Reducing cardiometabolic risk and promoting functional health in community-based elders with obesity and pre-diabetes: evaluating sustainable follow-up strategies

Research Protocol

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
Version 2	Effective 1/5/2021	Initial sessions during the 6-month base intervention protocol (in-person group sessions 1- 4, and one transition session to prepare for teleconference follow-up) were stopped as of April 2020 due to the Coronavirus disease (Covid-19) pandemic. All sessions were thereby implemented by group teleconference only. A session "0" was added for tele-orientation to the program. The learning content remained the same.	**Yes/approved**

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1.0 Study Summary

The confluence of obesity and pre-diabetes in older adults substantially increases the risk of diabetes, and accelerates functional decline, multimorbidity, disability, and death. More research is needed to refine and extend preventive interventions to reduce burden for elders and society. For over a decade efficacious 6- and 12-month Diabetes Prevention Program (DPP) based lifestyle interventions have been translated successfully and demonstrated positive impact. However, efforts to develop and evaluate more scalable programs conforming to current Medicare guidelines (MDPP) for longer term DPP interventions (up to 18- or 24-months) and help a greater proportion of enrollees achieve and sustain the recommended weight loss target of ≥ 5% are lacking. Our scientific premise is that the evaluation of translational DPP interventions, which has centered largely on strategies for weight loss induction, must be extended to include longer-term interventions that clearly demonstrate durable weight, cardiometabolic and functional health benefits for vulnerable elders in community-based settings. Our previous DPP-adapted research has documented the utility of group telephone follow-up after a 6-month DPP weight loss induction and shown that 63% of a 65–80-year-old volunteer sample with obesity and other risk factors were able to sustain ≥ 5% weight loss at 12-months.
Despite good evidence that longer duration lifestyle interventions yield better outcomes (reflected in recent Medicare rulings) translational studies of 24-month long DPP interventions with older adults are scarce. This study utilizes community-based settings to examine whether we can sustain the impact of an elder-focused DPP approach using potentially scalable telehealth treatment components over a 24-month period. We will recruit and enroll 65–80-year-old adults with obesity and pre-diabetes (N = 360) through networks of senior community centers that provide aging services and utilizing other older adult targeted database resources. The intervention program sequencing will be aligned with current Medicare (MDPP) policy. First, from 0-6 months, experienced lifestyle coaches will offer a DPP-video intervention anchored by group telephone coaching for all participants, at least 25% from ethnic/racial minority groups. Next, participants, will be randomized (up to N = 180 per arm; stratified by weight loss of < or ≥ 5%) to one of two 18-month follow-up conditions conducted between 6-24 months. We will compare the effects of (1) DPP-Behaviorally Intensive 30-Minute Groups or DPP-BI and (2) DPP Minimal Support 15-Minute Groups or DPP-MIN on measures of weight/adiposity (the primary outcome) at 12, 18, and 24 months. In addition, we will collect cardiometabolic, physical activity, physical function, psychosocial, behavioral, and other age-sensitive quality of life measures at these same intervals. Medicare claims data will be examined for a proportion of the sample, regarding types of medical utilization. If successful, this work will have immediate potential for MDPP lifestyle interventions, involving telehealth delivery, which are consistent with a chronic care model, and will benefit vulnerable aging individuals and society.

2.0 Objectives

Obesity in adults ≥ 65 years is prevalent[14] and elevates risk for diabetes,[15] multimorbidity,[16] functional decline[17] and healthcare burden.[18-20] The Diabetes Prevention Program (DPP) intensive lifestyle intervention[21-24] has been translated successfully by our group[5,25-28] and others[29-31] using primarily 6- or 12- month in-person programs, but translational studies have been hampered by lack of scientific rigor, incomplete reporting, inadequate focus on behavioral intensification for participants not meeting goals, and lack of scalable, longer duration interventions.[31] Because there is good evidence that achieving and sustaining clinically meaningful weight loss of ≥ 5% [32-34] over time is critical for durable health benefits, especially for vulnerable elders with obesity and pre-diabetes,[23,35,36] longer term tests of DPP-based behavioral self-management interventions are needed. These findings could have immediate

impact for the increasing number of state and national DPP programs being designed to meet the chronic healthcare needs of the Medicare population.[1,37]

Our central scientific premise is that DPP programs and associated benchmarks have been well-established for the 6 month weight loss induction intervention, but that the most effective strategies for conducting longer duration DPP interventions with vulnerable older adults in the community are lacking.[31,38] Our research group is well-qualified to develop and evaluate such an approach. We have shown that a 12-session, face-to-face, DPP intervention for elder volunteers followed by 6 months of modest interactive group phone support (one 30-minute contact/month) was associated with significant weight loss[28] (7.5 ± 5.5% and 63% achieving ≥ 5%) and associated health improvements at 12 months. Now we propose to extend our previous work to senior community center settings and test more scalable intervention strategies, in a two-arm trial, designed to achieve and sustain weight losses of ≥5% and produce cardiometabolic, physical function, and other health benefits over 24 months.

The proposed translational effectiveness study will commence with a non-randomized, video-delivered DPP intervention (our Group Lifestyle Balance-DVD)[4,25] anchored by telephonic group contact as a lower-cost model for achieving the primary weight loss induction of ≥ 5%, followed by randomization to either DPP-BI or DPP-MS (both telephonic coaching interventions, both aligned with a Medicare delivery schedule) for the next 18 months. After the 6-month induction period, participants will be stratified by weight loss achievement (< or ≥ 5%) and those assigned to DPP-BI will receive continued MDPP-prescribed behavioral group sessions (remotely) plus additional individualized activity coaching. Activity is critical at any age, but for elders with obesity and pre-diabetes, especially those who have not reached DPP weight targets by 6-months, it may enhance cardiometabolic and functional health outcomes compared to minimal contact alone.[7,39] Between 12-24 months the DPP-BI group will continue with group phone coaching sessions that are designed to integrate DPP weight management strategies with those aimed at critical self-care/healthcare behaviors for healthy aging ("5-keys")[8,10]. In contrast, those assigned to DPP-MS (control) will rely on brief group phone contacts alone *as the minimum scalable modality* for lifestyle behavior change accountability over this period.

We plan to recruit and enroll ambulatory adults, 65 years of age and older (up to N = 360) with BMI ≥ 27 kg/m^2 and pre-diabetes (FPG ≥100 and <125 mg/dl, or HbA1c ≥5.7 and <6.4% mg/dl) from senior community settings and using other database resources. Between 0-6 months, a base DPP intervention of self-directed lifestyle change videos, activity videos, and weekly group phone contact (16 sessions) will be provided to all enrolled. Between 6-12 months, individuals randomized to DPP-BI, will receive DPP sustained DPP-BI 30-minute group calls (6 sessions) and ≤ 2 individual physical activity consults. Between 12-24 months sessions reduce to one every two months (6 sessions). Those assigned to DPP-MS, will participate in brief unstructured group support phone contacts according to the same schedule. Participants, 25% from ethnic/racial minority groups (primarily African American), will be assessed at baseline, 6, 12, 18, and 24 months to determine the following specific aims:

Aim 1: Document the impact of DPP-BI compared to DPP-MS on weight at 12, 18, and 24 months.

Hypothesis 1: Overall, DPP-BI compared to DPP-MS will result in more favorable weight loss (average change and the proportion reaching ≥ 5%) at 12, 18, and 24 months.

