Health, Aging and Later-Life Outcomes Pilot Trial (HALLO-P)

A 9-month randomized pilot trial of 3 nutritional interventions in approximately 100 older adults with an indication for weight loss

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PRÉCIS

Study Title

Health, Aging and Later-Life Outcomes Pilot Trial (HALLO-P)

Objectives

This pilot study is part of a larger planning process to design a full-scale randomized trial to evaluate the long-term effects of caloric restriction (CR) and time restricted eating (TRE) on the health of older adults. The specific objective of the HALLO-P is to collect data to inform the design of the full-scale randomized trial to evaluate the long-term effects of caloric restriction and time restricted eating in older adults.

The pilot is a 9-month clinical trial of: 1) 20% CR delivered in-person; 2) 20% CR delivered remotely via video conferencing; and 3) 8-hour TRE with *ad libitum* caloric intake. We will collect measures of adherence, safety, and biomarkers of aging in all three groups. The pilot data will be used to refine recruitment criteria, estimate recruitment yields, and refine intervention approaches.

Design and Outcomes

HALLO-P is a 9-month randomized trial to assess the feasibility and acceptability of three interventions: 1) 20% CR delivered in-person; 2) 20% CR delivered remotely via video conferencing; and 3) 8-hour TRE with *ad libitum* caloric intake. All groups will be asked to increase physical activity by increasing their daily step count. It will enroll approximately 100 adults 60 years and older with an indication for weight loss (i.e., BMI=30-$\leq$40 kg/m^2 or Overweight (BMI=27-<30 kg/m^2) with at least ONE obesity-related comorbidity).

Primary feasibility outcomes

a) Degree of sustained CR **(Benchmark 1):** CR > 10% at 9 months;
b) TRE sustainability **(Benchmark 2):** At least 75% of participants eating within window on >80% of days; and
c) Retention of study participants **(Benchmark 3)**: Retention > 85% at 9 months.

Secondary outcomes

- Body weight change at baseline, 6 and 9 months
- Changes in fat and lean body mass assessed by DXA at baseline and 9 months
- Change in bone mineral density assessed by DXA at baseline and 9 months
- Change in resting energy expenditure assessed by indirect calorimetry at baseline and 9 months
- Change in physical activity energy expenditure assessed by ActivPAL at baseline and 9 months
- Change in energy intake assessed at baseline and 9 months using doubly-labeled water
- Change in total muscle mass at baseline and 9 months assessed by d3 creatine

(d3cr)

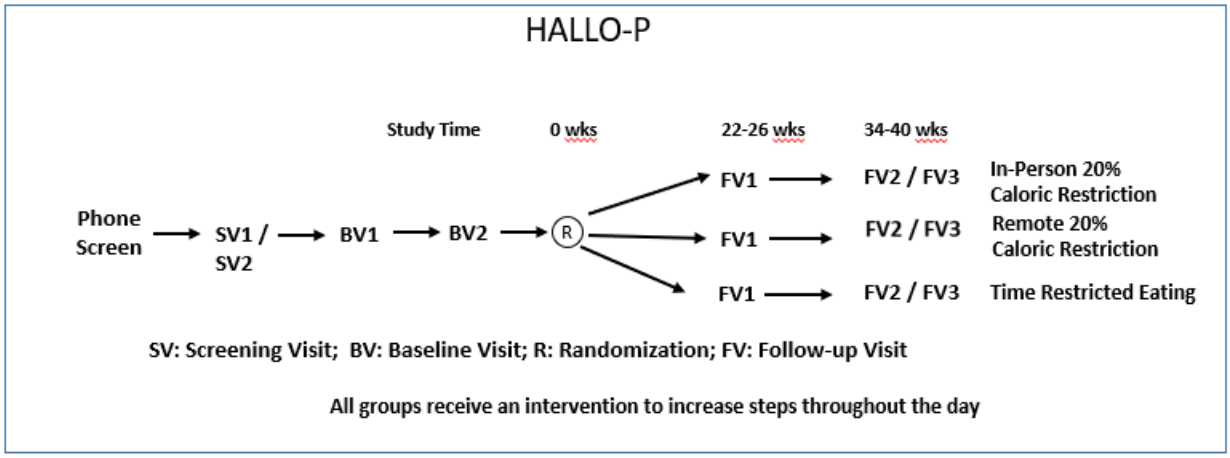
- Change in self-reported energy intake assessed using the ASA24 at baseline and 9 months
- Change in physical and cognitive function assessed at baseline and 9 months
- Change in age-related biomarkers at baseline and 9 months

HALLO-P will also collect the following information to guide the design of a longer-term study.

HALLO-P Feasibility Benchmarks

- Community Interest – Response rates to mailings and other outreach
- Recruitment Yields – Ratio of initial contacts to randomizations
- Participants with Inter-current Health Events – Health events that suspend intervention participation
- Intervention Delivery Costs – fixed and variable costs associated with each intervention arm

Study Schematic



Interventions and Duration

In-Person Caloric Restriction: This group will undergo a 9-month behavioral diet intervention targeting a 20% reduction in caloric intake. During the first 6 months, participants will meet in-person one time each month individually and three times/month in a group setting with a dietitian and/or behavioral coach. During the remaining three months of intervention, there will be one group and one individual meeting each month. Participants will keep diet records using the Fitbit app on a tablet and weight using a BodyTrace™ smart scale that transmits data through a study-specific Companion App. Participants will use wrist-worn Fitbit step monitors to track their physical activity and receive feedback via the app, with a goal to promote movement across the day, continuously increasing their daily step count. This arm was discontinued for the last wave (4) of the study to permit more participants to be randomized into the other two arms.

Remote Caloric Restriction: This group will have a similar 20% reduction in caloric intake and frequency of meeting schedule, and similar physical activity goal as the in-person arm. However, the remote arm intervention will be delivered via video conferencing.

Time-restricted Eating: This group will undergo a 9-month dietary intervention targeting consumption of all daily caloric intake within an 8-hour window of time, with no restrictions on caloric intake. During the first 6 months, participants will meet in-person once per month individually and three times per month in a group setting with a dietitian and/or behavioral coach. During the remaining 3 months of intervention, there will be one group and one individual meeting each month. Participants in TRE will be asked to log into the study-specific Companion App each day to document the beginning and end of their feeding cycles with timing of meals/snacks consumed. As in the CR arms, participants will use wrist-worn Fitbit step monitors to track their physical activity and receive feedback via the app, with a goal to promote movement across the day, increasing daily step count. Continuous glucose monitoring will be used at intervals to document glucose levels over a 10-day period.

