to be nonadherent to medication treatment especially if the obesity is secondary to that treatment (58). Weiden reported that obese schizophrenia patients were three times more likely to report missing their medication than patients who weren't obese (59). Treatment nonadherence can result in relapse of psychosis, rehospitalizations, and worse outcomes. The successful management of SGA associated weight gain and the prevention consequent medical sequelae such as diabetes and cardiovascular disease is a medical, ethical, and economic imperative in the VA Healthcare system. The recent publication of VA database material showed that 7.3%-- 4,132 of 56,849 patients developing diabetes after beginning an SGA and 88 patients were hospitalized in diabetic ketoacidosis (60). The incidence rate of 4.4% was considerably higher than the general population that has an incidence rate of 6.3 cases per 1000. Clozapine and olanzapine appeared to have the greatest liability in terms of diabetes compared to quetiapine and risperidone in this 2001 study. The costs of these new diabetes cases, not to mention acute hospitalizations for diabetes and DKA in veterans with SMI are enormous, and most likely underestimated by the proxy data obtained from administrative records. An estimate of the costs of taking care of diabetes compounded with SMI in the VA are staggering—billions of dollars (19). Clearly the "call to action" to combat "diabesity (diabetes and obesity) made by the surgeon general and the WORLD Health organization should be followed rigorously. Finally this research is clearly in line with the inspector general's report last year (9) mandating that the VA take action on the issue of antipsychotic medication associated diabetes, obesity, and metabolic sequelae.

IV. BACKGROUND AND WORK ACCOMPLISHED

A. Clinical Trials Research: The PI's experience in all aspects of conducting clinical trials in psychiatric patients --from the ethical considerations (17) to their administration, the clinical care of patients, and the collection and analysis of complex, comprehensive data sets-- is lengthy and comprehensive. The PI has performed clinical trial research for over 20 years. She has been PI and CO-I's on over 100 clinical investigations (VA, NIMH, Foundation and Industry Supported) and is adept at handling psychotic patients in complicated protocols (2, 39, 61). Not only has she performed clinical trials on novel antipsychotic medications, but also the PI has had extensive experience with implementing behavioral interventions to enhance the lives of patients with schizophrenia.

B. Psychosocial Skills Training for Schizophrenia: Psychosocial skill training is an effective adjunct to medication treatment in patients with schizophrenia and recommended by the American Psychiatric Association as part of a patient's treatment plan. The VA recognizes psychosocial skills training as an evidence based treatment for schizophrenia and now mandates SST be a part of the PRRCs at all VA healthcare centers. Psychosocial Skills Training involves presenting educational material to patients in a multi-modal fashion, using visual and auditory input, and then modeling the desired behaviors in classroom and homework exercises. The diabetes prevention program "Lifestyle Balance" contains these elements and more. The PI has implemented and modified psychosocial skills programs to use in inpatient settings in prior research. Also, in her current role as PRRC director, she herself has received extensive training and provided social skills training instruction to all PRRC staff. These skills training classes are a routine part of care in our psychiatric facility and we have carried out the lessons from these initial sessions with "booster sessions" to prevent relapse and rehospitalization in patients with schizophrenia (40). We have utilized psychosocial skills training techniques effectively in conjunction with intensive case management of patients, and patients have participated in a 1 year long series of classes in three previously funded NIMH trials we implemented as well as one previous merit review. Patients in the merit review program in which we compared the impact of psychosocial skills training with weekly booster sessions, did very well with this level of care. Compared to a "usual care group" the patients in the weekly classes had no relapses over the one year period, whereas 50%

of the patients in the "usual care group" relapsed. Thus, we have confidence that our patients will be able to engage in the more frequent "Lifestyle Balance" classes over a sustained period.

C. Recognition and Management of Metabolic Side Effects of SGAs: The PI has led the field in increasing physicians' awareness of side effects of the novel antipsychotic agents, (e.g., weight gain and diabetes) and have preliminarily demonstrated the benefit of behavioral interventions on SGA associated weight gain (2, 14) (See the background section of this application). In a retrospective analysis of 99 patients' charts we found that simple behavioral weight loss strategies that we routinely employ in our clinical care of patients, such as weighing patients at their visits, asking patients to keep a food and exercise diary, and encouraging exercise and healthy diets, resulted in modest changes in average weight lost. She has been among the first to note the association of SGA use and changes in lipid profile a monitoring program for following the metabolic side effects of antipsychotic medications that was designed in this laboratory was adopted by the American Diabetes and American Psychiatric Association and published in Diabetes Care in 2005. The PI has been an advocate pf physical monitoring of patients on antipsychotic medications for over a decade and has been involved in multiple publications in addition to the ADA/APA consensus statement on this topic (19, 20). The current application will allow us the opportunity to prospectively examine the impact of longer term behavioral interventions on antipsychotic associated weight gain and other metabolic changes.

D. Behavioral Weight Loss Treatments in Psychotic Disorders:

1. Pilot Study 1: A Wellness Class for Psychiatric Inpatients (62) The purpose of this pilot project was to educate acutely ill inpatients with psychotic disorders about lifestyle changes to combat weight gain that may be associated with some of these medications. Our goal was to assess patients' knowledge with an anonymous survey before and after a class to assure that this intervention is effective at the most basic level; i.e. that the patients can learn the material.

Methods: This pilot research was approved by the IRB and oral informed consent was obtained from all participants. All inpatients on an acute inpatient schizophrenia treatment unit were invited to attend a 30-minute presentation given once per week by a medical student and a pre-doctoral psychology assistant under the supervision of the primary investigator. The interactive class material included the health benefits of maintaining one's ideal body weight, making food choices according to the USDA Food Pyramid, proper food portion sizes, healthy meal choices when eating outside the home, and the importance of beginning and adhering to an exercise program.

Results: Subject Demographics: Of the subjects, 93% were male and 7% were female. Most of the subjects were middle-aged, with 85% of the sample falling between the ages of 41 and 60 years of age. 24% of those sampled did not graduate high school, 20% had graduated or had a GED, 35% had at least some college education, and 20% had post-college training. Of the male patients sampled, 37% were overweight and another 37% obese, with only 26% of normal weight. Of the two female patients sampled, one was overweight and the other obese. Eating Behaviors: Most patients indicate that they eat the majority of their meals outside of their place of residence, with only 41% eating most of their meals at their own home. The remaining patients ate most meals at fast food restaurants (23%), at board and care facilities (21%), at the homes of family members (13%), or at other restaurants (3%). Only 23% of patients prepared one or more of their meals each day. 20% prepared their own meals 3 times per week, and 22% once a week or less. 33% never cook at all. Knowledge Quiz: 70 subjects chose to participate and completed the pretest, 50 patients completed both the pre- and post-presentation tests. The mean percentage of correct answers on the pre-test was 85.6%, which rose on the post-test to 89.3%. This difference of 3.7% is statistically significant ($t = 2.43$, $df = 49$, $p < 0.02$), and the mean percent of improvement (%difference/pretest % correct) was 6.1%. Educational level of the patients was not correlated with the final percentage of correct answers ($r = 0.06$, $p = NS$), nor with improvement in test scores ($r = -0.28$, $p = NS$). In addition, 73% of the subjects expressed a desire to lose weight.

Conclusions: This pilot study demonstrated that psychotic inpatients are able to benefit from educational presentations about nutrition and a healthy lifestyle. After a single 30-minute presentation, acutely hospitalized patients showed a statistically significant improvement in test scores. The scores for both tests were quite high, suggesting that subjects had a good grasp of basic concepts related to food choices and fitness at baseline before the class. Nearly three-quarters of subjects expressed a desire to lose weight. Despite the high level of knowledge and stated interest in weight loss shown, however, the majority of participants were overweight or obese. Most subjects reported eating at home or at fast-food restaurants. Our goal is to expand this class, which is ongoing on our inpatient unit into the outpatient phase of treatment.

2. Pilot Study 2: Behavioral Weight Loss Classes for Patients With SMI (63)

This study was a pilot program to adapt and preliminarily test the Lifestyle Balance classes adapted from he diabetes prevention program in a group of SMI patients. 12 patients who gained significant weight on SGAs, (average BMI 35) agreed to participate in the preliminary testing to the DPP Lifestyle Balance classes as an augmentation to their clinical treatment. All of the patients experienced clinical benefit from their antipsychotic medications, in terms of control of psychiatric symptoms (many had jobs) but, have gained weight on the medications they are taking. Switches to medications with less weight gain potential had been tried in some of the patients, with little benefit. Eight of the patients have diabetes and virtually all have the metabolic syndrome with waists greater than 40 inches and most have hypertension. We gave them some information about how to prevent worsening of this condition thus we added this information to the first, introductory class. We collected anonymous surveys about each class to obtain feedback from these participants to optimize the learning experience. At the conclusion of each week's class, a 10-item survey evaluating the class and gauging knowledge of weight loss and exercise was given to the participants. Patients' initial knowledge of healthy lifestyles was assessed and they scored an average of 75% on a brief quiz. The vast majority of patients reported that they found those classes informative, useful, inspirational, and something which not only would they continue to attend, but which they would also recommend to a friend. All but one (who had recent back surgery) of the patients has begun exercising and all were able to keep food diaries. The most exciting thing about the preliminary group testing was that the patients were very encouraging of each other and subjective improvement in negative symptoms appeared to occur, this finding has been substantiated in our actual research.