Aim 2: Document the impact of DPP-BI compared to DPP-MS on cardiometabolic, physical activity/function, secondary outcomes, and behavioral adherence measures at 12, 18 and 24 months.

Hypothesis 2: Overall, DPP-BI compared to DPP-MS will result in more favorable cardiometabolic, physical activity/function, secondary outcomes, and behavioral adherence measures at 12, 18, and 24 months.

Exploratory Aim: We will examine differences in intervention response (weight, cardiometabolic, and function) by race (African American, Caucasian). For a proportion of the sample, we will explore Medicare data for group differences in medical utilization (medications, outpatient, inpatient, emergency visits) and participation in activity programs.

Evaluating incremental refinements to standard DPP approaches through community centers providing aging services, in alignment with MDPP[1,37] and other Medicare subsidized activity benefits, will improve our understanding of the most effective and potentially sustainable long term approaches for weight control and health maintenance in vulnerable older adults. A successful demonstration of 12-, 18- and 24-month interventions using video- and telephone-coaching strategies to sustain weight loss self-management and enhance behavioral activation for cardiometabolic control and functional health outcomes would have significant individual and public health benefit.

3.0 Background

Expanding on our previous work, we argue for employing an elder focused, behaviorally robust 24-month DPP[37] lifestyle intervention. With Medicare reimbursement for group lifestyle intervention now available, including virtual delivery options, but scant data regarding the most effective, sustainable weight-loss maintenance strategies, we conclude that refining and evaluating longer term healthy lifestyle maintenance programs for elders in the context of existing senior services can propel advances in preventive healthcare and potentially decrease medical burden for older adults and society.

Obesity is prevalent in the aging population and associated with cardiometabolic risk. By 2030 over 20% of the residents of the United States (US) will be over the age of 65[40] and obesity in this group is likely to have critical implications for 21st century population health**.** Increases in obesity (BMI ≥ 30 kg/m^2) among adults in all age groups have neither slowed nor stopped.[14] According to the US Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) reports [41-43] more than one-third of men and women ≥ 60 years have obesity. Women compared to men, aged 65-74, have the highest obesity prevalence rate among older adults at 44.2%. Obesity prevalence rates have been shown to fall by roughly 10% after age 75, although black women and individuals in rural communities[44] continue to demonstrate high rates of obesity well into late life. Moreover, many cross sectional and prospective studies of elders have shown the adverse health consequences of excess adiposity for metabolic, cardiovascular and general health outcomes (e.g., hyperglycemia, metabolic syndrome, insulin resistance, diabetes, inflammation, plasma lipids, arterial blood pressure, and other downstream physiologic abnormalities).[45-48] Uncontrolled hypertension, dyslipidemia, and cardiovascular disease have decreased over the last few decades in all BMI categories, including among obese adults, however diabetes has not.[49,50] Epidemiologic studies, such as the prospective Cardiovascular Health Study, have provided compelling evidence[51] that high BMI, central adiposity or weight gain during the period of ages 65-74 years is associated with increased diabetes risk.[15,52] The problem of obesity and diabetes is increasing throughout the lifespan in the US, but absolute prevalence rates of diabetes remain highest among adults aged 65-79 years[53] owing to increasing incidence and decreasing mortality.[54] Thus, this is a critical period for weight management and health promotion activities.

Obesity and diabetes in aging individuals accelerate risk for functional health decline. In addition to its association with cardiometabolic risk, obesity is consistently shown to be one of the top 2-3 modifiable risk factors for osteoarthritis and mobility disability in older adults.[17,55-57] Data from NHANES and Medicare research have shown that obese older adults are more likely than their normal weight counterparts to report problems with walking, using stairs, and lifting.[58] Although some investigators have argued that obesity is inversely associated with morbidity and mortality in elders (i.e.,

the "obesity paradox"),[59,60] the CDC and many medical and scientific organizations[61] have recommended that older individuals with obesity be identified, evaluated and treated with prudent lifestyle intervention strategies given the burden of comorbidities and accelerated functional decline likely to negatively impact life expectancy and quality of life.[45,62-64] In addition, normative age-related physiologic changes are associated with a progressive loss of lean muscle mass and function known as "sarcopenia" with prevalence estimates ranging from 25-50% of adults ≥ 65 years showing problems with body strength and endurance.[65] The term "sarcopenic obesity" has been coined to describe the problematic interplay of excessive fat mass and low muscle function. Functional decrements may operate through biomechanical pathways (e.g., lower extremity stress and pain) or through cardio-metabolic and pro-inflammatory pathways, all of which contribute to poor health outcomes. Although some have argued that weight loss among older adults may result in further loss of lean mass and compromise functional health,[66] several intervention studies have shown that sustained modest weight loss, particularly when combined with regular physical activity, is highly beneficial.[3,67,68] Additional research that indicates it is the confluence of obesity and diabetes that accelerates the physical function impairment and reduced quality of life seen in aging individuals, is especially pertinent to the current proposal.[45,62,63,69,70] Unless feasible and sustainable prevention efforts are mounted [3,63,64] an increasing number of aging adults will be living longer with obesity and the progressive burden of chronic conditions and mobility impairment.

Obesity, diabetes, and mobility disability accelerates loss of independent living. It has been documented that the average age of nursing home residents with obesity is 74, compared to age 80 for normal-weight residents[71]. Although serious deficits in activities of daily living and disability (e.g., getting in and out of bed, eating, and dressing independently) have decreased during the last decades of the 20th century overall, they have increased by 43% for those living with obesity[58]. A large prospective study[72] of community dwelling elders, aged 65-74 at baseline, examined the odds of nursing home admission over 2 decades and found that obesity increased the risk of admission by roughly 30%; obesity plus one additional risk factor (diabetes, hypertension, or smoking) doubled the odds. Maintaining functional independence is certainly paramount to older adults, caregivers, and the healthcare system. Thus, mitigating obesity and diabetes risk during this period seems particularly crucial for delaying the onset of more costly and restrictive levels of care.

Older adults respond well to diet and activity interventions but have been underrepresented in major clinical trials and community-based studies. Elders typically comprise <20% of the enrolled sample in major multicenter weight loss trials, but available data indicates they are very responsive to the behavioral regimens provided.[23,36,73] This was striking in the DPP trial, with individuals ≥ 60 years attending more sessions (including supervised group activity), self-monitoring more consistently, achieving weight loss of ≥7% [74] and increasing physical activity[36] at higher rates than younger participants. This observed outcome was associated with a decrease in incident diabetes of 71% over an average 34 months of active follow-up compared to the average decrease of 59% (ages 45-59) and 48% (ages 25-44) in the younger age groups. Figure 1a and 1b suggest that the long period of sustained weight loss (left, bottom line) among older adults was critical to diabetes prevention/delay (right, bottom line) compared to the metformin (middle line) and placebo (upper line) groups. However, older adults have not been the focus of most translational studies of DPP interventions and other cardiovascular risk intervention trials[75] and Medicare coverage decisions have often been extrapolated from younger persons. A translation study by West et al[76] delivered in senior centers by lay health workers compared a 12-session DPP intervention to an attention control program and found significant differences between groups, but weight loss did not reach 5% on average. More community studies evaluating longer duration programs are needed to document the full potential for meaningful weight and health outcomes.