Sample Size and Population

The HALLO-P target population is older adults with an indication for weight loss for whom participation is feasible and safe. Approximately to one-hundred participants will be randomized to the three study arms in a 1:1:1 ratio for the first 66 participants. The remaining participants enrolled will be randomized with equal probability to the remote CR and TRE groups. Randomization is stratified by sex.

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1 STUDY OBJECTIVES

1.1 Primary Objective

HALLO-P is a 9-month randomized trial to assess the feasibility of three interventions: 1) 20% CR delivered in-person; 2) 20% CR delivered remotely via video conferencing; and 3) 8-hour TRE with *ad libitum* caloric intake. It will enroll approximately 100 adults 60 years and older with an indication for weight loss (i.e., BMI=30-≤40 kg/m^2 or Overweight (BMI=27-<30 kg/m^2) with at least ONE obesity-related comorbidity).

The Primary Objectives are to assess the ability to sustain an adequate degree of CR in groups 1 and 2, to see differences in aging-related biomarkers at 9 months, and to see if an 8-hour TRE intervention can be sustained over 9 months. The pilot will also assess participant recruitment yields and retention at 9 months to gauge the potential to sustain a longer intervention period.

1.2 Secondary Objectives

As Secondary Objectives HALLO-P will assess:

1) Changes in body weight, fat and lean mass, total muscle mass, and bone density.
2) Changes in resting energy expenditure, physical activity energy expenditure, and energy intake.
3) Changes in physical and cognitive function.
4) Changes in aging-related biomarkers.

2 BACKGROUND AND RATIONALE

2.1 The Impact of Overweight and Obesity on Older Adults

Multi-morbidity (having > two health conditions) rises exponentially with age, and at age 70 its incidence is about 10% per year (1). Obesity (BMI ≥ 30 kg/m^2) is a major risk factor for common disabling conditions like osteoarthritis, cardiovascular disease, and diabetes, and the odds of multi-morbidity are sevenfold higher in persons with obesity than in those of normal weight (2). Even those in the overweight range (27≤ BMI <30 kg/m^2) have increased risk of disease and functional impairment (3). Older adults with multi-morbidity use a highly disproportionate share of health care resources: the 40% of Medicare Beneficiaries with 4 or more conditions accounted for 78% of Medicare expenditures in 2018 (4). Thus, interventions that reduce age-related multi-morbidity either through the treatment of overweight/obesity or slowing the aging process are urgently needed.

2.1.1. Caloric Restriction (CR) as Strategy to Ameliorate the Impact of Overweight and Obesity in Older Adults

In the short-term, the metabolic and functional changes seen with moderate caloric restriction in older persons point towards better health (e.g., lower IL-6, blood pressure, fasting glucose, and increased gait speed) (5). In primary care, women with obesity who successfully maintain a loss of ≥5% have significantly lower risk of obesity-related cancer, osteoarthritis, and health care utilization (6). The Look AHEAD study randomized 5145 persons (age 45-76) with type 2

diabetes to receive an intensive weight loss and exercise (ILI) or an education program (DSE). The ILI arm targeted 10% weight loss and increased exercise and was associated with reduced rates of advancing comorbidity, better mobility function and lower health care utilization (7-9). Whether these benefits pertain to older persons without diabetes is unclear.

2.1.2. Caloric Restriction Affects Aging Biology

These results jive with research findings from animal models evaluating caloric restriction. In many, but not all, animal models reducing caloric intake by 15-40% from ad libitum feeding prolongs lifespan and delays onset of numerous age-related health conditions (10, 11). Overlapping cellular and molecular mechanisms explain CR's effects on lifespan and health-span (12, 13). The most direct are those related to cellular energy homeostasis or 'energy- and nutrient-sensing' pathways, including AMP-activated protein kinase (AMPK), a master regulator of metabolism that activates catabolic pathways like glucose transport, glycolysis and fatty acid oxidation, and suppresses anabolic pathways such as fatty acid synthesis, cholesterol formation and protein synthesis (14, 15). The mammalian target of the Rapamycin (mTOR) pathway is inhibited by decreases in nutrient availability in order to conserve energy reserves by preventing protein synthesis and cellular growth, and strong experimental evidence links mTOR inhibition to extension of life and health-span (16, 17). Other nutrient sensing pathways such as insulin/insulin-like growth factor-1 signaling (IIS), and mammalian sirtuins, a family of nicotinamide adenine dinucleotide (NAD+)-dependent deacetylases, also appear to respond directly to CR and are implicated in life and health-span extension (18, 19). The cellular energy- and nutrient-sensing pathways work synergistically and converge with other hallmarks of biological aging, including activation of autophagy, an internal cellular recycling system that mobilizes available energy stores to preserve critical cellular functions, and reducing oxidative damage, pro-inflammatory cytokine / chemokines, and other cellular and systemic stress response signaling (12, 20, 21). In older humans, weight loss interventions up to 18 months show reductions in inflammatory biomarkers, cystatin-c and mortality-linked physiologic and functional measures (22-24), and a meta-analysis of randomized trials of caloric restriction showed that randomization to caloric restriction was associated with a 15% reduction in all-cause mortality(25). Identifying which biomarkers may serve as intermediates between CR and its potential health benefits is important in understanding the potential benefits of interventions designed to mimic CRs effects.

2.1.3. Potential Concerns Regarding Caloric Restriction in Older Adults

While most data support the short-term benefits of CR in older adults, there is uncertainty with respect to its long-term consequences. CR causes the loss of skeletal muscle and bone, thus potentially exacerbating sarcopenia and osteopenia (26). In a number of studies, muscle function measured by strength has been unaffected by CR despite measurable losses of skeletal muscle mass or volume (27-29). However, these studies are mostly short-term leaving a gap in knowledge regarding long-term consequences. Bone density was measured in the CLIP II study which compared CR alone or combined with either aerobic or resistance exercise. Total hip BMD was reduced by 2% in all three groups (30). Based on data from fracture prevention trials, this change would be expected to increase vertebral fracture risk by ~ 30%. Whether this finding would apply to non-osteoporotic older persons is unknown. In the Look AHEAD study which was conducted over 8-10 years, there was no difference between the groups in total or hip fracture rates but a 39% increase in fragility fractures in the ILI arm. In subgroup analyses, the

greatest risks were seen in those <56 yrs and those with baseline BMIs >37.7 kg/m² (31). The effect of CR on cognitive function in older adults is understudied. Unintentional weight loss in later life is associated with declining cognitive function and dementia risk (32). Short-term CR in non-elderly persons shows small improvements in cognitive scores (33). In a Look AHEAD ancillary study, the impact of ILI on long-term differences in cognitive function depended on baseline BMI: the ILI had worse cognitive function if baseline BMI >30 but better function if BMI < 30 kg/m² (34). In three short-term trials including older adults CR interventions were associated small cognitive improvements (35-37). Information relating to the long-term consequences of CR or related dietary interventions is needed to understand potential drawbacks and balance these against potential benefits.