3. Pilot Study 3: Dissemination of Lifestyle Balance Program Classes

As part of the work proposed in this grant is to test the Lifestyle Balance Program in other mental health programs, we have already begun disseminating the program locally. What we found when recruiting patients for our current research study is that 50% of the PRRC patients who were recruited for the research study declined. Many were too psychotic to realize that their weight was a problem. Thus, to help the PRRC patients that would not access the research program, nor the MOVE! Program we started to disseminate, in the past three months a weight loss program within the PRRC itself. The PRRC's weight loss programs include weekly classes on wellness, weekly weigh ins with our clinic nurse, and exercise classes that have yielded some positive results. In 6 months, since we started to disseminate our program into our own PRRC, 17 patients who participated in the disseminated weight loss program we began providing in our PRRC have lost up to 5 pounds. Other programs have approached us for help with weight loss in the SMI population including the dual diagnosis treatment program at our facility. We have trained the nurses in that program to provide Lifestyle Balance Classes. Over the past year we began collaborative efforts with our MOVE! Program leaders to be able to provide additional support to the MOVE! Team for patients with SMI who are not doing well in the conventional MOVE! Program. Also, outside of the VA system, Sharon McDaniel, RN is adopting the Lifestyle Balance Program into her clinic at the Didi Hirsch community mental Health Center, as part of her PhD thesis work. The ongoing classes provided in the PRRC by our nurse can also be accessed by the research program and MOVE! graduates and have served to assist them with continued weight loss and/or maintenance. These early experiences in disseminating the lifestyle balance classes and the principles of this weight loss program have shown us that each program will be adopting certain components of our program dependent upon the number of staff and time available of those staff to provide the intervention.

E. Progress Report for Funding Period for Merit Review 2006-2009:

1. Demographics: This Merit Review Grant was funded in June of 2006 at which point only 35% of the funds for the year were provided. We have screened 225 veterans to participate and 123 have been randomized. 113 were male and 10 were female. Of the 123 patients randomized, 78 of them are currently active participants or have finished the program. Of these 78 participants, 36 (29%) are African-American, 2 (1.6%) are Asian-American, 30 (25%) are Caucasian, 6 (5%) are Hispanic, and 4 (3%) identify as mixed or other ethnicity. In addition to severe mental illness, over 50% had substance abuse problems. To date (April 2009) there are still 18 active patients in the protocol. The current cohort of patients will not be completed with their full yearlong participation in the study until September of 2009.

The purpose of this study was to test a modified version of the multi-modal Diabetes Prevention Program which includes the Lifestyle Balance classes, exercise, and individual coaching over a one-year period of time in severely mentally ill patients who had antipsychotic associated obesity.

2. Preliminary Results:

a) *Weight Loss Findings:* Preliminary data analysis using a mixed model analysis on the basis of the current status of the patient cohort (at this point data for 46 participants who have completed 6 or more months, 22 of them have completed 1 year) shows that we can expect a difference of 11.8 pounds between

the lifestyle balance group and the standard treatment group, with a weight loss of 6.6 pounds for the lifestyle balance group, and a gain of 5.2 pounds for the standard treatment group (F (1,935) =25.1, p<. 001). This is more than twice the group difference we predicted in the original proposal (5.5 pounds). Our poster presentation in 2007 demonstrated that 37% of our patients enrolled in the active treatment arm of the study had lost 5 or more pounds compared to 0% of patients in the control group (usual psychiatric care). This preliminary data has also been submitted for poster presentations at the World Psychiatric Association to be presented in Italy in April 2008, as well as the international Congress on Schizophrenia Research in April of 2008. Range of weight loss for the first 6 months was from a loss of 50- pounds to a gain of 14 pounds for the intervention group and from a loss of 19 pounds to a gain of 29 for the usual care group.

b) BMI: Preliminary analysis shows a significant difference between the two groups (F(1,901)=20.04, with the treatment group decreasing by an expected 9.5 over one year, and the usual care group increasing by an expected 2.5 over one year.

c) *Cardiovascular Disease Risk Reduction:* In terms of the risk of cardiovascular disease our intervention shows a significant improvement for participants in the lifestyle balance program. Their expected risk decreases over 1 year is 2.6% F(1,825)=25.6, p<.01), which is equivalent to a cohen's d of .5.

d) *Metabolic Syndrome (ATP III definition):* Preliminary analysis shows the following expected impact on metabolic syndrome (high blood pressure, elevated glucose, elevated triglycerides) as estimated by using a generalized linear model with a logistic link function to be equivalent to an odds ratio of .6 over one year, i.e. the likelihood for metabolic syndrome for a patient in treatment group is at the end of one year by 40% lower than the likelihood for metabolic syndrome for a patient in the control group who started with the same value at baseline. This difference is not significant in the preliminary dataset, but if this relationship holds true over the complete sample, we will have enough power to detect it.

e) Diabetes: Preliminary analysis suggest that glucose levels decrease for patients in the treatment group by an expected 2.1 over one year, compared to an expected increase of 15 for the control group. This difference is not significant in the preliminary sample, but considering that this is equivalent to an effect size of d=.3 this might also be a significant effect in the final sample.

f) Psychological and Psychosocial Well Being: In terms of psychological and psychosocial well-being the preliminary data shows that participants in the Lifestyle Balance Program experience a decrease of negative symptoms. Their BPRS score for the negative symptoms facet decreases on average by 1.2 which corresponds to a d=.4.

Similarly, there is an increase of the social QOL of 12.6 for patients in the intervention while the patients in usual case experienced a decrease of 7.7. This difference corresponds to d=.6. These effects are not significant in the partial preliminary sample but we have enough power to detect effects of this size in the final sample. There are no differences that would be detectable in the final sample in positive symptoms and depression as measured by the BPRS and the HAM-D.

g) Impact of Particular Medication on Success of Weight Loss Intervention: Preliminary analyses of the data from our current Merit Review Study, using a mixed general linear model shows that there are significant differences in the degree to which patients on different medications profit from our Lifestyle Balance Program (F(5,7220=15.06, p<.01): patients on quetiapine, olanzapine and fluphenazine profit from the program, while the weight gain in patients on clozapine and risperidone does not appear to respond to the training program. These results are very preliminary due to the small number of patients in each of these patient subgroups at the moment.

h) Impact of a Multi-Modal Approach: The preliminary data analyses suggest that this intervention has an effect beyond what a pure exercise program can provide. Patients who reported at the baseline measurement that they were already exercising showed the same effect of the intervention as patients who had reported that they were not exercising (Test for the difference between these groups: F(1,862)=0.03, p=.86) (56).

3. Preliminary Conclusions from the Current Study: Though our study is not complete, we have excellent interim data that demonstrates that the Lifestyles Balance program, adopted from the DPP and administered for a year has positive impact. Even in the preliminary sample, we show significant positive impact on measures of the patients' weight, BMI, metabolic syndrome, and measures of cardiovascular disease risk factors. Other, more nuanced measures of physical and mental health also show sizable positive changes; these changes are not large enough to be detected in the preliminary, but the final sample as projected will provide sufficient power for them. We believe these changes in a population challenged with severe mental illness (and a significant proportion with a history of substance abuse) are quite encouraging.

Negative symptoms (apathy, anhedonia and asociality) are amongst the most difficult symptoms to treat in mental illness, and it is quite encouraging to see that patients' negative symptoms improved due to participation in this research. Perhaps improvements in self-esteem due to weight loss contributed to this effect. Due to the encouraging results we are seeing, we think it is crucial that we continue our efforts to extend the intervention (as obesity and mental illness are long term health conditions) and attempt to disseminate this intervention to other mental health care facilities.

4. Additional lessons that we have learned to date: Embarking upon a behavioral weight loss program for patients who have antipsychotic medication associated obesity presents many challenges. Though weight gain was due in part to antipsychotic medications, the illness itself and in many cases the concomitant history of substance abuse compound the difficulties in combating obesity in this population. We provided 16 classes about lifestyle balances interventions followed by monthly booster classes for one year. More than 50% of this group of patients also had substance abuse problems. We also provided individual lifestyle balances coaching, field trips and exercise opportunities. Recruitment for the study has been very successful. Many of the veterans live in board and care homes and other facilities such as residential drug rehabilitation programs. We have learned that it was very difficult for veterans in such facilities to modify their eating habits. Thus, we sent our program's dietician to the facilities to see if she could work with the cooks and these facilities. One facility was very open to this intervention, and our dietician made a great deal of changes to the weekly menu. For example, she taught the cook to prepare cauliflower mashed instead of mashed potatoes.

Many of the veterans living at board and care facilities or residential drug treatment programs who could not alter meal choices or have much impact on meal production opted, with good results to try Slimfast as a meal substitute. We found that this worked for a number of veterans. However, for the more cognitively challenged slim fast did not work because they would forget to not eat the meal and would eat the meal together with the slim fast. Thus, slim fast is not for all SMI veterans participating in a weight loss program. We learned that exercise and food diaries are difficult for some veterans with SMI to maintain, particularly those that have concomitant cognitive deficits and/or traumatic brain injuries. We now have a very rich set of multiple food diaries to analyze.