Weight management and other evidence-based lifestyle interventions such as "10- Keys™ to Healthy Aging" have potential to mitigate multiple chronic conditions in aging adults. Epidemiologic data show that older adults who maintain ≥ 4 healthy lifestyle habits (e.g., faster walking pace, more leisure physical activity, modest alcohol intake, BMI <30 kg/m^2 and not smoking) have 45% lower odds of incident heart failure.[77] Several large randomized trials of intensive diet and activity interventions demonstrate that weight loss in the 65+ age group with obesity also results in enhanced health related quality of life, vitality and physical function.[64,68,78,79] Moreover, in addition to cardiometabolic and musculoskeletal impact, obesity has been associated with an approximate 25% increase in odds of mood and anxiety disorders, including among adults ≥ age 60[80]. A community intervention study[81] of racially diverse older adults found that either a brief evidence-based problem solving therapy directed at mood regulation, or an individual nutrition coaching program directed at healthy lifestyle, performed equally well in reducing symptoms of depression over 24 months among elders with elevated depressive symptoms at baseline. Our GLB intervention (mean age 72) also demonstrated a "two-for-one" (weight loss and mood) benefit in the short term[28]. Therefore, our scientific premise is that older adults, at ever increasing risk for multiple chronic conditions,[16,18,82] may benefit from comprehensive behavioral lifestyle interventions that reinforce common self-management behaviors (i.e., goal-setting, self-monitoring, problem-solving) with capacity to address multiple risk factors. Indeed, this is the theoretical rationale for the development of elder-focused approaches such as "10- Keys to Healthy Aging",[8] and is wholly consistent with DPP intervention goals regarding the importance of maintaining a healthier weight for cardio-metabolic and functional health benefit. With the proposed study of longer duration maintenance interventions, we reason that integrating DPP-based weight maintenance and a "multimorbidity prevention" approach is synergistic, with potential to amplify motivation for self-care among elders.

Few DPP translational studies have documented longer term maintenance outcomes or moderators of success beyond 12-months. We know from clinical trials, overall, that continued contact,[83] self-monitoring,[74] self-weighing,[84] problem solving,[85-87] and adherence to physical activity are all implicated in the maintenance of long term weight loss and associated cardiometabolic and physical function benefits[88]. However, a recent meta-analysis of 44 DPP-based translation/dissemination studies demonstrated that a gap exists between that which has been demonstrated by obesity treatment efficacy research and DPP translational findings. Although short-term cardiometabolic benefits are evident, this systematic literature review found that the average number of program contacts in the first six months of DPP translational studies was 11 sessions and only 60% included a continued contact program of any kind. Moreover, translational programs that have offered follow-up interventions have reported that in-person attendance wanes significantly during the second six months of programming and may not be cost-efficient.[89] Thus, it appears critical that future studies address the feasibility and effectiveness of different strategies and formats for retaining participants to longer duration interventions, particularly after the initial period of weight loss induction to mitigate the likelihood of weight regain and loss of health benefits. Primary care based DPP translations have begun to examine the use of web-based[90] and telephonic support[91] to promote maintenance of weight loss and cardiometabolic improvements but these approaches have not been examined long term with elders, nor has the study of elder-focused physical activity programming and guidance been integrated or evaluated.

Enrollment/participation in community-based activity programs is a potentially promising approach for enhancing weight loss maintenance and functional health in elders. King and Guralnik[92] have argued that the best way to maintain functional health in an aging population is to increase their physical activity and social engagement; providing behavioral guidance for community-based activity program participation may offer a means to both ends. To date, most DPP interventions

have focused on self-monitoring and awareness of activity minutes or steps but not necessarily the merits of enrolling in structured or supervised activity programs. Increasing behavioral support for appropriate activity programs has potential to improve the weight and health of elders with cardiometabolic risk, such programs are often part of the services provided at senior centers and fitness facilities but are underutilized**.** Importantly, prospective research has shown that adjusted Medicare costs decreased in the two years subsequent to joining these types of activity programs (e.g., Healthways Silver Sneakers®, Silver&Fit®, EnhanceFitness®)[93]. Other data suggests that program participation of ≥ 1 time per week is related to lower adjusted health care costs at 12 and 24-months post enrollment,[94,95] compared to controls. However, less is known about the factors associated with joining or adhering to Medicare subsidized physical activity programs. Focus group data from a large health maintenance organization has suggested that non-users, compared to users, have more physical limitations due to health conditions and aging and want more professional guidance on how to adapt physical activity regimens.[6] Facilitators of enrollment included motivation to maintain physical strength, independence, and mental health, engaging and knowledgeable instructors, and the social camaraderie of certain programs and gyms. No studies, to our knowledge, have examined the impact of these types of elder-focused activity programs when combined with a structured weight loss/weight maintenance component.

Our own initial internal review of Silver and Fit™ data, the subsidized activity program for elders that is part of the UPMC Health Plan, indicated that in 2015 only about 12.5% of those enrolled in Medicare Advantage chose to participate in this activity benefit. For those who did elect to participate, most attended classes < 3 times per month. Undoubtedly, there will be considerable variability in the activity needs, preferences, and outlets that best serve a 65–80-year-old cohort with obesity, pre-diabetes and emerging chronic conditions. However, we argue that comparing the effectiveness of a weight loss maintenance intervention that incorporates physical activity program guidance, compared to a minimal contact control, has potential to advance our understanding of effective lifestyle weight management strategies and outcomes.

Lifestyle interventions for older adults with obesity and pre-diabetes have potential to reduce medical utilization and contain costs. Of particular relevance to the current proposal are studies that have documented accelerations in health care utilization that are associated with pre-diabetes in the 1 to 8 year interval prior to diabetes onset.[96-98] Nearly 1 in 4 older adults are estimated to fall within the glucose range that precedes frank diabetes, suggesting that even modest decreases in glucose impairment and health care usage could decrease economic burden. When comparing a pre-diabetes group to a reference group (without diabetes diagnosis or never glucose tested) adjusted rate ratios showed that the pre-diabetes group had 34% more ambulatory visits per year. Additional medical visits associated with pre-diabetes have been estimated to range from 9% more for serious cardiovascular and peripheral vascular disease to 92% more for hypertension for age and sex-matched controls.[96,97] Although the proposed investigation does not have sufficient follow-up duration to conduct formal cost-effectiveness analyses, our scientific premise remains that by exploring parameters such as medication use and medical utilization over the 24 month protocol period, we may be able to observe differences in the proxies of health economic burden between our two intervention conditions. With our UPMC Health Plan partners we are well situated to examine actual claims data and compare whether a more intensive, compared to minimal, 18-month maintenance intervention mitigates expected outcomes. Our shared partnership goal is to collect pilot data with potential to impact strategic care initiatives for Medicare services provision and propose longer and larger studies.

Summary. If successful, our study findings could have significant public health impact for late life individuals by documenting longer duration yet scalable strategies for improving cardiometabolic and functional health. In addition, our partnerships with established senior community service networks and

a large regional health insurer have potential to directly influence the design of preventive health intervention initiatives including the MDPP expansion opportunities currently proposed. Our findings will also have implications for a range of elder focused health services and add to our understanding of safe and effective lifestyle intervention weight management and preventive chronic care strategies for individuals aged 60+.

4.0 Study Endpoints

The Sustain study primary endpoint is 24-months, and important secondary endpoints are examined at 18, 12, and 6-months. All study endpoints are indexed from baseline assessment; however, randomization does not occur until the six-month assessment.