2.1.4. Alternative Approaches to Energy Intake Manipulation to Mimic CR's benefits

Researchers have used animal models to extend initial CR findings examining alternatives such as time restricted eating or alternate day fasting. In time restricted eating (TRE), animals receive all calories within a specified time interval but are allowed to consume as many calories as desired within that interval. Alternate day fasting provides unrestricted food access on most days but no calories or highly limited calories on other days. Diet manipulations involving alternate day fasting and/or TRE extend both lifespan and healthspan in yeast, worms, and rodents, and are effective in mice even when initiated late in life (38-40). TRE's benefits appear to depend on feeding periods being aligned with the circadian cycle(41). In humans, some studies report short-term metabolic benefits. Some weight loss typically occurs in these studies, but the magnitude is less than that observed with CR. The long-term effects of TRE on the health of older humans are unknown. However, it is an attractive alternative to CR because the potentially lower degree of weight loss would be expected to be associated with better retention of muscle and bone mass.

A growing body of evidence suggests that time restrictive eating (TRE) targets biological pathways affecting aging in humans and may be an alternative to caloric restriction (CR) in adults with overweight and obesity, particularly in older adults where CR may exacerbate muscle and bone mass loss. Most TRE studies with ad libitum food and beverage intake have resulted in a 2-4% weight loss as well as fat loss in individuals with overweight or obesity (42-44). In those TRE studies that assessed energy intake, TRE with ad libitum food and beverage intake led to a decrease in total energy intake which may explain the weight loss. TRE interventions also have beneficial effects on systolic and/or diastolic blood pressure; however, effects of TRE on glucose homeostasis, insulin sensitivity, and plasma lipid and cholesterol metabolism are conflicting (42-44). There are few studies of TRE in middle aged and older adults (45). However, TRE interventions in middle aged and older adults with overweight or obesity have shown similar results with significant weight and fat loss (46, 47) as well as improvements in systolic and diastolic blood pressure (48). A limitation of existing TRE intervention studies is the short duration, typically ≤12 weeks; thus, the long-term effects of TRE are unknown.

2.2. Study Rationale

The intent of HALLO-P is to demonstrate the feasibility of delivering 20% CR and 8 hours of TRE to older adults who are likely to represent participants in a long-term trial of these same interventions. One of the CR groups will receive their intervention remotely using approaches including internet-based conferencing in order to assess the adequacy of this approach for

achieving the target level of CR. In addition, all participants will receive instruction to promote light-intensity and weight-bearing movement throughout the day.

2.2.1. Rationale for 20% CR

Reducing caloric intake by 10–40% from *ad libitum* prolongs lifespan in some animal models. Within this range we sought a target that allows for adequate nutrition and is sustainable. In inactive older adults, aggressive CR targets are not feasible because baseline energy intakes are already low. For example, the INFINITE Study included 65–79 year-old sedentary adults with obesity (49). In the group randomized to a 600 kcal/day deficit (~26% CR), 42% of participants would have been prescribed a daily intake of <1100 kcals/d, which is too low to provide adequate overall nutrition. To minimize the loss of skeletal muscle, protein intake of 1.0-1.2 g/kg/day of baseline body weight is recommended (50). In diets with low absolute energy intake, this level of protein consumption can be unpalatable unless protein supplements are provided. The pilot will provide data on baseline energy requirements, the feasibility of formulating palatable and nutritionally adequate meals, and the need to provide protein supplementation. We will use the gold-standard measure of energy expenditure, Doubly-Labeled Water (DLW), in conjunction with Dual X-ray Absorptiometry (DXA)-measured body composition in order to assess energy intake at baseline and 9 months, to document actual CR levels. We will also measure resting energy expenditure (REE) and physical activity energy expenditure (PAEE; via actigraphy) to estimate weight-maintenance energy needs for comparison to DLW values.

2.2.2. Rationale for CR intervention delivered remotely

A remote intervention strategy would increase HALLO's resilience to disruptions similar to those experienced during the COVID-SARS2 pandemic. In addition, we anticipate that a remote intervention strategy would reduce the cost of intervention delivery and reduce participant burden. If this strategy produces adequate CR, it would allow for centralized intervention delivery in a multi-center study and allow for larger sample sizes at an equivalent cost compared to an in-person approach.

2.2.3. Rationale for Time Restricted Eating

The benefits of CR may not be due only to a reduction in total caloric intake but also to longer periods (and the timing) of fasting (51). Existing literature suggests that the cellular and molecular pathways implicated in TRE and alternate day fasting effects are nearly identical to those of CR, including AMPK activation, IIS signaling, mTOR inhibition, and inflammation (12, 51). Studies in humans of dietary feeding modulation without daily CR have demonstrated considerable weight loss compared with ad libitum feeding, reduced biomarkers of aging and risk factors for age-related diseases, and yet these feeding patterns did not appear to affect lean mass. Few studies have attempted to uncouple weight loss effects of calorie manipulation from weight loss-independent effects of dietary feeding restriction (52, 53). The human studies of TRE have to date been short and often uncontrolled, and with one exception do not include older adults. There is some evidence that obesity sensitive biomarkers are beneficially affected and that fat loss predominates over lean mass loss which is attractive from the standpoint of older adults.

Participants randomized to the TRE arm will be counselled to consume all caloric intake within a specified 8-hour eating window without a prescribed reduction in caloric intake. A zone of adherence is created by using a target of 8 hours ± 30 minutes.

