

Medifast® for Seniors Study
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Study Title: Medifast® for Seniors Study

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Background, Rationale and Context

Aging and obesity are prevalent risk factors for morbidity and mortality. By 2030, Americans aged 65 and older will number an estimated 72 million people,¹ half of whom will be obese.² Both advanced age and obesity are well-characterized risk factors for chronic disease and disability,³ suggesting that the individual and societal health burden of age- and obesity-related conditions will increase substantially.

Intentional weight loss in obese, older adults remains controversial. Although caloric restriction, resulting in significant weight and fat mass loss, ameliorates many clinical consequences of obesity, recommendation of intentional weight loss in aging remains controversial.^{4,5} Reluctance stems, at least in part, from loss of lean and bone mass known to accompany overall weight loss,⁶ and potential exacerbation of age-related risk of disability⁷ and fracture.^{8,9} Accordingly, current treatment guidelines call for weight-loss therapy that minimizes muscle and bone losses for older persons who are obese and who have functional impairments or medical complications that can benefit from weight loss.¹⁰

Emerging results from randomized controlled trials demonstrate caloric restriction *and* exercise interventions, resulting in weight loss of 7-10%, are associated with initial improvement in muscle strength and function in older adults;¹¹⁻¹⁶ however, in few cases has the effect of caloric restriction, independent of exercise, been evaluated.^{13,16} and no randomized controlled trials have examined the role of specific dietary components, as adjuvants to weight loss, on physical function. Evidence supporting a diet-based weight loss approach in obese, older adults with functional impairments has tremendous clinical significance as multiple behavior changes are often difficult to implement and maintain, and many older adults are unable (or unwilling) to engage in the amount of physical activity typically prescribed in lifestyle-based interventions.

Amount of dietary protein consumed during caloric restriction may be a key determinant in maintaining fat-free mass during weight loss. Adequate dietary protein is essential for skeletal muscle anabolism; and, epidemiological evidence in older adults point to a salutary effect of protein intake above the current RDA (0.8 g/kg/day) on body composition.^{17,18} Indeed, a recent position statement by the PRO-TAGE study group advises consumption of 1.0-1.2 g/kg/day in older adults *during weight-stable conditions* to aid in the maintenance of lean body mass and function.¹⁹ Practical achievement of this level of protein intake is often difficult for obese, older adults undergoing weight loss, yet may be critical to offset weight loss-associated lean mass loss. Preliminary data from our group show a lean mass sparing effect of high protein consumption during caloric restriction. In post-menopausal women undergoing a 5-month intentional weight loss program, consumption of a high (1.2 g/kg/day) versus low (0.6 g/kg/day) protein diet was associated with 50% attenuation (17% vs. 37%) of lean mass loss.²⁰ While promising, results have yet to be translated to functional changes in a tightly controlled trial of weight loss in obese, older adults.

The primary goal of this study is to determine whether adherence to a high protein (≥ 1.0 g/kg/d) weight loss program results in improved physical function by favorably affecting body composition compared to weight stability in obese, older adults. This will be accomplished by conducting a 24-week trial in 124 obese (BMI 30-42 kg/m²), older (65-79 years) men and women, at risk for mobility disability, randomized to either: **(1)** high protein intake (≥ 1.0 g/kg/d; n=62) during weight loss, or **(2)** weight-stable control (n=62).

Specific Aim 1: To compare the effects of high protein intake during weight loss versus weight stability on 24-week changes in physical function, primarily assessed by performance on the fast 400-meter walk test. *We hypothesize that participants randomized to a high protein weight loss intervention will experience greater improvements in 400-meter walk gait speed than participants who receive the weight-stable control condition.* **Specific Aim 2:** To compare the

effects of high protein intake during weight loss versus weight stability on 24-week body composition changes (assessed by whole-body DXA). *We hypothesize that participants randomized to a high protein weight loss intervention will present with a more favorable (i.e. higher) post-intervention lean to fat mass ratio compared to participants who receive the weight-stable control condition.*

In exploratory analyses we will also examine the effects of intentional weight loss on a compilation of physiologic and biochemical markers (including: respiratory and kidney function, cognitive processing speed, inflammation, and blood pressure), shown in epidemiologic investigations to predict mortality.²¹ Meta-analytic data from our group suggest a 15% reduction in mortality for obese adults undergoing intentional weight loss,²² and better understanding of the potential mechanism(s) underlying this association is of great clinical interest.