5. Expansion of Exercise Opportunities: In November 2007, the PI became the director of the local West Los Angeles Psychosocial Rehabilitation and Recovery Center (PRRC). Since her tenure began she incorporated daily exercise classes into the programmatic offerings in keeping with the recovery model and the wellness initiative embraced by the VA and PRRC. Thus, it became easier over the course of the research study to recommend that participants in the research program attend the PRRC for exercise classes. Yoga has become fairly popular as it seems to be particularly helpful, not only for weight loss but for anxiety symptoms of patients who participate in these classes. In keeping with the recovery model we provided a number of outings (miniature golfing, swimming, bowling, and trips to grocery stores and farmer's market) that were educational and provided some exercise. These were normalizing activities in the community.

As part of a national network of leaders who are changing day treatment centers over to PRRCs the PI believe that over the next few years we will have multiple opportunities to share and disseminate to our colleagues successful weight loss interventions for this population.

The PI is on a committee to develop complementary medicine resources at all the VA's in the Greater Los Angeles Network. It is hoped in the near future that yoga and tai chi will be available at all the sites participating in this multi-center study.

In summary, our ongoing research has been quite successful at achieving weight loss. It is to our knowledge, the longest term intervention proven effective in SMI patients (often dually diagnosed with substance abuse) with antipsychotic medication associated obesity. This program may close a gap in care for those patients who cannot or do not access MOVE!. Continuation of this work is crucial to see if we can optimize the maintenance effects of this program as well as disseminate this work.

V. Research Design and Methodology

A. The study is a multi-site, randomized, open, effectiveness trial with masked raters blind to treatment condition. 120 veterans (30 at each of 4 sites) will be randomized for participation in this study. The 4 sites and primary Co-investigators are:

West Los Angeles VAMC	Brentwood, CA	Donna Ames, MD
Long Beach VAMC	Long Beach, CA	Charles Nguyen, MD
Sepulveda, VAMC	North Hills, CA	Valery Chamberlin, MD
Los Angeles Ambulatory Care	Los Angeles, CA	Chandrash Shah, MD

B. The oversight and organization of the multicenter trial across all 4 sites will be coordinated by Dr. Ames as the Principal Investigator and her Program Manager located at the West Los Angeles site. At each of the 4 sites there is a designated co-investigator who will be responsible for weekly team meetings of all research staff that will encompass clinical and research issues. The overall PI will arrange a study start up meeting and monthly coordinating meetings to facilitate fidelity of the project between all 4 sites. Weekly coordinating meetings will be necessary during the first 6 months of start up.

The first 6 months will be used to hire and train all staff from all 4 sites on the intervention. The dietician from the West Los Angeles site has updated the class materials. We will be responsible for training all the health coaches at each of the 4 sites. The first 6 months of the grant funding period will also be used in part, to establish inter-rater reliability of raters for all study measures. Our study consultant, Dr. Robert Liberman, will assist with helping assure there is fidelity of all lifestyle balance coaches in their presentation of class materials and in their handling of veteran's progress in the research study. Dr. Liberman is an international expert in psychosocial skills training for patients with schizophrenia. The educational modules he developed to help with illness management have been disseminated all over the world. Thus, his expertise at dissemination of psychoeducational materials and a fidelity rating instrument to check on adherence to the intervention by the lifestyle balance coaches has been developed.

During the first 6 months of start-up time for the 3 new sites, we will need to develop a list of exercise options for each site from which veterans can choose to participate. At West LA VAMC a number of exercise options already exist and it is hoped that equivalent options can be developed at each site. Of note the most frequent option for exercise that was chosen was walking, so recommendations for walking trails, and/or development of a schedule for walking groups would be something that will need to be developed at each of the three new sites. Peer-to-peer exercise options (encouragement of groups of veterans to exercise together) can be developed at all 4 sites. Wellness programs and supervised exercise options though the department of physical medicine for those patients with cardiac problems are available at all 4 sites.

A web based data entry system and web page for our coordination of our program will be developed and completed. Case report forms will be available on the web page as well as a study bulletin board. The data management team from the VISN 22 MIRECC will finalize the web page and web based data entry system and assure that it is working at all 4 sites.

C. Inter-rater Reliability:
Initial inter-rater reliability will be maintained for the BPRS, CGI, Ham-D, and QOLS scales by utilizing recordings of taped live interviews -available by DVD - that all raters must assess during the initial start up phase and every 6 months thereafter. Initially each rater will assess 3 tapes and kappa will be determined for inter-rater reliability. Once the study is underway, to prevent rater drift, every 6 months all raters will rate a recorded interview that will be made available to them by DVD.

Inclusion/Exclusion Criteria: Patients recruited for this research study from four different sites will need to commit to a 12 month period of participation. This protocol will have two phases, an initial 2-month intensive phase (weekly classes and individual visits) followed by a 10 month (once per month) maintenance extension phase. Since many patients with SMI live somewhat transient existences, patients included in this study cannot be homeless and must have some type of stable living circumstance. All patients with SMI (e.g. psychotic disorders, schizophrenia, schizoaffective disorder and bipolar illness, post traumatic stress disorder) aged 18-70 who are taking antipsychotic medications, admitted to inpatient wards of the Greater Los Angeles VA Medical Center, Long Beach Medical Center, as well as outpatient programs at all four sites, of the Sepulveda VAMC, and the Los Angeles Ambulatory Care Center, West Los Angeles VA Mental Health Clinic, Schizophrenia Treatment Unit, Domiciliary, Exodus Lodge, and local Board & Cares and residential dual diagnosis treatment programs will be screened for possible participation in this behavioral weight loss program that includes diet, exercise, and Lifestyle Balance classes. We intend to recruit non-veteran females (to increase our representation of females in this research) from the Didi Hirsch Community Mental Health Center, in addition to our women's clinic here at West Los Angeles. Sepulveda VAMC has a large outpatient program, and a partial hospitalization program (that is converting to a PRRC) and MHICM programs from which to recruit patients. LAAC also has a large outpatient mental health program and 3 day treatment/partial hospitalization

programs (that are converting to PRRCs) from which to recruit. There are 10,000 patients classified as SMI within these three medical centers. Long Beach hospital also has a large outpatient as well as an inpatient program from which to recruit. Long Beach hospital served over 10,000 mental health unique veterans in 2008, of which probably half of these are SMI. To assist doctors in identifying which patients under their care are eligible for our study, we intend to obtain Waiver of HIPAA for screening purposes. With this we can obtain from the VA a list of eligible patients and approach their doctors to notify them of their eligibility and what the program involves so that the doctors can effectively discuss it with those patients and direct them to us. Finally, we intend to utilize social media to spread word of the study, requesting mention of it be made by the GLA VA Facebook page.

One hundred twenty patients clinically determined to require ongoing treatment with SGAs who have experienced 7% or more increase in weight or whose BMI has become greater than or equal to 25 during treatment with an SGA will be randomized to receive either the Lifestyle Balance Program (a MOVE! like behavioral weight loss intervention with psychoeducational classes) or Usual Care. These inclusion criteria have been chosen to selectively recruit only subjects whose adiposity is both clinically pertinent and reasonably construed to be due to the introduction of an antipsychotic. All patients will be asked to sign informed consent. Patients who are unable to give informed consent will not be entered into the study. Subjects with a history of substance abuse or dependence cannot participate in this study unless they are sober for three months. If a patient has a legal conservator, and wants to participate in the study, he or she will need the legal conservator to sign informed consent. If a patient is too medically ill to be involved in any type of exercise or weight loss program he or she will be excluded from the protocol (e.g. a patient with cancer on chemotherapy who is vomiting and losing weight should not be entered into this study).

The current Merit Review Grant funded in June of 2006 enrolled and randomized 123 patients. 113 were male and 10 were female. Of these 123 participants, 56 (45.5%) are African-American, 4 (3.3%) are Asian-American, 45 (36.6%) are Caucasian, 10 (8%) are Hispanic, and 8 (6.5%) identify as mixed or other ethnicity. Our targeted/planned enrollment will aim to increase the number and percentage of female patients. The ethnicity of patients involved in the upcoming study is likely to be the same, and will include a majority of ethnic minority groups.

Ethnic/Racial Category	**Females**	**Males**	**Total**
Black or African American	5	51	56
Asian	0	4	4
Hispanic or Latino	1	9	10
Caucasian	4	41	45
Mixed or Other Ethnicity	0	8	8
Total of all Subjects	10	113	**123**

B. Time Line and Targeted Recruitment: The first 6 months of funding will be utilized to train and hire new research personnel at all four sites to perform the lifestyle classes and begin recruitment and enrollment of subjects. Most patients will be able to complete the educational classes within 8 weeks. By utilizing multiple group leaders, we can run several cohorts of patients simultaneously and can start new groups at any time. Booster sessions will be provided at all follow up visits as a part of maintenance therapy. All patients will be followed for 12 months and will be able to complete participation by the third quarter of year 4, leaving 6 months for data analysis and manuscript preparation.

Time Line

Months 1-6	Mo. 7-12	Mo. 13-18	Mo. 19-24	Mo. 25-30	Mo. 31-36	Mo.37-42	Mo 43-48
Hiring and Training Lifestyle coaches, Build website	Recruit and begin study	Recruitment Continues	Recruitment Continues	Recruitment Continues, Classes and data collection continues	Recruitment ends, Classes and data collection continues	Classes and Data collection continues	Data analysis write paper
Anticipated N= 0	5-30	35-60	60	60	55-30	25-0	0

C. Informed Consent: Patients will be asked to give written informed consent at the beginning of the study. The participation of subjects with severe treatment refractory schizophrenia and other vulnerable populations in research protocols has led to some controversy over these individuals' abilities to give meaningful consent (14). We currently employ a rigorous and interactive test experience to aid subjects in learning the informed consent material and to assist us in determining subjects' level of understanding. We will be using an informed consent quiz in this protocol. We will also be using a teaching device, videotape that can assist subjects in understanding the consent process and become active learners in consenting to research. Because it is a long-term study we will re-check patients' understanding of their protocol participation on an ongoing basis (at least every 6 months) using our informed consent quiz.