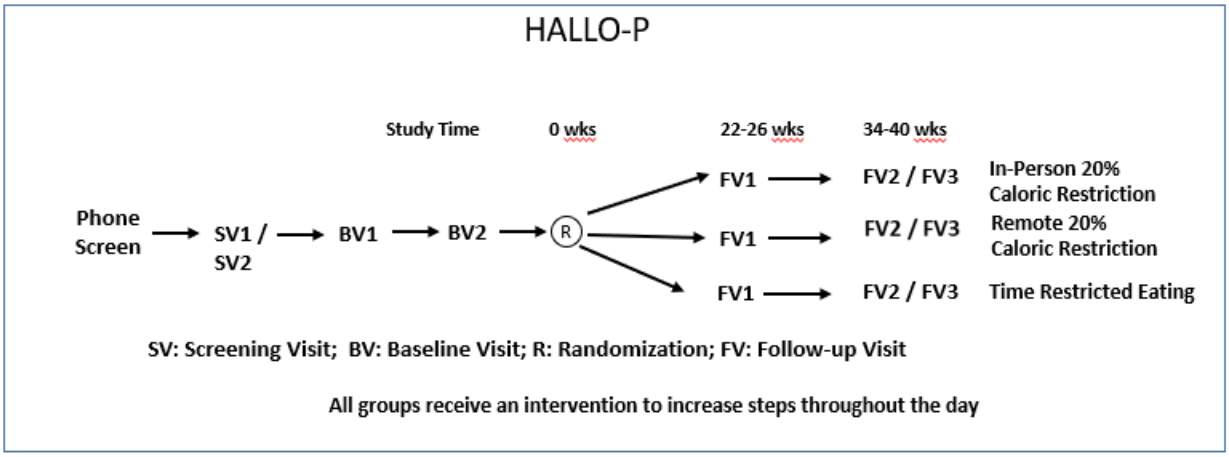
2.2.4. Rationale for Including Physical Activity Promotion for all Participants

An adaptation to CR is decreasing energy expenditure, in part, by reducing non-exercise activity thermogenesis. This can increase sedentary behavior, which is associated with increased disability risk (54). TRE is also associated with reductions in weight and physical activity (55, 56). Thus, we believe it is unwise to prescribe either CR or TRE for older adults without promotion of some amount of physical activity. The long-term loss of lean mass and bone amplify this concern (57). We found that CR coupled with an intervention that promotes movement across the day reduces weight regain compared to a traditional treadmill-based endurance exercise intervention (58, 59). Furthermore, both groups experienced improvement on a 400m walk test (60).

Using a similar approach in HALLO-P, we will promote a day-long movement program in all three groups to: (a) reduce prolonged periods of sedentary behavior across the day, and (b) help preserve and possibly enhance mobility. In addition, increase in stepping helps to address the reduction in voluntary energy expenditure observed in persons restricting energy intake. To accomplish these goals, the intervention focuses on increasing daily steps in frequent bouts and weight-bearing activities such as step-ups and stair climbing. The focal process measure is steps per day, with an emphasis placed on distribution of steps throughout the waking period of the day. Based on our prior experience (59-61), our initial step goal will target an ~20% increase over average daily steps as assessed via ActivPAL at baseline. The interventionist then progresses weekly goals based on the ability and tolerance of each participant using Fitbits to track activity and provide feedback to participants via the Companion App. Using this approach, by the final assessment visit, most participants can be expected to increase their average weekly steps in the range of 50 to 100 percent over baseline. This increase in activity is modest given the sedentary status of HALLO-P participants at baseline. Also important is that the longer-term study will have a group that does not include dietary interventions and we would deliver the activity component to this group to allow isolating its effects from those of the dietary interventions. This will offer value to those randomized to the non-dietary intervention arm which we believe is important to retention in a long-term study.

3 STUDY DESIGN

Overview. HALLO-P is a 9-month randomized behavioral intervention trial to pilot three strategies to change the amount or timing of food intake in order to evaluate these strategies for use in a long-term trial. The three strategies include 20% CR delivered in-person, 20% CR delivered remotely, and TRE within an 8-hour window each day. All participants will also receive an intervention to reduce sedentary time and increase the number of daily steps.



Inclusion / Exclusion. HALLO-P's recruitment target is approximately 100 older (60+ years), community-dwelling men and women residing in Forsyth County, NC or surrounding counties who have obesity (BMI = 30 - $\leq$ 40 kg/m^2) or are overweight (BMI = 27 - <30 kg/m^2) with an indication for weight loss (e.g., hypertension, hyperlipidemia, elevated waist girth, controlled diabetes). We will target up to 50% men but expect to be in the range of 35%-45% men, 50% > 70 yrs, and > 23% minority participants which reflects racial demographics of our region.

HALLO-P will exclude persons for whom the interventions are potentially unsafe, who have a history of eating or nutritional disorders, who are likely to drop out due to severe chronic illness or other reasons, or who show inability to perform self-monitoring activities required by the interventions. We will exclude those doing shift work because disturbances in circadian cycles may interfere with TRE. We will exclude persons with uncontrolled or previously undetected diabetes because disease management may interfere with the interventions and certain medical treatments may complicate outcome interpretation.

Randomization / Study Duration. Recruitment is scheduled to last approximately 12-15 months. Once eligibility is established and baseline testing is completed, participants will be randomized using blocked randomizations stratified by sex to one of the 3 intervention groups for the first 66 participants and blocked randomizations stratified by sex to either the remote CR or TRE groups for the remainder of the cohort. Randomized participants will be in the intervention for 9 months.

Primary & Secondary Outcomes.

HALLO-P is a pilot study to identify the feasibility of interventions designed to lead to either 20% CR or the maintenance of TRE with sufficient retention to support the goals of a longer-term study. The outcomes are:

Primary feasibility outcomes

a) Degree of sustained CR **(Benchmark 1):** CR > 10% at 9 months;
b) TRE sustainability **(Benchmark 2):** At least 75% of participants eating within window on >80% of days; and
c) Retention of study participants **(Benchmark 3)**: Retention > 85% at 9 months.

Secondary outcomes

- Body weight change assessed using home scales at baseline, 6 and 9 months

- Changes in fat and lean body mass assessed by DXA at baseline and 9 months
- Change in bone mineral density assessed by DXA at baseline and 9 months
- Change in resting energy expenditure assessed by indirect calorimetry at baseline and 9 months
- Change in physical activity energy expenditure assessed by ActivPAL at baseline and 9 months
- Change in energy intake assessed at baseline and 9 months using doubly-labeled water
- Change in total muscle mass at baseline and 9 months assessed by d3 creatine (d3cr)
- Change in self-reported energy intake assessed using the ASA24 at baseline and 9 months
- Change in physical and cognitive function assessed at baseline and 9 months
- Change in age-related biomarkers at baseline and 9 months

HALLO-P will also collect the following information to guide the design of a longer-term study.