Methods and Measures

Recruitment of study participants: We plan to recruit up to 124 obese (BMI=30-42 kg/m²), older (age=65-79 years) men and women with mobility disability from communities in and around Forsyth County, NC via media advertisements, mass mailings, and direct mailings. Based on our experience in recruitment of the designated population, we are confident in our ability to recruit older adults who meet the inclusion/exclusion criteria (see **Table 1**). We plan to recruit at a rate of 10-12 per month.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Age 65-79 years	Weight loss or gain (±5%) in past 6 months
BMI=30-42 kg/m ²	Prior bariatric surgery
Confirmation of self-reported mobility disability, as assessed by phone screen/clinical staff	Multiple food allergies
Self-reported sedentary behavior	Difficulty with hearing/vision that interferes with study participation
Non-impaired cognitive function (MoCA>18)	Excessive alcohol use (>14 drinks/week)
Stability of residence for next 2 years	Smoker (>1 cigarette/d within year)
Willing and able to follow dietary protocol	Insulin-dependent or uncontrolled diabetes (FBG >140 mg/dl)
Willing to provide informed consent	Uncontrolled hypertension (BP>160/100 mmHg)
Approved for participation by study physician	Abnormal kidney tests (GFR<40, creatinine >2.0)
Not involved in another behavioral or interventional research study	Regular use of medications that may influence body weight or composition
Able to provide own transportation to study visits and Intervention	Severe systemic disease (diagnosis of Parkinson’s disease, chronic liver disease, systemic rheumatic condition, gout, thyroid disease, end stage renal disease) or other systemic diseases/abnormal laboratory values which would preclude participants from safely participating in the protocol or impair their ability to complete the study
Not dependent on a cane or walker	Severe symptomatic heart disease or cardiovascular procedure within the past 3 months or history/current diagnosis/signs and symptoms of heart failure, with either reduced or preserved Left Ventricular ejection fraction.
No evidence of clinical depression, eating disorder, or other contraindications for participation in voluntary weight loss	Cancer requiring treatment in past year, except skin cancers
English literacy	Judged unsuitable for the trial for any reason by clinic staff

Participant screening, assessments and randomization

All participants who respond to our recruitment strategies will initially be screened via telephone to determine general eligibility. Individuals who pass the telephone screening will be scheduled for a visit at the Sticht Center on Aging for a screening visit. *Before any data collection, all participants will be asked to provide written informed consent to participate in the study and complete a HIPAA authorization form in accordance with the WFSM Institutional Review Board policies.*

Table 2 summarizes the proposed assessment timeline (see appendix for week-by-week assessment table). At the screening visit, all inclusion and exclusion criteria will be reviewed (including participant demographics and measurement of weight and height to calculate BMI). After confirmation of meeting demographic and BMI criteria (this may be the same day as the screening visit), participants will proceed with Baseline Visit 1 (BV1) assessments, including a fasting

blood draw for a metabolic panel, blood cell count, and blood for storage. After a snack, participants will undergo further assessment for blood pressure, depression (using the Center for Epidemiologic Studies Depression Scale; CES-D), cognition (using the Montreal Cognitive Assessment; MoCA), processing speed (Digit Symbol Substitution test; DSST), spirometry (FEV₁), waist circumference, and grip and leg power/strength. At the end of this visit, participants will be provided with instruction on how to collect accelerometry data and a 24-hour urinary specimen to assess protein intake, both of which will be collected at the subsequent testing session. Because several measures that are taken at the BV1 visit also serve as screening tests (including: blood work from the metabolic panel, blood pressure, depression, and cognition), any person with results from these tests that do not meet eligibility criteria will not be invited to enroll and as indicated, advised to share any abnormal test results with their physician. Also, any participant with abnormal test results at the follow-up testing visits will be referred for further medical evaluation.