D. Lifestyle Balance Treatment Procedures: All scales, the manual for the class participants, and a portion of the training manual for the Lifestyle Balance coaches including the adherence "toolbox" are included as appendices to this application (the full materials can be accessed at www.bsc.gwu.edu/dpp/manuals.htmlvdoc). Because some of the materials utilized in the original diabetes prevention program in 1996 are outdated (e.g the food pyramid has been revised) we have updated these materials during our current study and those new updated materials will be available at the study website which will be developed for this project. 120 patients will be randomized to either "usual care" or to a behavioral weight loss program. Those patients randomized to the behavioral weight loss program (Lifestyle Balance Program) will do the following:

1. Behavior therapy procedures. Three evidence-based, behavior therapy interventions will be incorporated into the Lifestyle Balance Program: (a) motivational interviewing, (b) contingency contracting and (c) social skills training for promoting optimal implementation of dietary and exercise assignments.

(a) Motivational interviewing. This intervention has been shown to be effective in a wide variety of disorders, including substance abuse/dependence, eating disorders, schizophrenia, mood disorders and anxiety disorders. Its primary purpose is to motivate patients to engage in a treatment, participate actively in the treatment and complete assignments that are essential if desirable, therapeutic change is to occur. The key element in the procedure is to educate the patient in the connection between the treatment being offered (e.g., Lifestyle Balance Program) and their desires to achieve their own, personally-relevant goals. In this fashion, it works in parallel with the "stages of change". The following elements comprise motivational interviewing: express empathy, develop discrepancy, roll with resistance and support self-efficacy. Each of these elements are anchored to behaviors of the clinician that can be operationalized, observed and evaluated for purposes of *fidelity assessment.* Fidelity scales have been developed and validated by researchers in the field of motivational interviewing and are based on sampling the interview and rating each of the 4 elements on a six point qualitative scale from "Uses consistently" to "Little use". A review of the value of fidelity measures to assess the effectiveness of motivational interviewing is found in: The efficacy of motivational interviewing and its adaptations.

(1) Express empathy: empathy, unconditional acceptance, genuineness and warmth are key elements as well as skillful, reflective listening in this element of motivational interviewing. Coaches will have to learn that ambivalence is normal; individuals may waver in their commitment to the Lifestyle Balance Program, but it is key for the clinician not to be reactive to this situation. Instead the clinician uses listening skills and follows the patient's narrative.

(2) Develop discrepancy between the kind of life they would like to have and their lifestyle in the present. The patient, rather than the coach identifies personal goals that usually bring them to a goal-oriented situation wherein the patient presents arguments for change. Change is motivated by a perceived discrepancy between present behavior (e.g., overeating, lack of exercise and obesity) and important personally relevant goals (wanting more endurance, energy and activity; interest in social relationships where obesity is an obstacle).

(3) Roll with resistance. Avoid arguing over change and do not oppose the patient's resistance; new perspectives are invited but not imposed; the patient is a primary resource in finding answers and solutions.

(4) Support self-efficacy. A person's belief in the possibility of change is an important motivator; the patient, not the coach, is responsible for choosing and carrying out change; the coach's own belief in the person's ability to change becomes a self-fulfilling prophecy.

(b) Contingency contracting. To enhance the patient's motivation for achieving goals set in the Lifestyle Balance Program, behavioral contingency contracting is used. Contingency contracting involves clearly specifying behavioral goals (e.g., "I agree to walk at least 30 minutes per day for at least 5 days per week). The contract has a reinforcement contingency for successful attainment of a goal (e.g., "If I meet my

exercise goal this week, I will reward myself by going to the VA canteen and buy myself a new shirt using the gift certificate I earned"). Fidelity ratings of Lifestyle Balance coaches in the use of contingency contracting will be assessed by review of contingency contracts that are written, "permanent products" of the interaction leading to the specification of the behavior, the reward and the contingency that relates the receipt of the reward to a particular set of lifestyle behaviors.

(**c) Social skills training (SST)** will be taught to the Lifestyle Balance coaches so they can use this modality in facilitating goal attainment in terms of community assignments for improvements on eating habits and exercise. The SST developed by Liberman and associates incorporates a sequence of steps that will be used to enable subjects to make incremental progress toward their goals for improving their eating habits, exercise and weight. These steps are:

(1) identifying a long-term, personally-relevant goal related to weight management (exercise, eating habits and nutritional choices, weight) and that will often involve being able to experience more energy, a higher level of activity and greater self-efficacy that can be instrumental to having a better quality of life.

(2) establishing a short-term goal for the coming week that is very well defined in terms of "what interpersonal situation" that mediates my long-term goal can I learn to use communication and problem-solving skills?; "with whom will I be interacting?" and "where and when will this interaction take place?"

(3) observing a model (usually the coach) demonstrate an appropriate way to communicate one's needs (e.g., purchasing healthy comestibles in a store) while learning vicariously

(4) participating in a role play that enables the patient to incorporate what was observed in the model to achieve a satisfactory level of social communication.

(5) coaching the patient when the latter is engaged in role playing using prompting, re-direction and positive feedback.

(6) giving the patient abundant positive feedback for achieving a reasonable level of skill in the communication that was practiced.

(7) giving the patient a homework assignment to practice that social behavior in the community where the "rubber hits the road".

Liberman and colleagues have developed and psychometrically validated a fidelity scale for SST.

2. Nutrition intervention: Patients randomized to Lifestyle Balance intervention will meet their Lifestyle Balance (LB) Coach on an individual basis at each visit. A diet and exercise program will be individually prescribed by establishing weekly action plans to achieve lifestyle changes and weight loss (42). Individual goals will be based not only upon weight, but also upon laboratory findings such as elevated glucose, triglycerides or hemoglobin A1c. The patient will be asked to describe what they eat for breakfast, lunch, and dinner on most days. Focusing upon the metabolic parameter that needs altering, e.g, the glucose, hemoglobin A1c, or triglycerides, with less emphasis on the weight, is often helpful for patients attempting to make healthier food choices. The LB coach/dietitian takes notes and is then able to assess what healthier options the patient is able to alter. The focus will be on 'adding' healthy foods, not 'taking away' favorite foods.

LB Coach/dietitian will establish the primary health care provider, case manager, and living arrangement for the patient in the first meeting. The primary health care provider or case manager will be contacted to establish a line of communication regarding the patient and their lifestyle regimen.

Patients living in board and care facilities or other residential facilities have little control of their food options and therefore are faced with challenges involving increasing whole grains or fruit/vegetable consumption. They are also served foods high in refined carbohydrates and saturated fats. The LB coach/dietitian can make suggestions, according to what the individual consumes often and illustrate how that individual could add a healthier option to a certain part of their meal regimen (i.e., if an individual drinks 16 oz of soda at 3:00pm everyday, suggest having either a diet soda or a fruit serving with a cup of water as a snack). One or two small, attainable nutrition goals are set for the patient to follow for one week only.

The patient writes in their food/exercise journal and includes, to the best of their ability, everything they eat and drink along with what type of physical activity they participate in, including specific amounts and times of the day for one week. The patient focuses on achieving realistic, small goals set with the LB coach/dietitian and these goals are reviewed weekly for the first 8 weeks of the study, and then monthly thereafter. At each session with the lifestyle balance coach the veteran establishes realistic goals that are written down and then followed up upon at the next appointment. Adherence to the goals will be checked at the next appointment by the lifestyle balance coach.

<u>Slim-Fast Criteria:</u>

Patients will be offered Slim-fast meal replacement shakes/bars as an option should they fall under the following criteria:

a) The patient believes they could replace one meal per day with a Slim-fast shake/bar without eating any other food within 2 hours of shake/bar consumption.
b) The patient agrees to turn in a food/exercise journal illustrating how the meal replacement shake/bar was used.
c) The patient loses at least 1-2 lbs in the first week of using the meal replacement shake/bar.

3. Physical Activity: All patients randomized to the multi-modal, Lifestyle Balance Program will be asked to increase physical activity. Prior to increasing physical activity (with a goal of 30 minutes of walking per day), patients will have physical exams. Risk stratification for ETTs (exercise tolerance test) will be done for all veterans entering the protocol according to the recommendations of the American College of Sports Medicine(64, 65). All veterans with moderate or high risk stratification who are interested in doing vigorous exercise or any veterans reporting cardiac symptoms will be given an exercise tolerance test. Patients who required an ETT prior to entering the protocol will repeat an ETT at conclusion of the study period. The information obtained from the repeat ETT will help assess for changes in functional capacity, cardiovascular fitness, and physiologic response to exercise in addition to reassuring safety for the veteran to continue a self-directed longer term fitness program at the conclusion of the study protocol period. This goal should be set for individuals that agree to increase physical activity, but if the patient is not motivated and/or overwhelmed with having more than one goal, the focus will begin with the nutrition goal and a recommendation of a gradual increase in physical activity will be set. Also, a goal to increase in physical activity could be something very small (i.e., patient went from driving to the store to walking to the store, patient started using the stairs instead of the elevator). Lifestyle change should be very gradual. A habit is formed over time, therefore LB coaches/dietitians/health professionals should be sensitive to an individual's ability to make changes, following the Stages of Change Model and assessing where the patient places on the Stages of Change Model is important.