HALLO-P Feasibility Benchmarks

- Community Interest – Response rates to mailings and other outreach
- Recruitment Yields – Ratio of initial contacts to randomizations
- Participants with Inter-current Health Events – Health events that suspend intervention participation
- Intervention Delivery Costs – fixed and variable costs associated with each intervention arm

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

The inclusion criteria shown in the table below will be used.

4.2 Exclusion Criteria

The criteria listed below will exclude participants for whom study participation may not be safe or who may have conditions that may affect adherence to the study protocol. All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation.

Criteria	Inclusion	Exclusion	Assessment
Age	60+ years (target - 50% ≥70 yrs)	<60 years	Self-report (phone)
Housing status	Community-dwelling	• Resides in assisted living or skilled nursing home • Resides with someone who is currently participating or previously participated in this study	Self-report (phone)
Obesity status	Class I obesity (BMI=30-≤40 kg/m^2) OR Overweight (BMI=27-<30 kg/m^2) with at	• BMI <27 or >40 kg/m^2 • BMI 27-<30 kg/m^2 without an obesity-related co-morbidity	Self-report (phone), then confirmed with measured weight and height at

	least ONE obesity-related comorbidity[1]		screening visit with shoes off
Physical function status		• Dependent on quad cane or walker • Inability to walk independently • Needing assistance with any Activity of Daily Living	Self-report (phone)
Cognitive function status		• History of mild cognitive impairment or dementia • Cognitive impairment (score <22) on Montreal Cognitive Assessment (MoCA)[2] (62)	Self-report (phone) Conducted at screening visit
Psychiatric status		• Depression (score ≥16) on the Center for Epidemiologic Studies Depression (CES-D)[3] (63) scale	Conducted at screening visit
Smoking/ alcohol use		• Use of >1 tobacco product per day or 4 per week, or vaped more than once a week within past year • Excessive alcohol use (>7 for women or >14 for men drinks/week) in the past month	Self-report (phone)
Nutritional status		• Weight loss or gain ≥5% in past 3 months • Vegan or other severe dietary restriction • Any contraindications for caloric restriction or overnight fasting • History of binge eating disorder assessed via the Binge Eating Disorder Screener-7 (BEDS-7)[4] (64) • Consume meals/snacks over a period of <11 hours per day	Self-report (phone) Conducted at screening visit Recorded during the 7-day behavioral run-in
Physical activity status		• Regular current participation in high intensity aerobic or resistance exercise training of >150 mins/week	Self-report (phone)
Sleep status		• Volunteer or paid work between 8pm-8am	Self-report (phone)
Orthopedic status		• Severe arthritis, fracture, chronic injury, or other musculoskeletal disorder that prevents walking independently • Joint replacement or other orthopedic surgery in past 6 months or planned in next 12 months	Self-report
Co-morbidity/health history		• Osteoporosis (t-score ≤ -2.5 on total hip and/or femoral neck scan) • Uncontrolled hypertension (systolic >160 OR diastolic >100 mmHg) upon repeated assessments (up to 3 times)) • Type 1 diabetes • Uncontrolled type 2 diabetes (HbA1c >7.5%), diagnosed within last year, or newly identified (HbA1c ≥6.5%)	Self-report or DXA scan at screening Screening BP Self-report and blood labs

		• Dialysis or abnormal kidney function (eGFR <30 mL/min/1.73 m^2) • Liver disease or abnormal liver function (ALT levels 2 times above normal) • Severe anemia (Hb <11/dL) • Potassium or sodium above or below normal limit • Uncontrolled thyroid disease (hypo/hyper) or requiring recent (past 3 months) adjustments in thyroid hormone supplementation or thyroid-stimulating hormone <0.45 or >4.5 uIU/mL • Stroke, heart attack, heart failure hospitalization, or revascularization procedure within the past year; New York heart failure Class >2; COPD requiring oxygen use; uncontrolled angina; PAD diagnosis within the last year; progressive neurologic disease (e.g., Parkinson's, ALS, MS); other diseases suggesting a life-expectancy <3 years • Cancer requiring treatment in past year, except non-melanoma skin cancers • Cholelithiasis, severe irritable bowel syndrome or Crohn's disease • Recent (within 4 weeks) acute respiratory illness, including confirmed Influenza or Coronavirus disease-19 • Major, uncorrectable vision or hearing loss	Self-report
Surgical/ hospitalization history		• Any history of stomach or small intestinal surgery (except appendectomy but including surgery for weight loss) • Major abdominal, thoracic/spine or non-peripheral vascular surgery within past year • Overnight hospitalization within past 6 months for any reason	Self-report
Medication use		• Regular use of: growth hormones, medications prescribed for weight management, prescription osteoporosis medications, certain prescription medications for diabetes including insulin, sulfonylurea, meglitinides, GLP-1 agonists, SGLT2 inhibitors • Use of oral steroids for >1 month within prior 3 months	Self-report
Non-compliance		• Failure to complete behavioral and technology run-in • Do not live within cellular signal coverage range	Behavioral run-in Coverage map at screening

		Unable/unwilling to: • Provide own transportation to study visits • Commit to study protocol, including random assignment or use of technology • Adhere to data collection visits	Self-report
Research participation		• Current participation in another intervention research study • Planned out-of-town trip greater than 3 weeks • Unwilling to provide informed consent, including consent to access personal electronic health records • Judged unsuitable for the trial for any reason by research team	Self-report Principal Investigator / Medical Safety Officer

[1] Obesity-related comorbidities: 1) elevated waist circumference (>35" in women, >40" in men); 2) hypertension 130-159 systolic or 80-99 diastolic (or on medication); 3) dyslipidemia (on medication or triglyceride >200 mg/dl or total cholesterol>240 mg/dl or LDL cholesterol>160 mg/dl); 4) controlled diabetes (Hba1c <7.5%); 5) other obesity-related comorbidity: clinically manifest coronary artery disease [e.g., history of MI, angina pectoris, coronary artery surgery, coronary artery procedures (e.g., angioplasty) if not within the past year], other atherosclerotic disease [e.g., peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease if not within the past year], or sleep apnea.
[2] The Montreal Cognitive Assessment is a brief, standardized test of cognitive functioning. Higher scores indicate higher cognitive function, thus participants must score ≥22 to be eligible.
[3]The Center for Epidemiologic Studies Depression scale is a 20-item self-report measure of depressive symptoms in adults. Scores of >15 indicate clinically significant depressive symptoms.
[4] The Binge Eating Disorder Screener-7 is a semi-structured interview and will be used to assess the presence of binge eating disorders.