The second baseline testing session (BV2) will occur in the Wake Forest University Department of Health and Exercise Science. During this visit, participants will undergo muscle function tests (expanded Short Physical Performance Battery (SPPB) test, Timed-Up-and-Go (TUG) test, fast 20-meter and 400-meter walk tests, and stair climb test), DXA scan (whole body, hip and spine), physical activity questionnaire (Community Healthy Activities Model Program for Seniors; CHAMPS), quality of life questionnaire (SF-12), disability questionnaires (Pepper Assessment Tool for Disability; PAT-D and Mobility Assessment Tool-short form; MAT-sf), and instructions will be provided for a dietary run-in (approximately 30 minutes). For the dietary run-in, all participants will be provided with and oriented to the Medifast® QuickStart Guide, sample meal plans, 3 one-day dietary trackers, a sampling of 12 Medifast Meal Replacement Products, 3 one-day Product Evaluation Forms, and asked to follow the Medifast 4 & 2 & 1 Plan™ for a three-day period occurring over the following week. Participants will be contacted by the study registered dietitian (RD) upon completion of the dietary run in period to assess their willingness and self-efficacy to adhere to the dietary protocol for the duration of the study (24 weeks). Participants who indicate that they are willing and able to follow the protocol will be randomized (RAND) to one of the 2 study interventions (high protein weight loss group vs. weight stable control group), with blocking stratified by gender, and treated in 5 successive waves (n=12-13 participants/group/wave). Randomization of the entire wave (n=24-26) will occur approximately 1 week prior to the start of intervention, and at this time the first monthly Medifast product order will be placed for participants randomized to the high protein weight loss group.

All assessments conducted at the BV1 and BV2 testing sessions will be repeated at two follow-up visits (FV1 and FV2), occurring during the last two weeks of active intervention (weeks 23-24). Lastly, a brief midpoint visit (MP; week 12) will occur for all participants, where only DXA and fast 400-meter walk tests will be performed.

Table 2. Proposed Assessment Timeline

Visit Code	Location of Visit Week Number	Sticht	WFU	WFU	WFU	Sticht	WFU
		-3	-2	-1	0-24	23	24
SV1	Informed consent, review inclusion/exclusion criteria (including demographics and BMI)	X					
BV1/ FV1	Fasting blood draw, snack, blood pressure, depression screen (CES-D), cognitive function (MoCA), waist circumference, cognitive processing speed (DSST), spirometry (FEV ₁), grip strength, leg muscle/power, instructions for accelerometry and 24-h urinary nitrogen test	X				X	
BV2/ FV2	Muscle function tests (expanded SPPB, TUG, fast 20-m gait speed, fast 400-m walk test, stair climb) DXA (whole body, hip, spine), CHAMPS, SF-12, PAT-D, MAT-sf, dietary run-in instructions		X				X
RAND	Randomization			X			
MP	DXA and fast 400 meter walk test (at 12-week visit, only)				X		
INT	Bi-weekly adherence monitoring (weight, dietary trackers, meet with study dietitian as needed). <u>Note:</u> official pre/post intervention weights will be captured at weeks 0 and 24, respectively				X		