Ultimately the goal however, is that all patients randomized to the multimodal, Lifestyle Balance Program will exercise 30 minutes per day for at least 5 days per week. As walking is the easiest exercise to encourage pedometers will be provided. We will also encourage patients to participate in other types of exercise and we will schedule supervised exercise activities at our PRRC as well as the Wellness Program run by Dr. Kunkel. Classes will be run by the Lifestyle Balance group leaders and/or an exercise instructor. Physical exams and ETTs will be done to assure safety prior to beginning exercise when patients have significant cardiovascular risk factors or history of previous myocardial infarction. Dr. Ames has initiated yoga and tai chi classes at the West Los Angles facility as part of the newly developed PRRC (psychosocial rehabilitation and recovery center). She is also part of a committee that will be establishing these types of classes at Sepulveda VAMC and LAAC. The Long Beach facility has a large campus ideally suited for walking, as does the Sepulveda and West Los Angeles sites. The LAAC campus is in downtown Los Angeles one block away from a large park that patients can be encouraged to walk around.

4. Food and Exercise Diaries: Patients in the Lifestyle Balance Program will be asked to maintain food and exercise diaries to discuss individually on a weekly basis with their case manager for the first 8 weeks and then once per month.

5. Knowledge Quiz: Patients will be asked to answer questions about their knowledge of healthy eating habits and nutrition. Questionnaires will be given at the beginning and end of the initial 8 weeks of classes, at 6 months and at 12 months

6. Class Schedule: Patients in the behavioral program will participate in 16 classes over approximately the first 2 months (2 classes per session). The classes on Lifestyle Balance (based largely upon the "Lifestyle Balance classes" utilized in the Diabetes Prevention Program) (42) are the following:

Welcome to the Lifestyle Balance Program	Fat Facts
How Antipsychotic Medications Affect Me	What's On Today's Table
Becoming Active: A Way of Life	Take Charge of What's Around You
Mindful Eating	Tip the Calorie Balance
Moving those Muscles	Your Food Away from Home
Weighing the Risks	Delicious Decisions
You Can Manage Stress-Mindfulness, yoga, taichi	Variety on Your Plate
Carbs: Simply Complex	Ways to Stay Motivated

7. Visit Schedule: Patients in the Lifestyle Balance Program will come to clinic one time per week for classes for the first 8 weeks of the study and then once per month for the remainder of the 16 months of the program. Some participants may require additional time. Class schedules will be flexible and be performed at the patients' convenience to facilitate patient adherence to the program. Booster classes will be given at the

once per month sessions. Booster classes will be selected from 50 available classes that are online in the Diabetes Prevention Manual. We have modified these classes and updated information (see appendix)

8. Reward System: Small rewards for achieving weight loss and exercise goals will be provided throughout the study period to patients in the Lifestyle Balance Program. Patients have an exercise card that is signed off by class teachers to prove attendance and earn small rewards.

9. Caregiver Help: Patients will be asked if they prepare their own foods. If not, we will ask if we can meet with them and their caregivers together to discuss dietary recommendations. These meetings will occur at baseline and every 3 months and as needed. Each patient will be assigned a case manager. The diabetes prevention program that is being adapted for this protocol has an extensive operations manual with a section devoted to methods of improving adherence to the Lifestyle Balance Program. Please see the appendix for our operations manual and particularly the "toolbox" section for helping patients adhere to the program.

10. Photographic Record: A de-identified photograph of each participant's body from the neck down will be taken during visit 1 and at the end of study.

11. Video Record: A digital video recording of an exit interview from the study with the patient's description of the keys to his or her success in losing weight will be made for those subjects who have lost 5 or more pounds at the end of the initial intervention phase.

12. Lifestyle Change Documentation: An action plan for each patient will be developed and actual changes in behaviors will be noted so that we can determine what changes recommended and interventions were most helpful.

E. Procedures for the Usual Care Group: As most psychiatrists are being advised to counsel patients on weight, diet, and exercise, Usual Care will be only some modest counseling. Referral to the MOVE program by their treating psychiatrist would not be discouraged. Patients will be encouraged to exercise and eat a healthy diet, and will be weighed at each visit. No classes on nutrition and no exercise classes will be given to these patients as part of this program. Patients in usual care will be seen on the same schedule as the experimental group, in order to equalize contact time. At every visit, patients will complete a questionnaire about their knowledge of healthy eating habits and nutrition. After 6 months, if patients in the "usual care group" wish to participate in the more rigorous behavioral weight loss program they will be given that opportunity. A de-identified photograph of each participant's body from the neck down will be taken during visit one and at the end of study.

SCHEDULE OF EVENTS

Visit	Time	Rater	0	1-7	8	9	10	11	12	13	14	15	16	17	18
Week			0	1-7	8	12	17	21	26	30	34	38	43	48	52
Month			0		2	3	4	5	6	7	8	9	10	11	12
Visit Log/Assessment Packet	--	--	X	X	X	X	X	X	X	X	X	X	X	X	X
AHA Exercise Risk Stratification	10	MD	X												
Brief Psychiatric Rating Scale (BPRS)	15	MD	X		X				X						X
CGI	5	MD	X		X				X						X
Hamilton Depression/ Beck Anxiety Scale	20	MD	X		X				X						X
Physical Exam	15	MD	X												X
Structured Clinical Interview for DSM-IV (SCID)	15	MD	X												
Antipsychotic Side-effects Checklist (ASC)	5	C	X		X				X						X
Assessment of Patient Food Preparation Activity	5	C	X		X				X						X
Biopsychosocial/Spiritual Wellness Self Appraisal (BPSS)	5	C	X		X				X						X
Demographics	10	C	X												

EXIT interview	5	C													X
Fidelity Checklist Change Assessment	10	Proj. Mgr	X						X						X
Framingham Hard Coronary Heart Disease	5	C	X												X
Healthy Lifestyle Balance Knowledge Quiz	15	C	X		X				X						X
Informed Consent Video	30	--	X												
Informed Consent Quiz	15	C	X						X						X
Labs: Lipid Profile, fasting glucose, HgbA1C, insulin/ HOMA calculation, c-reactive protein, microalbumin, creatnine	10	Lab	X		X				X			X			X
Lifestyle Habits Questionnaire	10	C	X	X	X	X	X	X	X	X	X	X	X	X	X
Motivational Interview	5	C	X		X				X						X
Quality of Life Scale	15	C	X												X
SAIQ- Insight Measure	10	C	X		X				X						X
Telephone Contact Assessment (as needed)	5	C													
Treatment Adherence Log	5	C	X		X				X						X
URICA Motivational Scale	10	C	X						X						X
Vitals: Weight, BMI, Waist, %Fat	10	C	X	X	X	X	X	X	X	X	X	X	X	X	X
Lifestyle Balance Classes	60	RD	X	X	X										
Lifestyle Balance Booster classes	60	RD				X	X	X	X	X	X	X	X	X	X
Personal Goal Sheet	10	RD	X	X	X	X	X	X	X	X	X	X	X	X	X
Eating Behavior & Exercise Adherence – additional interventions	2	RD		X	X	X	X	X	X	X	X	X	X	X	X
Caregiver dietary Information Session	60	RD	X			X			X			X			X
Food and Exercise Diary	15	RD	X	X	X	X	X	X	X	X	X	X	X	X	X
Exercise Tolerance Test	120	C	X												
Electrocardiogram	15	C	X												

Example Schedule for Lifestyle Balance Classes and Exercise Opportunities at West Los Angeles Site

Day of Week	Mon	Tue	Weds	Thurs	Fri
AM Class	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
PM Class	Booster	Booster	Booster	Booster	Booster
Day of Week	Monday	Tuesday	Wednesday	Thursday	Friday
Exercise Options offered at PRRC:	Walking Group 11:00am Yoga 1:00pm	Physical Fitness 8:00am Yoga 1:00pm Golfing 2:00pm	Yoga 2:00pm	Thai Chi 9:00am Field Trip 10:00am (eg farmers market, museum	Yoga 1:00pm

				walking)	
Exercise option Rehab wellness clinic	Daily available stationary bicycle and weight lifting	Daily available stationary bicycle and weight lifting	Daily available stationary bicycle and weight lifting	Daily available bicycle and weight lifting	Daily available bicycle and weight lifting

G. Study Assessments:

1. Screening and General Medical Procedures: The process of obtaining informed consent will culminate in a quiz on the details of the project and participating in research, which is repeated at 6 and 12 months. During the first visit, patients will have a comprehensive physical exam and psychiatric interview. An electrocardiogram and demographics will be recorded. Framingham risk assessment for cardiovascular disease will be calculated and repeated at the end of the study. Routine vital signs, blood pressure, and pulse will be measured at each visit. Patients at high risk for cardiovascular disease and/or current symptoms of angina may need referral for an exercise tolerance test before embarking upon the exercise component of this behavioral weight loss program. Dr. Kunkel, our co-investigator in charge of the outpatient rehabilitation medicine department, has agreed to assist us with expediting exercise tolerance tests for patients wishing to participate in exercise as part of their weight loss plan.