4.3 Study Enrollment Procedures

Recruitment. Recruitment strategies will include a mix of community advertising via talks/seminars and IRB-approved flyers; advertising in the Wake Forest OAIC's Volunteers in Touch with Active Living (VITAL) newsletter (distributed to 22,000+ older, community-dwelling adults who provided informed consent to receive study recruitment newsletters), newspapers and other media outlets (e.g., tv, radio or social media); mass mailing of IRB-approved study postcards; and mass mailing/emailing of IRB-approved letters of potentially eligible adults selected from WFBMC's electronic medical record.

Screening. Eligibility will be established based on an initial phone screen, a screening visit that includes a fasting blood draw for assessment of clinical blood chemistries and a bone densitometry test, and a short run-in period. Screening visit data will be entered into the study data management system. The system only permits a randomization assignment to be generated for participants who have complete eligibility assessment data and who meet all eligibility criteria.

Consent and Enrollment. The first study contact will be a phone interview which is initiated based on a potential participant's expressed interest in the study. On initial contact the interviewer will obtain and document verbal consent to collect basic demographic information (age, residence, sex, race/ethnicity). Then, the interviewer will describe the study and ask the participant if they are interested and whether they would be willing to do a phone administered

questionnaire to establish eligibility. Eligibility questions that can be provided over the phone will be asked to establish eligibility for further screening.

Participants who are eligible after the phone screen will be scheduled for an in-person screening visit. A trained study examiner will obtain full informed consent to participate in the study before any data collection. The informed consent form (ICF) obtains information describing both the screening and all other study procedures, including the intervention. The examiner will again describe the study and the requirements for participation, review the informed consent form in detail with the participant, and address any participant questions. Once the participant has had their questions addressed the participant will sign the informed consent and receive a copy for their records. The original signed consent will be placed in the participant's study file. Participants are considered enrolled in the study after providing consent, but do not count towards the goal of ~100 until randomized.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The randomized study design for HALLO-P involves a target of approximately 100 participants randomized to one of three interventions: (1) in-person 20% caloric restriction (CR); (2) remote 20% CR (see *Calorie Restriction Goals* below for more detail); (3) in-person 8-hour restricted eating (TRE). All 3 interventions last 9 months with both individual and group contacts delivered on an identical frequency in all intervention groups. For the first 6 months, participants meet weekly and then twice a month from months 6-9.

The conceptual model that serves as the foundation for the caloric restriction (CR) and time restricted eating (TRE) interventions is depicted in the Figure below. Older adults' ability to *self-regulate* their eating behavior involves both *conscious* (65, 66) and *nonconscious (67, 68)* processes. Core conscious-based constructs include *self-efficacy* (69, 70), *outcomes and outcome expectations* (71, 72), and *impediments* to regulating eating behavior which often operate outside of conscious awareness. *Nonconscious impediments* include, among other factors detailed in the behavioral toolbox, physiological states that increase appetite and habitual patterns of eating conditioned to social (73) and environmental cues (74). People also engage in habitual patterns of eating to regulate the discomfort of negative emotions (71, 75).

Figure 1: Conceptual Model for Caloric Restriction (CR) & Time Restricted Eating (TRE)

Key structural components of interventions for effective CR have evolved across time (76-82), and were progressively adopted by 4 major NIH funded multi-center clinical trials. These major

advances have been integrated into our CR trials with older adults over this same period (58, 83-85).

5.1.1 The Use of a mHealth Platform for Adaptive CR and TRE Interventions

Technological innovations (web-connected tablets, wearable monitors, and smart scales) now allow for behavior change strategies to extend into a person's daily life and to be adaptive in near real time to participants' progress. These tools offer improved approaches for self-monitoring key processes central to either CR or TRE and support other action plans important to successful treatment. Specific to the CR intervention, we will use an equation using in-home weights (captured with the smart scale) to model and monitor adherence to CR in real time, a strategy that was successful in CALERIE (82, 86) and will be adapted for HALLO-P. For the TRE intervention, we will track adherence to feeding schedules via the app using a Feedogram visual self-monitoring and feedback tool to quickly identify problems that arise. Importantly, interventionists also see the data from the app in real time and, when participants fall outside a *"zone of adherence"*, they can tailor strategies based on the conceptual model and toolbox discussed in greater depth in a separate document. A study-specific app named the *Companion App* will provide immediate reinforcement for achieving goals via mastery badges (87) and allows for interactive communication between participants and the intervention team. HALLO-P builds on experience garnered in several CR interventions with older adults for the past 4 years; (58, 87, 88) which has led to the development of methods to engage older adults in the design of the mHealth applications and provides hands-on training to optimize older adults' comfort and confidence in use of the technology (58, 88).

5.1.2 The HALLO-P Interventions

<u>*Overall Design*</u>. For the first 6 months of intervention, participants in all three groups will meet as follows: (a) 1 time each month individually with a behavioral coach and/or a Registered Dietitian (RD) as needed; and (b) 3 times per month in a group setting. The groups will be formed in waves as participants join the study with the size of each group between 8-12 participants. Participants in the CR group will keep diet records using a smartphone/tablet (study to provide) and record home weight using a BodyTrace™ electronic smart scale that transmits data to the center automatically and provides a vehicle for interventionists to adapt the intervention as needed for each participant. Those in TRE will log into the app each day to document the beginning and end of their feeding cycles with timing of meals/snacks consumed. These data also provide a vehicle for interventionists to adapt the intervention as needed as in the CR group. It is also important to note that all 3 intervention groups include a physical activity component that aims to have participants "move more and move more often across the day." We will provide Fitbit step monitors as a means of tracking activity with the initial goal of increasing daily steps by 20% from baseline levels and spreading out movement across the day and incorporating additional weight-bearing physical activity such as step-ups and stair climbing. To ensure participants' understanding of the requirements of their intervention assignment, each participant will receive a brief group-specific nutrition orientation following randomization but prior to the start of the intervention. Likewise, each participant will receive a brief group-specific technology orientation designed to build confidence in the use of technology following randomization and before the start of the intervention. The group sessions will be used to create a sense of community with others, educate and discuss with participants the health benefits of

either CR or TRE, share experiences with the interventions, and facilitate group problem solving. During months 7-9 of the intervention, there will be one group and one individual meeting each month.