Study Interventions

High Protein Weight Loss Group - Participants randomized to the high protein weight loss group will follow the Medifast 4 & 2 & 1 Plan™, targeting ~10% weight loss over the 24-week study. Weight loss will be monitored bi-weekly to ensure the safety of the study participants. This level of weight loss will be achieved through a combination of meal replacement products (MRPs), meal plans, and individual nutrition/behavioral counseling. Participants will follow the Medifast 4 & 2 & 1 Plan which includes consumption of total of 4 Medifast MRPs per day, with the addition of 2 lean and green meals and 1 Healthy Snack. Medifast MRPs each contain ~90-110 kcals and 10-15 g protein. The lean and green meals will be prepared by the participants and each will consist of 5-7 oz. lean protein, 3 servings of non-starchy vegetables and up to 2 servings of healthy fat. The snack will consist of one serving of fruit, dairy, or grain. Participants will be guided by the study RD on their food purchasing and preparation of the other meals and will be encouraged to consume only what is approved from the menu.

In addition to receiving dietary counseling, all participants randomized to the high protein weight loss group will attend behavioral counseling group classes led by the RD. These classes will be held bi-weekly for the duration of the study (with an additional phone call at week 1) to provide participants an opportunity to review specific questions and problems. Group counseling sessions will provide support and introduce new topics in behavioral weight control including self-monitoring, portion control, mindful eating, coping with negative thoughts related to overeating, eating at regular times, and stress management. Weight will be measured bi-weekly, at each class, to provide additional feedback and to increase motivation. Official study baseline and post-intervention weights will occur at weeks 0 and 24 of intervention, respectively. Additionally, participants will complete daily food logs which will be reviewed by the RD to verify compliance to the diet. If it is evident, either through inadequate body weight loss or diet records, that participants are not compliant with the diet, additional individual counseling sessions with the RD will be held to improve compliance. Also, at week 24, participants in this group will be asked to complete a program evaluation form to solicit feedback on overall weight loss program product satisfaction and desired future usage, as well as product quality and taste feedback and recommendations.

Weight Stable Control Group – Participants randomized to the weight stable control group will be monitored bi-weekly by study staff (with an additional phone call at week 1) to ensure weight stability over the course of the study. Participants will be weighed on a bi-weekly basis and encouraged to maintain weight within $\pm 5\%$ of baseline. To promote compliance and retention, participants will also be invited to bi-weekly group educational sessions, where non-weight loss health related topics (including: What is Successful Aging?, Preventing and Delaying Disease and Dysfunction, Managing Medications Effectively, and Talking Effectively with Your Healthcare Provider), will be discussed by study staff. Lastly, if weight stable participants are able to attend 75% (i.e. 9 of 12) educational sessions, all baseline and follow-up testing sessions, and maintain weight stability over the course of the study (defined as less than a 5% differential between weight measured at week 0 and 24), they will be eligible to receive up to 3 months of Medifast MRPs along with a 30-60 minute RD-led dietary instruction session on how to follow the Medifast 4 & 2 & 1 Plan.

Methods for Study Assessments

The nature, purpose, and risks of all procedures and protocols will be explained to each participant prior to obtaining written consent. All examiners are trained in the standardized conduct of all assessments before data collection. Participants will be instructed to wear appropriate and comfortable clothing, and standardized written instructions will be provided prior to each study visit.

Study Measure(s)

1. **Height, body mass, BMI, & waist circumference.** **Height** without shoes will be measured to the nearest 0.1 centimeter using a stadiometer and **body mass** will be measured to the nearest 0.1 kilogram using a calibrated and certified balance beam scale. Height and body mass will be used to calculate **BMI**. **Waist circumference** will be measured to the nearest 0.1 cm with a Gulick-II spring-retractable steel tape.
2. **Muscle function and strength measures** include the tests described below. Each will be conducted before and after the interventions, with the exception of the 400-meter walk test, which will also be performed at the study midpoint (12-weeks). **Gait speed** will be assessed using the fast 20-meter and 400-meter walk tests. The 400-meter walk tests was originally developed in Health ABC²³ and used by our group in the CLIP and LIFE studies.^{12,24} Participants are asked to walk 10 laps of a 40-meter course (20 meters out and 20 meters back). A script is used to standardize instructions to all participants. It says: “You will be walking 10 complete laps around the course, about ¼ mile. Please walk as quickly as you can, without running, at a pace you can