5.0 Study Intervention

<table>
<tr><td rowspan="17">Session 0 added 4/1/20 (when sessions 1-4 in-person meetings were stopped)</td><td colspan="2">DPP Base Intervention Sequence: All Participants
Distribute Core Sessions Workbook and Self-Monitoring Materials
(45-60 minutes, weekly)</td></tr>
<tr><td colspan="2">0-Be a Good Phone Group Member</td></tr>
<tr><td colspan="2">1-Welcome to the Sustain-DPP Study</td></tr>
<tr><td colspan="2">2-Be a Calorie Detective</td></tr>
<tr><td colspan="2">3-Healthy Eating</td></tr>
<tr><td colspan="2">4-Move Those Muscles</td></tr>
<tr><td colspan="2">5-Tip the Calorie Balance</td></tr>
<tr><td colspan="2">6-Take Charge of What’s Around You</td></tr>
<tr><td colspan="2">7-Problem Solving</td></tr>
<tr><td colspan="2">8-Four Keys to Healthy Eating Out</td></tr>
<tr><td colspan="2">9-Slippery Slope of Lifestyle Change</td></tr>
<tr><td colspan="2">10-Step Up Your Activity Plan</td></tr>
<tr><td colspan="2">11-Make Social Cues Work for You</td></tr>
<tr><td colspan="2">12-Ways to Stay Motivated</td></tr>
<tr><td colspan="2">13-Strengthen Your Physical Activity</td></tr>
<tr><td colspan="2">14-Manage Your Stress</td></tr>
<tr><td colspan="2">15-Mindful Choices, Mindful Eating, Mindful Movement</td></tr>
<tr><td colspan="2">16-Take Charge of Your Lifestyle</td></tr>
<tr><td></td><td colspan="2">Randomization to Follow-up Conditions</td></tr>
<tr><td>6 Months</td><td>A. Active Comparator
DPP Behaviorally Intensive (DPP-BI):
30-45 Minute Calls (monthly)</td><td>B. Placebo Comparator
DPP Minimal Support (DPP-MIN):
15-Minute Calls (monthly)</td></tr>
<tr><td rowspan="2"></td><td>New workbook and self-monitoring materials distributed.

17- A New Balancing Act</td><td>No workbook or self-monitoring materials. Two standard prompts per call:

(1) Discuss past month lifestyle successes and challenges (2) Share strategies and positive ideas for healthy lifestyle maintenance</td></tr>
<tr><td>18- Stay Active for Life</td><td></td></tr>
</table>

	(plus 1 to 2 one-on-one PA telephone consults; delivered by Session 20)	
	19- Build Your Own Eating Pattern	
	20- Take Care of Your Heart	
	21- Stay Positive	
	22- Look Back and Look Forward	
12 Months	DPP-BI Healthy Aging: 30-Minute Calls (every 2 months)	DPP-MIN: 15-Minute Calls (every 2 months)
	New workbook distributed. 22-Stay Vital Longer	No workbook. Two standard prompts per call: (1) Discuss past month lifestyle successes and challenges (2) Share strategies and positive ideas for healthy lifestyle maintenance
	23-Keep Bones, Joints, Muscles Healthy	
	24-Care for Mind Body Health	
18 Months	DPP-BI Healthy Aging: 30-Minute Calls (every 2 months)	DPP MIN: 15-Minute Calls (every 2 months)
	New workbook distributed: 25- Know Your Numbers	Two standard prompts per call: (1) Discuss past month lifestyle successes and challenges (2) Share strategies and positive ideas for healthy lifestyle maintenance
	26-Stay Socially Connected	
	27-Live Healthier Longer	
24 Months	End of study	End of study

Table 1: Overview of 24 Month Intervention Sequence by Randomized Follow-up Group

Videos + Teleconference Coaching (0-6 months). The 24-month intervention (Table 1) commences with a 16-session program administered to all enrolled. Participants receive both hard copy DVDs (DPP sessions 1-12 only) and instructions for how to access session videos on a password-protected website. Participants are directed to watch session videos independently (15-20 minutes per each) and follow along with the intervention workbook when participating in groups either in-person or by phone. Because the first several weeks of weight change have been shown to be highly predictive of long term intervention response[106] we elected to provide in-person groups for the first 4 sessions to enhance commitment, group cohesion, and behavioral accountability for self-weighing and self-monitoring. As of 4/1/20 when in-person meetings ceased due to the Covid-19 pandemic, ALL intervention delivery converted to teleconference. Participants were asked to self-report their weekly weights for the first five weeks on a dedicated phone line as a proxy for in-person weighing. A preliminary Session 0 was added to orient the group to the phone conferencing procedures and "good virtual group etiquette" at the outset. Participants received materials to complete the base 16-session intervention (workbook, DVDs, Calorie King ® Calorie Counter; Food and Activity Diaries) by pick-up or mail delivery. An Accusplit Eagle activity monitor was distributed at the baseline assessment with instructions on how to complete the step assessment and mail-back a step-tracking post-card before Session 2. Participants also received Go4Life (NIA) activity videos and other web-linked resources featuring older adults doing aerobic, strength, balance, and flexibility exercises with instruction on safe progression.

Continued Group Teleconference Coaching for the Active Comparator and the Placebo Comparator (6-24 months). Following the six-month assessment visit, randomization to one of the two 18-month continued contact conditions followed stratification by weight loss achievement of < or ≥ 3.5%, and also incorporated age, sex, and race as balancing variables. The two conditions are: (Active Comparator) DPP Behaviorally Intensive or DPP-BI:30-Minute Calls (monthly) and (Placebo Comparator) DPP Minimal Support or DPP-MIN:15-Minute Calls (monthly). Both group conditions have the same follow-up dose/frequency (total of 18 group contacts) and each cohort meets with the same lifestyle coach as they did during their base sequence.

The DPP-BI condition was designed to be behaviorally intensive and aligned with principles of MDPP implementation. Structured workbooks were used to guide all DPP-BI sessions. In addition, those assigned to this arm were offered up to 2 additional one-on-one phone consultations with a Masters-level physical activity specialist for tailored guidance and feedback on their activity goals between Sessions 18 and Session 20. Subsequent DPP-BI sessions incorporated concepts from the "5-Keys to Healthy Aging" and integrated self-care/healthcare for blood pressure, blood glucose, LDL cholesterol, healthy bones, muscles and joints, and mood (depression). Such health maintenance and weight loss maintenance health goals were mutually reinforced during this phase. Lifestyle coaches followed a standardized leader guide and session scripts. Phone sessions were designed to last about 30 minutes and the protocol dictated not to exceed 45 minutes.

The DPP-MIN condition was designed to provide brief, unstructured phone contacts that rely on the group members sharing and discussing their successes and challenges of the past month with minimal input from the Health Coach. There are no workbooks, or self-monitoring materials provided. Each session lasts about 15 minutes. Lifestyle coaches did not present new intervention material, nor did they follow a standardized script for delivering session content. They used group facilitation prompts such as noted in Table 1.

Interventionists. This study utilized lifestyle coaches with backgrounds like those typically hired as health and wellness coaching staff by large healthcare plans, or by community agencies that maintain healthy aging programs with permanent staff. We selected individuals with Master's level preparation and demonstrated experience in DPP implementation and/or group lifestyle coaching. All interventionists received standardized 16-hour DPP-GLB training at the start of the study, 2-hours of booster training annually, and protocol and procedure updates monthly.