2. Weight Loss Measures: Weight loss measures including measurement of weight, body mass index (BMI), waist circumference, and body composition (% body fat) will occur at each visit of the study. Weight will be obtained on the same clinic scale for all patients. All weight measurements will occur at the same time of day for each appointment. Height measurement will be made at the first screening appointment to calculate BMI. The measurement of the 'waist' is taken at the point midway between the iliac crests and the costal margins. Measurement of the waist is thought to reliably relate to cardiovascular risk, as it reflects visceral adiposity (66) and can assist in diagnosis of the metabolic syndrome. A waist measurement of 35 inches or greater is part of the diagnostic criteria for the metabolic syndrome diagnosis for women and greater than 40 inches meets diagnostic criteria for men. Percent body fat analysis will be performed using a small machine that patients hold in their hands for one minute. This machine emits an electromagnetic signal that uses the differential impedance of bodily tissues to calculate percent body fat. Patients using pacemakers cannot use this device because of concerns of possible interference.

3. Laboratory Measures: Laboratory measures that include hemoglobin A1c, fasting blood glucose, cholesterol, triglycerides, c-reactive protein, and insulin to determine insulin resistance as calculated by the HOMA method. Urine will be collected and tested for diabetes. Laboratory tests will be completed at 3-month intervals.

4. Psychiatric Assessments: These measurements are being done to assess the impact of the behavioral program on overall psychiatric condition as well as the psychiatric factors that impact weight loss. Formal psychiatric assessments will be done at baseline at the end of the 8 weeks of classes, 6 months, 12 months, and end of study. Quality of life will be assessed at baseline and end of the study.

a) Brief Psychiatric Rating Scale (BPRS): The BPRS is a 24 item scale that assesses many aspects of psychopathology including positive psychotic symptoms, (hallucinations, paranoia, unusual thought content and conceptual disorganization) as well as symptoms of anxiety and depression (67). The BPRS will be used to screen positive, negative, and cognitive symptoms that might impact patients' ability to lose weight (15 minutes).

b) Clinical Global Improvement Scale (CGI) The CGI is a 7-point scale that measures the severity of a patient's psychiatric illness as well as improvement compared to baseline. (5 minutes)

c) Quality of Life Interview- Brief Version (Heinrichs): This interview scale has become standard in the field of assessing the quality of life from the perspective of a patient with SMI. The scale will be administered at baseline and at the end of one year (68). (15 minutes)

d) Cognitive Assessments: The cognitive screening we will use in this study will be the summary score of the cognitive items on the BPRS and the Self Appraisal of Illness Questionnaire (SAIQ) will measure the level of insight into psychiatric and medical condition. These tests will be assessed at baseline, 8 weeks, 6 months, 12 months, and at end of the study (69). (20 minutes).

e) Hamilton depression scale: This 18 item scale will be administered at baseline, 8 weeks, 6 months, 12 months, and at the end of the study.

f) Motivation Assessment: Behavioral treatment of problem behaviors involves helping patients with their motivation to change. Five stages of change have been conceptualized for a variety of problem behaviors. The five stages of change are precontemplation, contemplation, preparation, action, and

maintenance. Precontemplation is the stage at which there is no intention to change behavior in the foreseeable future. Many individuals in this stage are unaware or underaware of their problems. Contemplation is the stage in which people are aware that a problem exists and are seriously thinking about overcoming it but have not yet made a commitment to take action. Preparation is a stage that combines intention and behavioral criteria. Individuals in this stage are intending to take action in the next month and have unsuccessfully taken action in the past year. Action is the stage in which individuals modify their behavior, experiences, or environment in order to overcome their problems. Action involves the most overt behavioral changes and requires considerable commitment of time and energy. Maintenance is the stage in which people work to prevent relapse and consolidate the gains attained during action. For addictive behaviors this stage extends from six months to an indeterminate period past the initial action. Most of the patients who will join this study will do so presumably, because they are at the Action stage in this hierarchy. Patients' motivational state will be assessed at baseline, 8 weeks, 6 months, 12 months, and end of study utilizing the URICA, a validated and reliable measure of motivation (70).

g) Biopsychosocial/spiritual Wellness Self Report Scale. To measure the sense of wellness the patient has in biological, psychological, social and spiritual realms, this scale is a 4 item scale with a maximum of 10 points per item reflecting level of wellness that the patient feels.

H. Adherence Methods: Each patient will be assigned a lifestyle balance coach/case manager. The model we use in our treatment of patients is intensive case management and a minimum of bimonthly contacts for each patient. Patients assigned to the "usual care" group will also have case managers and equal contact so that contact time will be equal for each group. We have had extensive experience with utilizing a case management approach with all of our previous clinical trials, and successfully used during our current merit review program. The diabetes prevention program that has been adapted for this protocol has an extensive operations manual that has a long section devoted to methods of improving adherence to the Lifestyle Balance program. Please see appendix of this grant for our operations manual and particularly the "toolbox" section for helping patients adhere to the Lifestyle Balance program.

Adherence is dependent, in part, on environmental and caregiver influences. Many of our patients have little influence over the food that is fed to them in board and care homes. We will assess patient's involvement in food preparation and their willingness to involve their caregivers in helping make necessary dietary changes. Our Lifestyle Balance coaches will act as a liaison to patients' caregivers, family, and or board and care operators and will provide on-site nutritional and cooking education and to assist these care providers with understanding the dietary needs of the patients involved with our behavioral program. In some cases, we may need to recommend meal replacements such as Slimfast when patients are having difficulty with portion control. Patients' participation in their own food preparation will be assessed initially as well as their willingness to have us contact their caregivers to provide support and education towards the dietary goals of this program. Our patients will be asked to provide a food and exercise diary. If patients are having difficulty with losing weight, they will be asked if they would be willing to allow a case manager to attend their meals for a few days to assist them in making healthy choices.

Adherence to the Lifestyle intervention and fidelity of the lifestyle balance coach as well as the patient, will be checked with a specially designed instrument that helps assess lifestyle balance intervention adherence and prompts the lifestyle balance coaches to make necessary suggestions for patients having difficulty making lifestyle changes.

I. Exercise Opportunities: Over the past three years of funding, at the West Los Angeles site, we have made arrangements for innovative exercise opportunities that are enjoyable and thus, enhance adherence to the program. Exercise groups are available every day in the PRRC to increase convenience for the patients. Patients will also be able to go to an introductory12-week long exercise program on the VA grounds called the Wellness program in the department of rehabilitation medicine, and utilize exercise equipment there. Wellness programming is also available at the Sepulveda and Long Beach sites. Part of the duties of study personnel will be to identify and develop daily exercise opportunities at the 3 other sites. Over the first 6 months of the start up time for funding these opportunities should be developed. In cases where patients require an ETT and exercise in a monitored setting, Dr. Kunkel or other designated Physical Medicine and Rehabilitation physician will advise individual exercise programs. Similarly, if people are having difficulty adhering to the exercise regimen we will make every effort to assist them in finding a way to make their exercise goal. In work that we have done in the past, we have found that in-vivo assisted skills training is beneficial to patients with schizophrenia.

This population will not respond well to authoritarian treatment but will respond well to consistent positive reinforcement for every bit of progress. Positive reinforcement is crucial. We will temper our

expectations and applaud any and all positive movement. Patients with low level of motivation will be rewarded with positive affirmations for merely attending the class consistently as an achievement, thus seeing changes in the patients' attitudes, behaviors, and even some weight loss.

Lifestyle Balance Coaches and physicians will meet as a team to discuss patients who need additional interventions to meet their expected dietary changes and exercise goals. We have developed a flow chart that our Lifestyle Balance Coaches will utilize to assist patients with adherence to the program. The number and types of interventions required to assist patients in making healthy lifestyle changes will be tallied. For the most part, these are the modalities described in the grant that can be ascertained in an objective manner for data analysis purposes. Lifestyle coaches' adherence to the training program will be assessed by a simple fidelity measure and an independent objective consultant who will randomly observe coaches meeting with veterans in the lifestyle balance intervention group.

Because weight gain can be a deterrent for patients to adhere to antipsychotic medications, one of our hypotheses is that people in the lifestyles intervention group will have higher rates of adherence to their psychiatric medications than patients in the "treatment as usual" group. We will rely primarily upon the VA computerized record system to determine the percent of psychiatric appointments attended by patients as well as the percent of medications refilled. In addition, we have developed and will utilize several objective measures of adherence to treatment.

J. Additional Interventions: In the event that the patient is not losing weight or is unable to adjust to their diet or exercise regimen, we will request the patients permission for additional intervention so that we may assist them adhere to their exercise and diet. Additional interventions are optional and may include:

1. Additional Exercise Interventions

a. The research physician will review the patient's medical chart to determine if their current medications may be contributing to fatigue, sedation, and/or lack of motivation. Consultation with the patient's treating psychiatrist may lead to suggestions about medication adjustments to be made by the treating psychiatrist (as it would be done in usual care) to optimize energy and motivation of patients.
b. The patient's rewards may be adjusted to optimize their motivation to exercise (See DPP Toolbox Appendix).
c. The patient's exercise goal expectations may be adjusted.
d. We may assist the patient in finding an exercise location. The patient will be given the opportunity to take exercise classes at the VA or may be given a membership to a safe exercise facility.
e. We may provide the patient transportation or bus fare so that the patients may attend the exercise classes.
f. If the patient is injured or has any other physical problem, his/her exercise regimen and goal expectations may be adjusted to fit their needs.