maintain over the 10 laps. After you complete the 10 laps, I will tell you to stop.” On each lap the assessor offers standard encouragements (“Keep up the good work”, “Good job”) and indicates the number of laps completed and the number remaining. Participants can stop and rest if necessary, but are not allowed to sit, and are given a maximum of 15 minutes to complete the test. The reliability and validity of the 400-meter walk test are excellent,^{25,26} and performance is an important prognostic indicator for total mortality, cardiovascular disease, and mobility disability in older adults.²⁷ **Physical performance** will be assessed using the expanded Short Physical Performance Battery (SPPB). The expanded SPPB consists of 5 repeated chair stands, standing balance (semi- and full-tandem stands and a single leg stand for 30 seconds), a 4-meter walk to assess usual gait speed, and a narrow 4-meter walk test of balance (walking at usual pace within lines of tape spaced 20 cm apart).²⁸ Scores for the traditional 0-12 point SPPB can also be obtained from these tests. We will also assess physical performance using the Timed-Up-and-Go (TUG). TUG measures the time a person takes to stand up from a standard chair, walk 3 meters, turn, walk back to the chair, and sit down again.²⁹ A practice trial is given, followed by two timed trials and the results of the timed trials are averaged. **Stair climbing time** will be assessed by measuring the fastest time achieved to climb 4 steps on a 4-step staircase (test will be performed 2 times). **Lower extremity muscle power** will be measured using the Nottingham Power Rig, a safe, convenient method for assessing power output from the lower limb which has been used reliably in older adults.³⁰ Participants will sit in a chair and unilaterally depress a foot lever attached to a flywheel as hard and as fast as they can. Power output, derived from the acceleration of the flywheel, will be recorded in Watts. Power will be averaged for each leg following 5 trials at maximal effort. Participants that have had a unilateral hip or knee replacement should not have that side tested. Participants who have had eye surgery (e.g., cataract surgery) within the past month should not be tested. **Lower extremity muscle strength** will be measured using an isokinetic dynamometer (Biodex/KinCom) at one speed (60°/sec) with the participant sitting and the hips and knee flexed at 90°. The dynamometer will be adjusted for each participant and all adjustments will be recorded to duplicate the position for subsequent assessments. Start and stop angles will be set at 90° and 30°. Participants will be asked to extend the knee and push as hard as possible against the resistance pad. Strength is expressed as peak torque in Newton-meters (Nm). The best performance of 3 trials will be selected for each side, and the averages of the left and right leg will be used in analyses. **Grip strength** will be measured twice in each hand to the nearest 2 kg using an isometric Hydraulic Hand Dynamometer (Jamar, Bolingbrook, IL) and the mean value from the stronger hand used. Participants will be excluded from performing the test if they report hand-pain or recent hand or wrist surgery.

3. **Body composition. Dual Energy X-ray Absorptiometry** (iDXA, GE Medical Systems, Madison, WI; located in the Health and Exercise Science Department, WFU). Whole body scans will be acquired with the participant supine and aligned with the scanner table as prescribed by the manufacturer. DXA will also be used to analyze bone mineral density (BMD) using specific scans of the anterior-posterior (AP) spine (L1-L4) and proximal femur. Coefficients of variation (CV) from repeated measurements are 1.0% for lumbar spine BMD and 1.0% for femur BMD. All scans will be performed and analyzed by our trained DXA technician who is certified by the International Society for Clinical Densitometry and has vast experience in body composition measurements in older adults. Every scan will be examined to evaluate for proper patient positioning and analysis, and reanalysis or rescanning will be performed if necessary. Any artifacts will be noted and, if possible, excluded from the measured region. Daily quality control scans are obtained with GE’s phantoms. If results are more than 2 SD from baseline we repeat the phantom scan. If the results of both scans are more than 2 SDs from baseline we do not measure any more individuals and have the scanner serviced. Each week, the daily phantom data are analyzed to detect drifts. If changes in software or the machine occur, the scanner will be calibrated with the new software to ensure consistency.
4. **Accelerometry** will be used to objectively assess physical activity over a 7 day period at baseline and at follow-up. The **ActiGraph wGT3X-BT** is a compact, hip mounted electronic pedometer, using a 3-axis accelerometer and digital filtering algorithms to measure the amount and frequency of movement over 24 hours for up to 40 days. It provides physical activity measurements including raw acceleration, activity counts and vector magnitude, energy expenditure, steps taken, physical activity intensity, and body position.
5. **Cognitive function.** This will be assessed during screening using the **Montreal Cognitive Assessment (MoCA)**, participants must score >18 to be eligible. We will also assess psychomotor speed, attention, and