Interventionist fidelity to the protocol intervention was measured for each of two conditions. We modelled our session-by-session fidelity checklists on those used in prior DPP-GLB studies[107]. We audio-recorded 10% of interventionist phone sessions for future independent coding.

Intervention Fidelity Assurance/Session Monitoring. We used standardized intervention materials to promote rigor and reproducibility. A study investigator supervised the intervention delivery monthly and an independent rater listened to and rated 10% of session recordings to ensure that health coaches followed the intervention manual and delivered intervention content as intended. Feedback was provided.

6.0 Study Design/Timeline

Study design. This single-site study used an individually randomized, 2-arm, 24-month, translational effectiveness design. We aimed to enroll N = 360 participants (180 per condition). To meet total enrollment targets for the study (Table 2), we estimated a need of 6 waves of recruitment with the first wave commencing in the final two quarters of Year 1, two waves per year in each of Years 2 and 3, and a final wave in Year 4. Because group telephone interaction constituted a large proportion of the core and follow-up intervention, we limited initial group size to approximately N = 8-10 participants. As

such, we aimed conduct 2-6 intervention groups, per each recruitment wave, over the course of the study. Anticipated recruitment was Year 1 (N = 62), Year 2 (N = 124), Year 3 (N=124), and Year 4 (N = 50). Outcome assessments were conducted at 0, 6, 12, 18, and 24 months for all participants in the two-arm study. However, due to various Covid pandemic shutdowns and re-openings at both the University and community level, we extended our recruitment, enrollment, and intervention timeline through Year 4 and into Year 5 of the study necessarily ending intervention and assessment at 18 months for the Wave 6 cohort.

Table 2. Study Design and Timeline of Protocol and Procedures

	YEAR 1			YEAR 2				YEAR 3				YEAR 4				YEAR 5			
	Q1-2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Protocol start-up																			
Wave 1 recruit	N=64																		
assess		0		6		12		18		24									
intervene			C	C	P	P	P	P	P	P									
Wave 2 recruit			N=64																
assess				0		6		12		18		24							
intervene					C	C	P	P	P	P	P	P							
Wave 3 recruit					N=64														
assess						0		6		12		18		24					
intervene							C	C	P	P	P	P	P	P					
Wave 4 recruit							N=64												
assess								0		6		12		18		24			
intervene									C	C	P	P	P	P	P	P			
Wave 5 recruit									N=64										
assess										0		6		12		18		24	
intervene											C	C	P	P	P	P	P	P	
Wave 6 recruit											N=40								
assess												0		6		12		18	*
intervene													C	C	P	P	P	P	P

Study Assessments (Blue); Core Program 0 to 6 Months (Green); Phone Follow-Up 6 to 18 Months (Pink)
Manuscripts, Meetings, Partner Follow-Up and Planning Activities (Purple)
Note: * for Wave 6 (N = 40) the 24 month assessment will occur Q1, Year 6

7.0 Inclusion and Exclusion Criteria

To maximize generalizability and potential for broad dissemination, eligibility requirements were designed to be minimal. Inclusion criteria were as follows: (1) Age 65+ years at baseline with no upper age limit, acknowledging that other exclusionary criteria would be present for the oldest old, (2) BMI ≥ 27 kg/m2 confirmed at a screening/baseline visit, (3) Fasting plasma glucose >100-125 mg/dl or HbA1c >5.7-6.4% mg/dl confirmed at screening/baseline visit, (4) Medical clearance and approval for participation in the intervention protocol was required from all enrolled. If, for any reason, the provider believed that participation in a 24-month diet, activity and weight loss program was not safe or feasible, the candidate was excluded. Those without a primary healthcare provider were referred to low-cost community resources.

Exclusion criteria were as follows: (1) Prior diagnosis of diabetes or currently using medications to treat diabetes, (2) permanently confined to a wheelchair (other assistive devices were deemed acceptable), (3) unable or unwilling to give informed consent (4) Unable or unwilling to self-monitor food, activity, and weight as indicated in the intervention orientation, (5) Significant dementia or hearing loss that would preclude group participation (6) Significant psychiatric impairment that would preclude group participation under normal circumstances in the community, (7) Currently using weight loss medications, (8) Weight loss of 4.5 kg or more in the last six months, (9) Bariatric surgery within the last two years (those who were greater than 2 years post-surgery were considered if they had not lost 4.5 kg or more in the last six months) (10) Plans to leave the community permanently within the next 12 months, plans for extended travel or other demands that would result in less than 50% attendance to the

intervention (in some instances patients are encouraged to pursue future baseline cycles of recruitment). In addition, those with diabetes and other exclusions were referred to other healthcare resources as needed.

8.0 Vulnerable Populations

The following special populations were not targeted for recruitment: prisoners, institutionalized individuals, or others who may be considered vulnerable. Fetuses, neonates, children <18 years, and pregnant or lactating women were excluded based on our inclusion and exclusion criteria.

9.0 Number of Subjects

We projected that at least 1620 subjects would need to provide verbal consent to undergo phone screening procedures prior to consent and enrollment to reach a target N = 360 subjects for the Sustain study.

10.0 Recruitment/Enrollment Methods

Recruitment methods included contacts with members of senior centers, senior housing facilities, hospital-based community foundations, research data registries, and other entities providing services (and research opportunities) to older adults. Outreach to potential participants included in-person talks, electronic and postal mailings, posters and brochures, and paid advertising in senior-focused magazines and minority-focused newspapers. Participant recruitment activities commenced with the cooperation of the administrative directors and support staff of such organizations. The study was presented as an obesity management/diabetes prevention research program tailored to aging adults that could be complimentary to the health care or senior services they were already receiving. Using this natural infrastructure as a platform for lifestyle intervention/healthy aging dissemination efforts was intended to enhance sustainability and magnify public health impact. The PI and staff were available for follow-up questions, and it was made clear that choosing whether or not to participate would have no bearing on their community center activities or their medical care. We emphasized that the study duration (and expected commitment) was 24-months, and up to five assessment visits, but that they were free to withdraw at any time, even after signing informed consent. Staff used a uniform script to respond to individuals who voluntarily contacted a dedicated study line within 1-14 days to begin this process.

The Sustain study employed a multi-step screening and enrollment process as follows:
(1) Verbal Consent was given to make an initial determination for inclusion/exclusion based upon self-reported demographic information, medical history, interest in the intervention study, ability and willingness to participate, 2) Written informed consent was obtained at the Field Screening where trained study staff collected a Cholestech finger-stick blood sample to measure HbA1c levels to provide confirmation of pre-diabetes status (i.e., 5.7-6.4%) and a height/weight measure to ascertain minimum BMI of 27 kg/m2. (3) Subjects were informed immediately at this screening step whether they were eligible to continue to the baseline visit and it was scheduled within one-two weeks, on average. Prior to April 2020, the Field Screening was conducted in the community, proximal to where participants lived, but post-Covid these locations were slower to resume business and all in person research activities were conducted at the University-based offices of the Sustain study.

Participant Compensation. Participants received payment for research assessments in the amount of $25 each for visits conducted at study months 0 (baseline), 6, 12, 18.

11.0 Study Procedures

Assessments at 0 (baseline), 6, 12, 18 and 24-months

All the following assessments occurred either in the community (pre-Covid) or in the University clinic offices. Standard assessment duration was about 1.5 hours.