The key difference between the remote and in-person CR arms is that the remote arm will be delivered via video conferencing, leveraging unique group formation activities (e.g., breakout rooms, ice breakers) developed in a recently completed pilot study (88). The TRE group does not monitor caloric intake or body weight. For similarities and differences between intervention arms see the table below.

Common Elements and Distinctions between HALLO-P Intervention Groups			
Component	**In Person CR (Waves 1-3 only – 1st 66pp)**	**Remote CR**	**Time Restricted Eating (TRE)**
Individual Sessions (10-40 min by need)	1 i per month (in-person, video or by phone)	1 videoconference / call monthly	1 per month (in-person, video or by phone)
Group Sessions (30-45 min each)	3 in-person monthly for first 6 months; 1 monthly thereafter	3 videoconference calls monthly for first 6 months; 1 monthly thereafter	3 in-person monthly for first 6 months; 1 monthly thereafter
mHealth App	Graphic feedback on zone of adherence & movement, group chat, within-day surveys	Graphic feedback on zone of adherence & movement, group chat, within-day surveys	Graphic feedback on feeding windows & movement, group chat, within-day surveys
Physical Activity	Increasing steps throughout the day with an initial increase of ~20% with progression based on the ability and tolerance of each participant	Increasing steps throughout the day with an initial increase of ~20% with progression based on the ability and tolerance of each participant	Increasing steps throughout the day with an initial increase of ~20% with progression based on the ability and tolerance of each participant
Dietary Goal	20% caloric restriction (CR)	20% CR	8h Time Restricted Eating (TRE); no CR
Use of toolbox	Yes	Yes	Yes
Computer Tracking	Yes	Yes	Yes
Mathematical Derived Weight Goals for CR	Yes	Yes	No
Objective Marker of Adherence: CR/TRE	Doubly-labeled Water	Doubly-labeled Water	Continuous Glucose Monitoring

From a behavioral perspective, adherence to all 3 interventions is guided by a common framework for implementing this conceptual model using a *toolbox* to facilitate dietary goals. In addition, whereas the primary objective of the individual sessions is to tailor treatment, all 3 intervention arms receive training in key areas related to the specific goals of the intervention; these are reinforced through both individual and group sessions whether these are in-person or remote.

5.1.3 Use of mHealth App and Tracking Appetite Metrics

Relying on our conceptual model, the interventions will combine specific nutritional and behavioral guidance for each participant to achieve adherence to treatment goals. Coaches and the RD have the ability to select specific nutritional and behavioral/environmental strategies

from a "toolbox" based on individual needs (see the separate toolbox document in MOP). Using the HALLO-P mHealth app, participants in both CR groups will: (a) *track the content of all food* intake and body weight each day for the first two months and then at least every other week thereafter; (b) *receive feedback in near real time* that tracks participants' daily weights, providing feedback and, when necessary, near real time adaptation to the intervention so that they remain in their personalized "zones of adherence" to the trajectory of weight across time using a predicted model developed by Hall et al. (89); (c) *receive feedback* on total calories, the average daily calories consumed each week, and the average calories consumed each month; (d) *receive reinforcements in real time* for meeting study goals in the form of both "mastery" badges (88) and app notifications; and (e) *following an ecological momentary assessment (EMA) protocol* (i.e., collection of responses in participants daily life with an app) report on several appetite related metrics across the day (this feature is turned-on during the first month of the study and for a week during every month thereafter)—these data will be utilized to provide feedback on patterns of appetite throughout the day.

For the TRE group, participants will use the Feedogram as part of the app to *track the beginning and end of their eating cycle each day along with meals/snacks consumed,* for the first two months and then at least every other week thereafter for month 3-6, and at least one week in each month for months 7-9. The app also enables participants to: (a) receive prompts when outside the zone of adherence for TRE, (b) *receive feedback each day* on their success in meeting the TRE interval; receive weekly and monthly feedback on the %frequency of meeting the TRE interval; (c) *receive reinforcements* for meeting study goals in the form of both badges and app notifications; and (d) *following an EMA protocol* report on several appetite related metrics across the day.

Daily physical activity level, body weight (CR groups only), macronutrient intake (CR groups only), timing of meals/snacks (TRE group only), and *Companion App* usage will be tracked using the *Companion App* suite during the 9-month pilot as these data will be integral to the provision of each intervention. Daily **physical activity** will be monitored using the Fitbit. Participants will synchronize the device throughout the day using an anonymized account on the study-provided tablet. These data will be retrieved in near-real time from Fitbit servers using the Fitbit Web application programming interface (API) and stored in secure internal servers. For those in the CR arms, we will use a BodyTrace smart scale to collect daily **body weight** from each participant. This device is equipped with an AT&T cellular data chip that wirelessly transmits weight data in real time. We will retrieve the weight data using the BodyTrace API. Participants in the CR arms will use the Fitbit app on the study-provided tablet to track **dietary intake**. Participants will receive the tablet with the app signed into an anonymized account. The intervention team will have access to daily macronutrient reports through the website to assist in providing feedback to participants, and these data will be exported from the web portal by the intervention team for each participant at the end of the pilot study. Participants in TRE arm will log into the *Companion App* each day to document the beginning and end of their feeding cycles with timing of meals/snacks consumed.

5.1.4 Toolbox

All 3 interventions are adaptive, meaning that strategies used to modify eating and movement behavior in CR and the timeframe for food consumption in TRE are implemented in near real

time when participants' weights in CR or timeframe for food consumption in TRE deviate from established zones of adherence. The behavioral toolbox to guide the selection of strategies is based on a conceptual model which is part of the toolbox and serves as the foundation for understanding eating behavior. The intervention guide document details the algorithms for implementing the toolbox which is activated by way of tracking daily data via the mHealth app on all participants.

5.2 Handling of Study Interventions

5.2.1 Caloric Restriction Goals: The calorie level assigned for each person assigned to one of the CR groups will provide him/her with a daily caloric deficit of approximately 20%. The individual absolute calorie level is derived from subtracting 20% from each person's estimated daily energy needs for weight maintenance. The calorie level assigned for each person assigned to one of the CR groups will provide him/her with a daily energy intake (EI) approximately 20% lower than his/her baseline EI. Baseline EI will be determined by measuring Total Energy Expenditure obtained by DLW from Baseline Visit 1 and 2, or through estimating EI using body weight and composition, resting energy expenditure and physical activity level.
No woman will be prescribed with less than 1100 kcals/d and no man less than 1300 kcals/d.