working memory using the **Digit Symbol Substitution Test (DSST)**.³¹ Participants are given a series of numbered symbols and then asked to draw the appropriate symbols below a list of random numbers. The score is the number of correctly made matches in 2 minutes (120 seconds). The cognitive function tests will be audio recorded by the assessor using a hand held digital recorder. The recordings will be used to properly score the tests as well as be available for quality control testing. The recordings will be deleted once the study is over and the data that was entered has been verified.

6. Biomarkers of longevity. To generate preliminary data for future grant proposals, we will collect information on a compilation of physiologic and biochemical markers shown in epidemiologic investigations to predict mortality. **Ventilatory capacity** will be assessed by spirometry recorded by the EasyOne™ PLUS spirometer to record average FEV₁ over three reproducible trials. **Kidney function** will be assessed by obtaining a basic metabolic panel (BMP) at baseline and follow up. **Blood pressure** and pulse will be measured in the right arm, using an automatic Omron device, with the participant in a seated position after having rested quietly for 5 minutes. They will sit with feet flat on the floor and legs uncrossed and will be asked not to talk during the rest period or during the measurement. Appropriate cuff size will be used. Systolic and diastolic blood pressure will be defined as the average of two repeated measures. **Interleukin-6** will be assessed in plasma samples that will be measured in blood drawn after an overnight fast at baseline and follow up. All assays will be conducted in the Cytokine Core laboratory directed by Dr. Barbara Nicklas (WFSM). We will also take advantage of the study design to collect and store serum and plasma for later assessment of biomarkers to identify potential mechanisms underlying the effects of the intervention on muscle and bone loss during weight loss.
7. Self-reported variables: Demographic characteristics including age, gender, race, education level, and socio-economic status will be recorded and used as covariates if necessary. Physical activity will be measured using the **CHAMPS Physical Activity Questionnaire for Older Adults** at baseline and follow-up.³² Activities of daily living will be assessed using the **Pepper Assessment Tool for Disability (PAT-D)** at baseline and follow-up. This questionnaire covers 3 domains: (1) basic activities of daily living (ADLs) (moving in and out of a chair, moving in and out of a bed, gripping with hands, using toilet, dressing, getting in and out of a car, and bathing); (2) mobility (walking several blocks, lifting heavy objects, walking 1 block, lifting/carrying 10 lbs, climbing several flights of stairs, and climbing 1 flight of stairs); and (3) instrumental ADLs (light housework, participating in community activities, managing money, visiting with relatives or friends, using the telephone, and taking care of a family member). For each item, respondents answer whether they experience 1) no difficulty, 2) a little difficulty, 3) some difficulty, 4) a lot of difficulty, 5) unable to do or, 6) did not do for other reasons. Answers are averaged across the items, in order to better assess the overall perceived disability burden by a person. Additionally, activities of daily living will be assessed using the **Mobility Assessment Tool – Short Form (MAT-sf)** at baseline and follow-up. This is a novel, computerized tool for self-assessment of functional performance designed to reduce bias from factors such as age, gender and body image. The **Short Form 12 (SF-12)** will be used as a generic measure of health related quality of life.³³ The questionnaire consists of two norm-based composite T-scales, assessing mental health and physical function. Lastly, mood will be assessed using the 10-item **Center for Epidemiologic Studies Depression Scale (CES-D)**.
8. Compliance and satisfaction: Although we will attempt to control compliance by the use of behavioral strategies, there may be inter-individual variability in compliance to the weight loss protocol. Therefore, participant **weight** will be collected at regular, bi-weekly intervals for both groups. Additionally, participants randomized to the high protein weight loss group also will be asked to provide information on **daily dietary intake** and complete a **satisfaction survey** at the end of intervention to express thoughts and feelings about following the Medifast 4 & 2 & 1 Plan. Lastly, **24-hour urine nitrogen** will be assessed to ensure differential protein intake by sending participants home with a container and instructions at baseline and follow up. Participants will be asked to: (1) void at 8 AM and discard the specimen; (2) collect all urine including the final specimen voided at the end of the 24-hour collection period (i.e., 8 AM the next morning); (3) screw the lid on securely. The sample can be stored at room temperature or refrigerated for up to 14 days and when the sample is returned, it will be sent to Labcorp for analysis.