Weight and Height: was taken twice using a standardized protocol. Weight was measured to the nearest 0.1 kg at all screening/assessment points using a digital scale (SECA 880) placed on a hard, flat surface. Height was measured at all screening/assessment points in street clothes, without shoes, using a portable stadiometer and rounded to the nearest 0.1 cm.

BMI: was calculated as average weight divided by average height squared (kg/m2).

Fasting HbA1c, Glucose, Insulin and Lipids (total, HDL and LDL cholesterol, and triglycerides): were collected via standard venipuncture procedures for all assessments at 0, 6, 12, 18 and 24 months, after at least an 8 hour fast (last food/drink consumption will be documented prior to collection of sample) or through a fingerstick assessment when venipuncture was not possible. The sample collected was no more than one teaspoon for a fingerstick sample and no more than one tablespoon, or 120 ul (microliters) for venipuncture. Procedures were performed by skilled phlebotomists with experience working with older adults. Until March 2020 samples were processed through the Northwest Lipid Research Laboratories at the University of Washington. When this lab closed in June 2020, specimens were processed at the Advanced Research and Diagnostic Laboratory (ARDL) at the University of Minnesota in Minneapolis.

Waist Circumference: was measured as an index of truncal fat using a standardized protocol. A Gulick tape was placed around the bare abdomen horizontally at the midpoint between the highest point of the iliac crest and the lowest part of the costral margin in the mid-axillary line. Measurements were taken three times and averaged.

Blood Pressure: was measured using an automatic inflatable digital blood pressure monitor (OMRON HEM90HXC) with appropriate cuff size according to a standardized protocol.

International Physical Activity Questionnaire (Older Adult Version): is a 4-item questionnaire that asks participants to describe their usual physical activity during a typical day and a typical week, in each of the following categories --time spent sitting, walking, doing moderate physical activities, doing vigorous physical activities.

Objective Physical Activity Measurement: Participants used a hip-worn pedometer to assess physical activity. They self-reported daily step counts, and the primary measure calculated was average daily step count over a 7-day recording period.

Objective Short Physical Performance Battery (SPPB): Evaluation of physical functional ability was assessed with four short tests (about 3-5 minutes each) including (1) a 4-meter walk test (gait speed); (2)

standing balance (feet together, semi-tandem, full tandem); (3) a chair stand test (rise from chair five times); and (4) grip strength test using a Jamar dynamometer.

Falls History: an interviewer administered survey documented number of falls, serious falls, and fear of falls experienced during the past year

Prescribed Medication List: Participants were asked at each visit to update a list of all their currently prescribed medications (and dosages) taken regularly.

Montreal Cognitive Assessment (MOCA): a widely used interviewer administered screening instrument for mild cognitive dysfunction, was used to assess several mental function domains.

All of the following were sent to participants to be completed at home and brought back to the clinic at the time of each major assessment visit, or mailed back. Clinic staff checked all of these measures for completeness and phone participants if there were missing items.

Center for Epidemiologic Studies-Depression Scale (CES-D): This 20-item scale is a self-administered instrument for assessing depressive symptoms.

SF-12v2 Health Survey: Quality Metric's SF-12v2 is a self-administered shorter version of the SF-36v2 (used to reduce burden). We used this extensively norm-referenced measure of functional health and well-being, which captures the same eight health domains and produces a physical component (PCS) and mental component (MCS) summary score that may be compared to the longer version.

Patient Activation Measure: PAM is a self-administered 22-item scale measuring knowledge, skill and confidence for self-managing health and healthcare.

Weight and Activity Lifestyle Questionnaire: is a self-administered 13-item scale to measure participant beliefs and expectations about self-managing eating and activity behaviors in the face of certain emotions, social situations and environments.

Mediterranean Diet Assessment Tool: This 14-item self-administered index was used because it has been shown to be sensitive to shifts in dietary quality related to interventions, both in the presence and absence of significant weight loss.

Rate Your Plate: We used the Rate Your Plate-Heart 2010 version, a 24-item, self-administered questionnaire that assesses the degree to which eating patterns are consistent with heart healthy dietary guidelines.

CHAMPS Physical Activity Questionnaire: is a 41-item self-administered instrument, which measures the weekly frequency and duration of various physical activities commonly done by older adults. MET-weighted variables are readily coded, and the measure is sensitive to changes following activity interventions in persons aged 65-90.

Self-Reported Medical Conditions: The Duke Comorbidity Index is a self-administered inventory that asks, "Has your doctor ever told you that you have or have had" (any of 19 specific medical conditions that can be categorized into 8 health domains).

Family History of Diabetes and CVD: Research participants were asked to provide information about whether there is a family history of type 2 diabetes or other cardiovascular disease in a first degree relative.

Self-Reported Medical Utilization Outcomes:
Medical Utilization was measured by 4 questions from the Stanford Chronic Disease Self-Management Program evaluation protocol. This protocol measures the number of times, in the previous six months, an individual has visited a physician/health care provider (outpatient), a hospital emergency room, the total number of separate hospital admissions, and the total number of nights spend in the hospital.

Sustain DPP Satisfaction and Acceptability Survey: was collected for qualitative assessment of participant satisfaction. This post-intervention survey contained Likert scale items and 5 open ended questions.

Complementary and Integrative Research Lab (CAIR) Pandemic Impact Survey: As of 9/30/20 we added one 19-item survey with the approval of our NIH/NIDDK sponsor and IRB. The survey asks several questions about the psychosocial impact of COVID-19 and how it has affected either the study participant or someone close to them. We hypothesized that the primary study aims (and the pre-specified outcomes of weight change, physical activity, physical function and other measures) had the potential to be influenced (negatively and positively) by the pandemic.

UPMC Health Plan Medicare Metrics:
We obtained de-identified descriptive statistics for medical claims for consenting Sustain DPP study participants who were also UPMC Health Plan Medicare Advantage members. This was done to compare the two randomized intervention groups (using UPMC Health Plan aggregate data only) on the following claims-based information: categories and number of prescription claims, number of outpatient, inpatient and emergency room visits, percentage of participants utilizing physical activity benefits (i.e. Silver and Fit).

12.0 Data and Specimen Banking

There is no a priori data sharing plan for data or specimens. Blood specimens were centrally analyzed by both the Northwest Lipid Research Laboratory (University of Washington, Seattle) until they closed in July of 2020, and then by Advanced Research Diagnostics Laboratory (ARDL) (University of Minnesota, Minneapolis). No stored samples were banked. An investigator with interest in the data files for this study would need to contact the PI at vendittiem@upmc.edu.

13.0 Sharing of Results with Subjects

The data collected in this study are specific to the research and are not designed to assess medical conditions. The investigators are not responsible for failure to find existing abnormalities. In the unlikely event that a participant's data (e.g., bloodwork biometrics) show a possible abnormality, the PI or Co-I (Study MD) contacts the participant and advises medical follow-up for the problem, including a referral

to a primary care provider (PCP). For participants who already have a PCP, and provide verbal permission, the study doctor may inform the PCP of the finding and determine if follow-up is advisable. The decision as to whether to proceed with further examination and/or treatment lies solely with a participant and their PCP. The study does not cover the costs of any follow-up actions.

End of study information provided: Participants will be mailed a letter from the PI describing the results of the study, including a copy of the main outcomes paper when available.

14.0 Withdrawal of Subjects

Participants may be withdrawn from the research without their consent under the following circumstances:

- the investigator decides that continuation can be harmful to the participant,
- participant develops a new condition or undergoes treatment that will make their subsequent follow-up data in the study unusable,
- the study is cancelled, or there are other administrative reasons.