2. Additional Dietary Interventions

a. The patient's lifestyle coach may request to attend meals at their place of residence to observe their eating patterns and make positive suggestions.
b. We may provide further education to their Board and Care and/or caregivers about the importance of the patients' dietary needs.
c. The patient may be asked to substitute a meal or snack for a Slimfast, energy bar, or other food substitute.
d. The patient's dietary goals may be adjusted to a more comfortable level
e. The patient may be asked to repeat some classes and take additional booster sessions to relearn the material taught in class.
f. The patient may be reeducated about the risks and negative impact of obesity on their health.
g. The patient may be given take-home reminders such as pamphlets, fat counters, and other materials.
All the additional exercise and diet interventions mentioned above are optional.

L. Minimizing Risks: Patients will be carefully examined medically and psychiatrically. Safety for exercise will be assessed and if necessary, patients may be referred for an exercise tolerance test and a monitored exercise program. If the behavioral intervention appears to be worsening psychiatric or medical symptoms patients will be discharged from the study. Specifically, patients will be discharged if their psychiatric symptoms are judged to be minimally or more worse on the CGI, from their previous visit. Patients who are observed to be gaining weight or having concerning changes in lipids, or glucose will be given any and all additional medical treatments for such metabolic changes. All additions or changes of medications to assist with metabolic changes will be recorded. No attempt to control psychiatric medication condition will be made in this study, as we wish to optimize patients' outcome. Types of drugs given will be carefully documented and examined in post hoc analyses. All usual care patients will have the option of open treatment after six months

if in the opinion of the investigator, weight changes and/or metabolic changes warrant intervention that is more rigorous.

M. Rater Reliability: Rater reliability is maintained by all raters co-rating patients in reliability sessions. A start up meeting will include co-rating sessions to assure reliability of assessors. All psychiatric raters have undergone inter-rater reliability quality assurance testing on a yearly basis as part of their ongoing work in clinical trials research. Raters will be assigned specific patients and will be expected to rate that same patient throughout the year. Raters will be masked to randomized condition.

N. Statistics and Data Analyses

1. General Data Analysis Issues: Data Management:

A. Organization of the Data Core support (Catherine Sugar Ph.D., Director, Gerhard Hellerman, PhD senior statistician)

The multi-site study data will be managed locally at each site and will be supported by the VISN -22 MIRECC Biostatistics Core (VISN-22 MIRECC P.I. S. Marder, M.D.) . Affiliation with the VISN-22 MIRECC Core provides the research team with expert general and specialized consultation. The Core also includes statisticians, database and MS Windows applications development programmers and other research support staff. Dr. Ames has utilized the core for other multi-site studies she has developed. Both she and her colleague, Dr. Rosen in Long Beach have experience with the proposed web based data management system.

B. Database Management: The database requirements for multi-site projects such as this are well served by Internet-based solutions. The MIRECC data core are expert in providing active database websites that allow users (via password protected logon) to enter, edit, and view data directly to a centralized database on our server in Los Angeles. When appropriate, extracted subsets of the data can readily be provided for download locally at the sites. All registration of participants and subsequent data entry is thus entered into the common, central database. Our data systems provide for double entry, full validation of fields, project tracking to permit investigators to review recruitment and data flow, and reports to summarize those matters for effective project management. Members of the Data & Methodology Care are expert in SAS programming, and in the other languages such as Visual Basic and C++, Internet languages (ASP, HTML and DHTML), and scripting languages such as JavaScript and VBSScript, and are familiar with a wide variety of statistical analysis software, including general libraries such as SPSS and specialized modeling tools such as EQS, LISREL, Mplus, HLM, and many others.

C. The centralized database will be available on the Internet (ASP) in a password-protected system built on ODBC.ADO (Access, SAS, SQL7) database tables as appropriate. Our server is 64-bit SSL protected (the secure socket technology widely used on the web for secure transactions, e.g., e-business). Centralized database of composite, “core” data makes reporting to all sites, quality assurance, and distribution of composite data to relevant investigators possible. Local personnel at the sites using Internet Explorer do data entry beginning with basic registration of new patients at recruitment. Because all the software is on the centralized server, no special data management/entry software needs to be installed locally. Any maintenance or changing of the system is also done on the central server, i.e., in one place. Recording a “start date” for each participant makes it possible for the system to track progress, note upcoming appointments and missing data, and prepare summary reports that are then immediately available for viewing or download.

D. Registry: All study recruits will be rapidly registered at the point of signing the informed consent IC into the registry on the centralized Internet-accessible database. Basic descriptive data will also be entered at this time.

E. Data flow: We will maintain two separate databases. One will be the in-process data files, stored and maintained as received from the sites but not yet processed for QA. The second will be final “cleaned” database for analyses. Extracted subsets for specific analyses will be prepared as required. The Data Core will serve as the central “hub” for all data processing. Each key step in this process (initial entry of data; internal checking and QA, e.g. missing forms or items; modifications and updates; final storage in the cleaned database) will be logged on the Internet system, making it possible for the PI and site coordinators to have a snapshot of the data system at any time.

F. Output & reports: Summary tables of database contents will be organized by site and by measure; these may display either numbers of tests completed, substantive data summaries, or actual (anonymized) data records. Abstracted composite datasets can be readily prepared centrally and sent back to relevant investigators for local statistical processing. Any database changes made (e.g., additional summary variables) will in general be returned to the central core.

G. Communication between sites & core: We will have a staff member assigned to monitor, log and process data, and provide full-time access to Data Core support by phone and electronic means. Mechanisms for data transfer are described above.

H. Static & dynamic database: Quarterly "snapshot databases" (archived) will be produced to ensure stability in interim analyses. We do not plan to perform interim analyses of outcome data for any reason other than what may be required by DSMB. Interim reports will be provided for quality assurance and administrative purposes, e.g. tracking recruitment as required by NIMH to assure adequate recruitment of women and minorities. We are aware that interim analyses have implications for power calculations. Preserving confidentiality of reports is extremely important. (Fleming and De Mets, 1993). As noted, we will also keep documentation of changes made (e.g. corrections) in the cleaned database to document any discrepancies between equivalent analyses.

I. "Quality assurance" will be done locally ("preprocessing") on individual measures. Some QA will be done centrally to evaluate inter-site differences and time trends. Central oversight will check for missing data, range checks (in general, the data entry software itself prevents these errors), and outliers. In addition:

a) Subsets of cross-site/cross-measure data can be made available to investigators at the sites for quality assurance checking and certification.
b) A tracking system will register test submission and entry into database on an ongoing basis. Reports will be available securely online on site progress with recruitment and data entry.
c) Regular reports on cross-site comparability in terms of:
i. recruitment rates
ii. completion of all procedures
iii. descriptive statistics on all measures
iv. simple ANCOVAs or other appropriate statistics to compare sites
v. annual "calibration" analyses and reports on normal QA participants

Reports will be available securely online on each site's progress with recruitment and data entry. In this manner, and interacting with the other sites at monthly conferences and through the oversight and related committees, we will be able to review reports on cross-site comparability in terms of recruitment rates, completion of all procedures, descriptive statistics on all measures, simple ANCOVAs or other appropriate statistics to compare sites.

Computing resources include a local area network of IBM-compatible desktop computers in the project offices. All data will be key-entered by project staff on an ongoing basis, using a system that provides for double entry verification and complete field validation. The study data management system will enable the rapid and accurate entry of data from the clinical evaluation and psychosocial assessments. Data management and analysis will be performed using the SPSS, SAS and R statistical packages dependent on which specific package supports specific analyses best.

Prior to statistical analyses, the data will be inspected to determine the advisability of scale transformation to normalize distributions or reduce variance heterogeneity (e.g., logarithmic or power transformations) and to identify missing data, outliers, or other unusual features that might bias results. Where multiple measures may overlap or be redundant, preliminary analyses will explore whether it is possible to reduce these using techniques from scale development such as factor analyses. Preliminary analyses are also performed to compare treatment groups on descriptive and clinical characteristics at baseline to ensure randomization has succeeded. If there are significant differences between the treatment groups at baseline we will create propensity scores and include them in all further analyses as covariates to compensate for potential bias. We will also test if there are significant site effects, and if necessary we will include a site variable in the mixed linear mode analysis, and model time as nested in subjects and subjects nested in sites.

To address concerns about excessive Type I error rates, the principal analyses are designed to answer clearly stated major research hypotheses, and are based on well-specified dependent variables. The samples are large enough to expect that confidence limits may be reasonably narrow, and findings may be robust enough to permit conservative adjustments of p-values for multiple testing. Bonferroni and other adjustments are necessarily somewhat arbitrary as Saville notes in his argument against their use (71). Additional analyses that are exploratory will be clearly identified as such. All tests will be two-tailed at alpha=0.05.