Statistical Analyses

Sample size: Unpublished data collected in older participants undergoing a 6-month weight loss intervention indicate that we can anticipate a clinically meaningful 400-meter walk gait speed difference of at least 0.05 m/s, with a common group standard deviation of 0.19 m/s and a correlation of 0.85 between baseline and 6-month measures. Using the method of Borm et al (2007),³⁴ we assume using an analysis of covariance (ANCOVA) analytic approach fitting the randomization effect and baseline gait speed, then 53 subjects completing the intervention per group will yield 80% power using a two-sided alternative hypothesis at the 0.05 level of significance. Assuming a conservative drop-out rate of 15%, we plan to enroll 124 participants (n=62/group).

Database management: To facilitate data transfer and preserve records that can be audited, we will use hard copy forms collection. All data will be manually entered within one week of collection into the study database. Our data entry system will protect confidentiality and data security and the use of text containing identifying information will be avoided. Data will reside on a server in a Microsoft SQL server database with daily backup.

Data analyses: Regression diagnostics, residual plots, and exploratory analyses will be performed to find appropriate transformations for all variables to satisfy linearity, homogeneity of variances, and normality assumptions. Descriptive statistics consisting of frequency tables and percentages for categorical variables, and means, standard deviations, medians, and ranges for continuous variables will be tabulated and presented by intervention group and time point. Exact 95% confidence intervals (CIs) will be provided for the estimated proportions and approximate 95% CIs for estimated means. The primary outcome of the intervention effect on fast 400-meter walk gait speed will be analyzed using an ANCOVA model fit with the main effect of treatment arm and adjusted for baseline values of fast 400-meter walk gait speed. The primary test will be covariate-adjusted main treatment effect of the weight loss intervention compared to the control group, and we assume a Type I error rate of 0.05 for the two-sided alternative hypothesis. Secondary measures of body composition will be analyzed similarly, using baseline values of the particular body composition measure as a covariate in the outcome model. Other data including feasibility and compliance data collected in this study will be used to inform future studies of weight loss in older adults. All statistical analyses will be conducted assuming intent-to-treat so that participants will remain assigned to the initial randomization group regardless of treatment adherence, and participants who do not adhere or discontinue treatment will still be encouraged to provide outcomes data. Our group has past success in retaining participants by maintaining frequent contact with individuals who encounter barriers to participation and creatively accommodate and counsel, as necessary, to encourage the maximum degree of participation. To ensure the results are not overly influenced by missing data, a multiple imputation sensitivity analysis of the primary outcome will be performed using both baseline and post-randomization characteristics to inform the missing data imputation, assuming observations are missing at random.