In the event a participant withdraws or is asked to leave the study, they will still be compensated for the study activities they have completed.

15.0 Risks to Subjects

This is a minimal risk study with prudent measures in place to protect the health and well-being of research participants and their privacy and confidentiality. Risks associated with participation in this study include the following:

(1) Potential risks associated with reduced caloric intake and increased physical activity, such as musculoskeletal injuries.
(2) Patient privacy and confidentiality breach.
(3) Inconvenience associated with data collection.

These risks are mostly associated with the characteristics of the target patient population and the procedures involved in the research. The risks are reasonable in relation to the anticipated benefits and will be minimized by using sound clinical research procedures and risk mitigation strategies. Although we cannot guarantee that risks will not occur, we will implement the following measures to minimize potential risks to participants in the study.

Protection against Risks Associated with Weight Loss Strategies. The premise of the study is that prudent yet comprehensive lifestyle interventions, which include evidence-based strategies for dietary modification, physical activity and behavior change, are necessary to meet the targets set forth in national guidelines for managing obesity and obesity-related cardiometabolic and other comorbidities. By managing BMI according to these evidence-based guidelines for intensive behavior therapy, intervention participants may be exposed to risks associated with caloric reduction and physical activity not experienced in routine care.

The interventions to be tested in this clinical trial promote a balanced, calorie-controlled diet approach and recommend against very low-calorie diets (<1200 kcal/day) or losing weight too rapidly (> 2 lbs.

per week). Participants will be advised to avoid crash or fad diets that promise marked, rapid weight loss. Instead, they will be advised to adopt a moderate caloric reduction by 500-1000 kcal/day through healthy substitutions and portion control, rather than omission or elimination of specific foods or food groups. Given the average age anticipated in this participant sample, the intervention will encourage consumption of plant-based and lean-meat proteins and low-fat or fat-free dairies at most meals. The selection of low-calorie, nutrient-dense foods in accordance with USDA-recommended healthy dietary patterns will be emphasized. Participants who wish to lose additional weight after reaching the program's weight loss goal (5-10% of baseline weight) will be encouraged to do so only insofar as they maintain a normal BMI and the rate of weight loss does not exceed 2 lb/week.

To minimize risks associated with increased physical activity, consistent with the current public health physical activity recommendations for Americans, the study interventions promote achieving 150 minutes or more per week of moderate-intensity physical activity in a gradual manner. If participants reach the 150-minute goal but are not achieving the weight loss goal, they can gradually increase to 60-90 minutes/day of moderate physical activity, as tolerated. We will also recommend resistance training activities 2 times per week, consistent with NIA public health guidelines. Moderate-intensity physical activity is deemed feasible for adults with chronic conditions or functional limitations, and the benefits are believed to outweigh the risks. We will emphasize brisk walking—a physical activity recommended as being safe for most adults—as the preferred mode of exercise. Participants will receive information about how to be active safely considering their conditioning, interest, context, and environment.

Protection against Breaches of Participant Privacy and Confidentiality. All information to be obtained during the study will be considered strictly confidential and only used and disclosed as permitted under the HIPAA regulations. All eligible patients must sign the HIPAA authorization as a part of the informed consent to participate. Only aggregate data will be included in scientific presentations and publications resulting from this study; the identity of individual participants will not be revealed. In addition, the following measures will be taken during the conduct of the study to ensure adequate protection of participant privacy and confidentiality:

- All investigators and staff will be adequately trained to protect participant privacy and sign an agreement to do so.
- Personal identifiable information (PII) and protected health information (PHI) collected for the purpose of the research study will be assigned a unique anonymous study ID number. The study IDs will be used on all study forms and for data storage, tracking and reporting.
- Both the anonymized health information and the information linking the study ID numbers to participants' identities will be stored in a password protected database on a secure network fitted for protection of such information, which will be accessible only to the research personnel who have a need to know.
- The information linking the study ID numbers to participants' identities will be stored separately from the anonymized health information.
- We will follow the latest industry standards for data encryption, server authentication, and client authentication to ensure secure data transmissions at all times.
- No participant data, even if de-identified, shall be saved onto any portable devices, such as laptop computers or USB drives.

Protection against Risks Associated with Data Collection. All study measures are either objectively measured by trained research staff, or self-measured or self-reported by participants. There are no greater risks associated with completing the required measurements in this study than those ordinarily

associated with such measurements in routine health care. For surveys and questionnaires, participants are reminded at each assessment that they do not have to answer any question they do not wish to answer.

16.0 Potential Benefits to Subjects

Although several potential benefits may be expected from participating in this study, we cannot guarantee that any individual participant will experience these benefits. All participants, including the Placebo Comparator, will receive an evidence-based lifestyle intervention aligned with the MDPP. The interventions to be tested promote modest weight loss through healthy eating, increased physical activity, and behavioral self-management. These healthy lifestyle factors have known health benefits, including but not limited to, lowering the risk of type 2 diabetes for those at high risk as well as prevention and control of hypertension and hyperlipidemia. Improvements in these lifestyle factors and health outcomes may in turn lead to better quality of life. All the benefits are likely to be long-term and outweigh any possible short-term risks.

17.0 Data Management and Confidentiality

Data Management.

Data security.

18.0 Data Analysis Plan

All analyses are conducted in consultation with the study biostatisticians, using SAS 9.4 (SAS Institute, Inc., Cary NC). Descriptive analyses and graphic displays are used to identify outliers, missing data, and patterns of attrition. Demographic variables and baseline measures are contrasted between the Active Comparator: DPP-Behaviorally Intensive 30-Minute Groups (DPP-BI) and the Placebo Comparator: DPP Minimal 15-minute Calls (DPP-MIN) conditions. In all outcome analyses we will use an intent-to-treat (ITT) approach in which participants remain in the study arm to which they are randomized regardless of attrition. The primary analytic strategy is a linear or generalized mixed-effect models approach in which treatment group, time, and time by group interaction are treated as fixed effects, and subject is treated as a random effect to account for individual subject variability. Hypothesis tests are two-sided, and significance will be set at the 0.05 level. Mixed models are applicable to longitudinal datasets that contain missing observations, with the assumption that the data are missing at random. Our prior intervention studies suggest that we can anticipate 90% retention at 6 months and greater than 80% retention over the 18-month extended intervention period (at 24 months) with no differential attrition between arms. Those who drop out or are lost to follow-up are compared to those who have completed intervention for research assessments using standard parametric and non-parametric methods, as appropriate. We will examine the patterns of missingness and, if necessary, account for missingness in outcome analysis (e.g., the covariate approach). Regression modeling will be conducted to adjust for covariates such as race, sex, age, socio-demographic factors, and other designated baseline clinical variables.