2. Attrition: Dropout from treatment does not necessarily mean participants will refuse follow-up assessments, and we will attempt to obtain full follow-up data on all enrolled participants regardless of degree of participation and include all enrolled participants in analyses when any outcome data are available (intent to treat). Attrition can compromise randomization, so preliminary analyses will compare baseline characteristics

of subjects available for analysis at each data point with those who are missing to evaluate sampling biases. Attrition naturally lends itself to analysis using survival regression models. Rates of attrition in the treatment groups will be depicted using Kaplan-Meier curves and simple comparisons performed using the log-rank test. More detailed examination of covariates that may predict dropout will be done using proportional hazard survival regression, which permits entry of both fixed (e.g., baseline status or descriptive-demographic characteristics) and time-dependent covariates that change over time (e.g., change in clinical status on prognostic variables). Dropout information is known for all subjects, so multiple logistic regressions can also be employed to evaluate multiple predictive factors without attention to timing of dropout. If trajectories of change on clinical outcome variables or interim (six month) data predict dropout, that would be taken into account in interpretation of the outcome analyses (e.g., sampling bias). We will compare subjects included in the analyses at any point with those who have dropped out on variables such as overall change from baseline, trajectory (slope or speed of change), and status at the last data point. There is no perfect statistical solution to missing data, but if dropout is deemed to be a possible source of bias in the analysis, we will consider additional analyses that specifically address sampling bias (e.g., two-stage modeling, propensity score stratification (72, 73)) weighted analyses or sensitivity analyses such as multiple imputation that examine the robustness of findings to assumptions about the outcomes of lost cases. As noted below, the proposed longitudinal (repeated measures) analyses are likelihood-based general (or generalized) linear mixed models, which permit missing data (see (74) for a recent, explicit comparison of five alternative data analysis approaches to the missing data problem which strongly cautions against analyses based only on complete cases and comments favorably on the use of linear mixed model methods).

3. Repeated measures analyses: We propose to longitudinal (repeated measures) analyses to maximize the additional power we gain by observing the same subjects across 12 months.. Repeated measures analyses permit contrasts at each time point, and also describe and compare trajectories of change (trends), speed and durability of effects. We will also conduct separate cross-sectional to provide outcome data for ongoing safety review, interim progress reports, study oversight and conduct.

The primary design for longitudinal (repeated measures) analyses of continuous outcome scales will be a 2-group (treatment) mixed general linear model of timepoints nested within participants. This is very general linear model that permits flexibility in specifying the nature of the covariances among the dependent measures, allows time-dependent, within and between subject covariates, and permits incomplete (i.e., missing) data. Analyses of trends across the monthly assessments will be done using growth curve model within the mixed model analysis of covariance design with repeated measures described above. We propose to model a linear trend of time unless inspection clearly suggests nonlinearity. By fitting a slope over time (and intercept) for each participant who has baseline and at least one other measure, this method makes good use of all the data, and is robust even if some of the some measures are missing. The use of the mixed general linear model for all cross-sectional and linear hypotheses ensures that results will be comparable across different analyses and provide a framework to include group, person and time-specific covariates if it becomes necessary. The preliminary analyses have shown that this analysis strategy provides meaningful results even with partial data and suggests that we will exceed the originally projected power.**4. Stratification:** Randomization will be stratified by type of antipsychotic and presence of mood stabilizer medication (e.g., depakote, lithium) to assure balance on olanzapine and clozapine by randomizing within three strata – olanzapine, clozapine, and all other antipsychotics -- using three separate randomization lists. Because such stratification can adversely affect statistical power by creating artificially comparable (and heterogeneous) groups, two dummy variables coding olanzapine and clozapine at baseline will be included in all analyses as covariates.

4. Statistical Plans:

Primary Hypotheses:

a) SMI patients with antipsychotic associated obesity who participate in a behavioral intervention that includes classes on Lifestyle Balance will gain more knowledge (i.e., greater change scores on before/after survey test instrument) about general health issues (e.g., nutrition, importance of exercise.) than a control group receiving “usual psychiatric care”.

b) SMI patients with antipsychotic associated obesity who participate in a behavioral intervention program will achieve better cardiovascular (e.g., sustained weight loss, better glucose tolerance, improved lipid profiles, and improvement in other biological measures, e.g. insulin and c-reactive protein) and mental health (e.g., improvements in general measures of psychopathology, subjective quality of life, etc) outcomes than the control group. A larger proportion of patients who take the Lifestyle Balance classes will actually make lifestyle

changes (objectively measured by food and exercise diaries) than patients in the usual care group given ordinary counseling.

c) A larger proportion of patients who take the Lifestyle Balance classes will actually make lifestyle changes (objectively measured by food and exercise diaries and exit interviews) than patients in the usual care group given ordinary counseling. Analysis plan: For all hypotheses concerning the effects of the treatment program use analysis of repeated measures using the assessments at baseline, 8 weeks, 6 months, and 12 months. These analyses will provide information about maintenance of treatment effects. We will use a mixed general linear model with timepoints nested within patients. For hypothesis (c) we will adapt the mixed general linear model to dichotomous data by using a logistic link function to model the likelihood of life style changes. We will include all patients with at least one post-baseline data point in the analysis to maximize power. We will also consider the appropriateness of linear growth curve mixed effects models, i.e., fitting an intercept and linear slope for each treatment group as fixed effects, and separate intercepts and linear slopes for each patient as random effects. Analyses of linear trends over time with a single df effect are often more powerful tests of differences in trends than multiple df profile contrasts across the separate time points.

General linear mixed effects models permit missing data but assume that data are missing at random. We will explore this assumption by comparing attrition rates in the study groups, and by comparing patients with and without post-treatment data on baseline scores and other baseline characteristics. If missing at randomness does not seem like a valid approach we will use multiple imputation based on different models of missingness to determine the degree of potential bias due to the way we approach the problem of missing data. Based on our experience with similar data we don't expect the data to violate missingness at random, but if it does we will use the results of the multiple imputation based on the EM algorithm to derive confidence intervals for our parameter estimates.

For Primary Hypothesis C, intraclass correlations will be run to assess the concurrent validity of the BPSS (compared to the WHO-QOL) to examine the relationship between study participation and biopsychosocialspiritual wellness.

Secondary Hypotheses:

a) Negative and Cognitive Symptoms will affect weight loss. Specifically we hypothesize: i.) High levels of negative symptoms as rated by the BPRS negative symptom cluster will correlate negatively with weight loss; ii.) Motivation to change level will impact weight loss directly; iii.) High levels of cognitive impairment as measured by the BPRS cognitive cluster will correlate with low weight loss, and; iv.) Insight into illness (as measured by the SAIQ) will correlate directly with weight loss. v.)High motivation as measured by the URICA will correlate with successful weight loss

Analysis plan: We do not expect to see meaningful weight loss in the usual care group, and thus do not expect meaningful correlations based on these hypotheses. Accordingly, the primary tests of each of these hypotheses will be done by computing Pearson correlations between the specified variables within the treatment group. Supplementary analyses will be done within the context of the mixed effects designs described above, including these variables as possible treatment effect moderators. Separate analyses for hypotheses (i.) through (iv.) above will be done to examine possible interactions of each of these variables considered separately with treatment group. These analyses will test whether treatment may be more or less effective as a function of these variables (negative symptoms, motivation to change, cognitive cluster, insight). If so, we will stratify the groups according to these variables to simplify presentation of the results, e.g., treatment outcomes presented separately in groups with more versus less cognitive impairment).

b) SMI patients involved in the Lifestyle Balance Program will have better adherence to psychiatric treatment than the Usual Care group as measured by percent of psychotropic medication refills and percent of appointments attended.

Analysis plan: We will compute these dependent measures (percent of psychotropic medication refills and percent of appointments attended) to create summary scores within each of the three study follow-up epochs (baseline- 8 weeks, 8 weeks- 6 months, 6-12 months). These will be analyzed using general linear mixed effects models with repeated measures, including baseline stratification medication as a covariate. We will test group, time and interaction effects, and perform between-group contrasts for each time period.

To determine what patient characteristics, e.g. Medication group, diagnostic or symptom status is most conducive to positive outcome we will use classification analysis using the recursive partitioning algorithm to determine which patient characteristics at baseline are the best predictors for positive outcomes. Recursive partitioning is a computationally intense data mining technique that allows for the analysis of multiple predictors simultaneously while protecting against type I error inflation due to multiple testing and it provides non-parametric confidence intervals by using cross-validation (75).

It provides valid statistics even in cases where there are more potential predictors than observations, and allows us to include all demographic, psychosocial, psychiatrical and medical data know at baseline as potential predictors. The results of this analysis will suggest which patients are most likely to profit form further interventions, and it will also characterize the most at risk patients.

c) Subjects will continue to give meaningful, informed consent to participate throughout the study. They will see no significant decrease in their score on the informed consent quiz given every 6 months.

Analysis plan: A general linear model (GLM): ANOVA will be performed to compare the informed quizzes score results at 0, 6, and 12 months during the subjects' participation in the study.

5. Power Analysis: All calculations are based assuming a conventional medium effect size (f=.25, Cohen 1988); and a two-tailed alpha set at 0.05..Tuomilehto et al. estimated the SD of weight loss at roughly 5 kg across several treatment conditions (lifestyle changes vs. control) (76). A medium effect would thus translate into a group difference of about 2.5 kg or about 5.5 pounds. With an enrollment of N=120 and an estimated attrition rate of 45% we expect that at least 66 subjects will provide complete the study and provide 4 data points. The power analyses below are based on a sample size of N=66, i.e. this is a very conservative estimate due to the fact that the mixed linear model allows us to include cases with missing values in the analyses and that while they don't provide as much information as complete cases they still provide some information and will increase power. For the between-group comparisons, N=66 yields power=.7199 for main differences between groups if we assume that the within subject correlation is r=.50., Power to test the for the difference in outcome trajectories of time – our main outcome variable is 0.99, and even if the effect is as small as f=0.15 we will have sufficient power to distinguish between the trajectories of the two treatment groups (power=0.83) insuring that we will get significant, insuring that we Preliminary data analyses shows that these assumptions are quite conservative and that effect sizes seem to be slightly larger than projected, suggesting that the final power will exceed the estimates presented here.