Human Subjects Protection

Subject Recruitment Methods

We will recruit individuals using community-based recruitment strategies including mass and direct mailings and the local newspapers. We will also advertise in the VITAL newsletter (BG99-559) and participate in community outreach events.

Informed Consent

Written informed consent will be obtained from each subject. The informed consent process will follow the procedures of the WFU Institutional Review Board. The study interviewers will explain the purpose, methods and extent of the study to prospective participants. The potential participant is asked to read the informed consent form and ask questions. The form is written in simple easy to understand language. We require study staff to review all of the key aspects of the study verbally with the potential participants. Staff is provided with a structured checklist for this purpose. Staff is then required to question potential participants to ascertain whether s/he has understood the information. Potential participants who are illiterate or have impaired vision must have the consent read to them, followed by review of the checklist, opportunity for questions, and discussion. This process will take place in a quiet, private room in the Sticht Center. A copy of the signed and dated consent form will be given to participants, and the original document will be placed in subjects' individual study files, which will be stored in a secure location. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we will access personal health information only after obtaining informed consent.

Potential Risks

1. Blood draw. Slight discomfort, bruising, and/or infection at the sight of puncture for blood drawing, but blood will be drawn only by trained and experienced phlebotomists who will minimize the discomfort as much as possible.
2. Physical Performance Testing. There is a risk of the participant losing their balance and falling associated with the physical performance-based testing (e.g., the fast 400-meter walk test, balance tests, rising from a chair, muscle strength and power testing). In rare instances persons doing the fast 400-meter walk test will experience leg or chest pain, heart palpitations, shortness of breath. In very rare situations exercise can result in heart attack or sudden death. We will minimize this risk by: (1) safely escorting participants to chairs located along the walking course should they become unsteady; (2) following them at a close distance; and, (3) being at their side should they need assistance. There is a risk that participants may experience muscle soreness, strains, pulls, falls or joint injury or discomfort as a result of the physical performance testing procedures. A warm-up and range of motion practice will be conducted before maximal strength testing. In addition, if a participant reports pain, dizziness, lightheadedness or other medical problem during the test, the test will be terminated.
3. DXA scans. Exposure to radiation from the whole body, anterior-posterior (AP) spine (L1-L4), and proximal femur DXA (45 mRem total) for baseline, mid-point, and follow-up scans.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection, subject identifying information will be destroyed at the earliest opportunity (following a minimum of 3 years of record retention per the Wake Forest School of Medicine IRB policy), consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff, and also to Medifast Clinical Affairs personnel. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff, including the study physician, Rebecca Henderson, MD. In addition, all project related data and safety will be reviewed biannually by the WFUSM's Older Americans Independence Center's (OAIC) independent Data Safety Monitoring Board (DSMB).

Reporting of Unanticipated Problems, Adverse Events or Deviations

Participants will be queried at bi-weekly intervention sessions for adverse events (AE). Events will be recorded on AE tracking forms and categorized based on severity (mild/moderate/severe), seriousness (yes/no), and relatedness to the study intervention (unrelated, possibly, probably, and definitely). Any unanticipated problems, including serious and unexpected adverse events, as well as deviations or protocol changes will be promptly reported by the principal investigator or project manager to the IRB, the WFUSM OAIC DSMB, and Medifast.

Use of biological samples by other investigators

Biological samples may be used by investigators other than the investigators of the current study under the terms outlined in the informed consent form. The use will be limited to non-commercial purposes. The names and other personal identifiers of the study participants will not be sent to any recipients of the blood samples.

Storage and disposal of biological material

Biologic samples will be stored at Wake Forest University Medical Center for up to twenty years after the end of the trial at which time the samples will be destroyed. Biological specimens will be stored in locked -70°C alarmed freezers located in a locked room. The lab coordinator and the PI have access to the keys of the freezers. All the

specimens will have numerical study IDs with no personal identifiers of the participants. These are stored under the Pepper Center Repository (IRB#1219).

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