Research Questions

Analysis Plan for Hypotheses 1 and 2: We will apply mixed effect models to evaluate differential changes in weight measures at 6, 12, 18, and 24 months from baseline, with fixed terms of group (DPP-BI vs. DPP-Min), time as a factor (6,12,18, and 24 months), and the group by time interaction. We employed the following steps as the pre-randomization balancing logic: (1) group subjects by weight loss status (≤ 3.5 vs. > 3.5 percent at 6-months) and age (≤ 70 vs. > 70 years at baseline), (2) group subjects by sex (male vs. female) and race (Black/African American or Black/Mixed/Other vs. White/Caucasian), (3) group subjects using all 4 factors (based on 2x2 frequency table) and (4) randomly assign the subjects in the same cell into 2 conditions (DPP Plus vs. DPP Minimal). Subject was included as a random term. To test the differential treatment effect, evaluated the coefficients that are associated with the group and the group by time interaction by using an F test. Planned contrasts will be set up from the mixed models to compare the improvement in weight from baseline to Months 12, 18 and 24 between the two conditions (DPP-BI vs. DPP-Min). In addition, a generalized mixed-effect model was fit to the binary outcome of achieving ≥ 5% weight loss at 6, 12, 18, and 24 months, with the logit link, which includes similar fixed and random terms as above. Average percent weight loss and the proportions achieving ≥ 5% weight loss are compared between the two groups at 12, 18 and 24 months. Similar analyses were performed for fasting glucose, HbA1c, and insulin (and other biometric measures), physical activity/function, and other secondary outcomes at subsequent assessment points.

The planned contrasts were set up to compare differential changes from baseline to Months 12, 18, and 24. Benjamini-Hochberg's method was used to control for the overall type I error for multiple secondary outcomes. More intensive modeling is performed to account for factors that are known to affect the outcomes as well as those that have been found to differ between treatment conditions at baseline and at Month 6 (the timepoint at which participants are stratified by < or ≥ 3.5% weight loss and other factors and randomly assigned to the two 18-month conditions). We also perform analyses in which we restrict our linear and generalized mixed-effect analyses to those who did not reach ≥ 5% weight loss at 6 months and set up the contrasts to compare DPP-BI with DPP-MIN, on average, and the proportion reaching ≥ 5% at 12 months and 18 months from baseline.

Exploratory Aim. We examine available Medicare data for those insured by a large regional payer to assess group and time from baseline differences in medical utilization metrics (e.g., type of outpatient, inpatient, or emergency visits) and participation in activity programs, for a proportion of the sample. We will extract Medicare data on numbers of outpatient, inpatient and emergency visits, and number of subjects participating in activity programs, and compare the numbers between the two conditions using linear and generalized regression models. We will explore the potential moderation effects of sex and race. We will include the interaction of sex by group or race by group in the mixed-effect models, as well as the three-way interaction of sex, group and time or race, group and time, if the group by time interaction is significant in the original model.

Power and Sample Size Considerations. We powered this study on the main comparisons between the Active Comparator: DPP-BI and the Placebo Comparator: DPP-MIN on average weight loss at 12 months from baseline (24-month data is not readily available). With 180 subjects per arm and projected 90% attrition at Month 12, we would have 80% power to detect effect sizes of 0.31, using two-sided t tests at the 0.05 level. Our prior Pitt Retiree study observed approximately 7.5 % weight reduction at 12 months among those subjects who received active intervention for 12 months, and 5.5% reduction at 12 months among those in the placebo comparator group. Assuming similar effects and similar standard deviation of 5.8% as observed in the Pitt Retiree study, we expect to see a standardized group difference ranging 0.34 at Months 12 between DPP-BI and DPP-MIN. Hence we anticipate that our projected. sample size will enable us to detect group differences with power greater than 0.8 for our primary weight outcome.

19.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

In this minimal risk Sustain study, we utilized a Data and Safety Monitoring Plan (DSMP) to ensure the safety of study participants and the validity and integrity of data in compliance with NIH/NIDDK and our local IRB. The DSMP was reviewed annually by a single data safety monitoring officer via written report and teleconference.

An AE is defined as any untoward medical or psychological event experienced by a subject during or as a result of his/her participation in the study that represents a new symptom or an exacerbation of an existing condition whether or not considered study-related based on appropriate medical judgment.

SAEs are any adverse experience that results in any of the following outcomes:

- Death
- Imminently life-threatening event/illness
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Pregnancy resulting in a congenital anomaly/birth defect
- Any event requiring medical or surgical intervention to prevent permanent impairment or damage. In this study, this is defined as physician confirmed diagnosis of any of the following: angina pectoris, heart attack, stroke, transient ischemic attack, heart failure, coronary angioplasty or bypass surgery, peripheral vascular disease, incident diabetes, serious musculoskeletal injuries (e.g., fractures, ruptured ligaments), liver failure, kidney failure, and cancer (except for non-melanoma skin cancer).

Non-SAEs are all adverse events that do not meet the above criteria for “serious.”

Blinded Reporting. Safety information for this study is reported to the Safety Officer by masked treatment group (i.e., without revealing the treatment assignment of each group). With each report, summaries of the numbers and rates of all AEs by masked treatment group are provided.

Expedited reporting. All unexpected SAEs must be reported to the safety officer within 5 business days of discovery, regardless of any judgment of their relatedness to the study treatment. The safety officer may require a conference call to review relevant information (and the site study physician's determination of whether there was any possible relevance to the study) and discuss and approve the investigators' Corrective and Preventive Action Plan, if warranted.

Data quality monitoring. The safety officer receives an annual report on data quality and completeness. At a minimum, this report will include the following: (1) participant accrual and follow-up completion/retention by site in relation to goals and timeline; (2) the randomization process and group comparability on the balancing variables; (3) data completeness for primary and secondary outcome measures; and (4) protocol exemptions, deviations and violations. Follow-up data will be reported for all participants, irrespective of random assignment, during the course of the study.

Study Stopping Rules. Formal stopping rules for safety, efficacy, and futility are not proposed given that this is a minimal risk clinical trial as the behavioral intervention to be tested are based on prior research in different populations without major harms (e.g., mortality or serious medical complications). Second, while we hypothesize that the intervention will lead to significant and clinically meaningful improvements in weight loss and other outcomes of interest, we expect the probability of major health benefits (e.g., reduced incidence of disease or reduced mortality) that would trigger early stopping for efficacy to be negligible over a 24-month follow-up period.

20.0 Provisions to Protect the Privacy Interests of Subjects

21.0 Compensation for Research-Related Injury

There are no plans for the study to provide free medical care or to pay for research-related illnesses or injuries, or to provide other forms of compensation (such as lost wages or pain and suffering) to participant for research related illnesses or injuries. As part of the informed consent process participants are advised to contact the site PI to report any illness or injury experienced from taking part in the Sustain study.

22.0 Economic Burden to Subjects

There are no costs to participants for intervention.

23.0 Consent Process

Multi-Stage Informed Consent. All study participants involved in the Sustain study must provide written informed consent before baseline assessment. Study personnel obtaining informed consent are experienced in obtaining informed consent and have receive standardized training in trial-specific protocols as well as mandatory trainings in good clinical research practice. For Sustain, there will be an

initial screening consent (verbal authorization for phone or field screening) and subsequently written informed consent. We allow sufficient time and resources to meet the ethical obligations to research participants and to foster a progressively increasing understanding of the research as well as the development of rapport between subjects and research staff.

Informed Consent Process Training. We will conduct effective and efficient informed consent to ensure that participants understand the following: (1) that the study is for research purposes and in no circumstances does it supplant medical care provided by their health care provider(s), (2) the risks and benefits of the study, (3) the available alternatives, and (4) that their voluntary decision to participate or to not participant in this research will be accepted without penalty (i.e. without jeopardizing their medical care or relationship with their clinical sites). In reaching a decision about participation, it is essential for the potential subject to demonstrate an ability to use this information in a rational manner. Thus, in considering the risks, benefits, and available alternatives, subjects must show that they understand the aspects of these factors that are unique to them as individuals.

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