5.3 Concomitant Interventions

HALLO-P will deliver the step intervention to all 3 groups, using Fitbits to track and feedback activity data to participants via the companion app. The goal will be to promote daily movement; increasing daily steps from baseline. Also, participants will be advised to consume calcium (up to 1200 mg/d) and vitamin D (800 IU/d) supplements to mitigate the risk of BMD loss. The RD will also promote consuming 90 g of protein/day evenly distributed across daily meals in the CR groups; a target monitored via the tracking app for food intake. Finally, a high-quality diet focusing on eating patterns promoting satiety over the fasting period will be recommended to TRE participants.

5.4 Adherence Assessment

The primary measure of adherence to the CR regimen will be the change in energy intake from baseline to 9 months calculated using the DLW-measured change in TEE in conjunction with the DXA-measured fat and lean body mass changes over 9 months.

Change in self-reported energy intake will be a secondary adherence measure.

Change in scale-measured body weight in line with our model of expected body mass loss under the assumption of 20% CR is a secondary measure of adherence.

Adherence to the TRE regimen will be assessed through data collected by the Companion App where participants will log occasions of caloric ingestion during waking hours. Participants will be considered compliant if they consumed calories within an 8-hour window on 80% of days. An objective secondary measure of adherence will be through the use of continuous glucose monitoring for 10-day intervals using spiking glucose blood levels as a biomarker of caloric intake.

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

HALLO Pilot Study Measurements	Phone screen	Screening visit 1	Screening visit 2	Baseline visit 1	Baseline visit 2	Inter-vention	6-month visit	Inter-vention	9 month visit 1	9 month visit 2
Visit Code	TSI	SV1	SV2	BV1	BV2	INT	FV1	INT	FV2	FV3
Screening & safety assessments										
Phone screen/phone consent	x									
Screening visit: Informed consent/HIPAA form, demographics, CES-D. Montreal Cognitive Assessment (MoCA), Binge Eating Disorder Screener-7, Readiness to change survey		x							CES-D, MoCA	
7-day behavioral and technology run-in			x							
Vital signs (height/weight/BP/pulse/waist circumference)		x					x		x	
Medical history and medications		x								
Blood lipids, HbA1c, CMP, CBC, TSH		x							x	
Extra tube of blood (SST) for instrument QC		x								
DXA body composition (whole body) / bone density (hip, lumbar spine)		x							x	
Medication Updates/Health Status Updates			x	x	x	x[#]	x	x[#]	x	x
Siteman cancer online risk assessment & Cancer Screening Questionnaire							x			
Intervention process and adherence measures & feasibility/acceptability										
Total energy expenditure (TEE; doubly-labeled water)				dose / collect urine	collect urine				dose / collect urine	collect urine
Physical activity energy expenditure (PAEE; ActivPAL)				dis-pense	return				dispense	return
Continuous glucose monitoring (CGM)*						x		x		

HALLO Pilot Study Measurements	Phone screen	Screening visit 1	Screening visit 2	Baseline visit 1	Baseline visit 2	Inter-vention	6-month visit	Inter-vention	9 month visit 1	9 month visit 2
Questionnaires/Computerized Task: Power of Food Scale; Weight Efficacy Lifestyle Questionnaire; Food Craving Inventory; SF-36; Perceived Stress Scale; PROMIS 13a Fatigue Scale; Pittsburgh Fatiguability Scale; Pittsburgh Sleep Quality Index; PROMIS Interest in Sexual Activity; Emotional & Uncontrolled eating; Walking Self-Efficacy; Delayed Discounting, STOP & Epworth Sleepiness questionnaires				x					x	
Night Eating Assessment				x						
Ecological momentary assessments (EMA) of hunger, desire to eat, and anxiety by study Companion App, Fitbit physical activity monitor, Body Trace smart scale^, App-based dietary tracking^						x		x		
Interview: Positive/Negative Outcomes Associated with CR and TRE, Closeout Survey										x
Clinical/biological outcomes										
Resting energy expenditure (REE)				x					x	
Biomarker assays				x			x		x	
Biological sample storage including blood and urine				x			x		x	
D3 creatine dilution (d3cr)				x					x	
Physical performance/strength: Expanded Short Physical Performance Battery (eSPPB) / expanded SPPB, 400 meter walk (fast), grip strength					x					x
24-hour dietary recalls (ASA24)				x					x	

*- TRE only – at ~3mo (weeks 8-12) and ~8 months (weeks 28-32)
^- CR only
[#] Commons signs and symptoms will also be assessed monthly during intervention at the individual sessions.

6.2 Description of Evaluations

Study evaluations include: 1) assessments of eligibility (Telephone screening interview, Screening Visit 1 and Run-In/Screening Visit 2) and safety (queried at each clinic visit and monthly during intervention), 2) outcome assessments (conducted during two baseline visits, a 6-month follow-up visit, and two 9-month follow-up visits), and 3) assessments of adherence (collected during intervention) according to the schedule in Table 6.1. Details about each evaluation are below. We will follow the above table as best we can but may need to adjust the visit schedule depending on availability of staff, equipment, etc.

6.2.1. Screening Visit 1 (SV1). Participants who remain eligible for the study following the phone screening will be scheduled for an in-person Screening Visit to continue assessing the study inclusion/exclusion criteria. Participants will be asked to fast for at least 10 hours the night before this visit and will first sign consent prior to any study measures consisting of the following:

- Vitals (height, weight, BP, pulse, waist circumference)
- Readiness to change survey indicating they are willing to change behavior and comply with intervention
- Blood draw for lipids, comprehensive metabolic panel (CMP), complete blood count (CBC), thyroid stimulating hormone (TSH), HbA1c, and blood for biomarker instrument quality control (20ml or ~1 Tbsp)
- Snack, then whole body, hip, and lumbar spine DXA for body composition and bone density measurements
- Medical history and medications will be ascertained via self-report.
- Questionnaires including the following: demographics, Center for Epidemiological Studies Depression (CES-D), Montreal Cognitive Assessment (MoCA), and the Binge Eating Disorder Screener-7

If blood chemistries, bone densitometry, or any other items measured at the screening visit are exclusionary, the participant will be contacted by the study staff and excused from the study with referral to a health care provider if necessary. Testing may be repeated on a case-by-case basis for re-evaluation.

6.2.2. Screening Visit 2 (SV2) / Run-in evaluation. All participants who remain eligible for the study following the SV1 will be scheduled to return for a visit to begin the process of a behavioral run-in. During this visit, participants will be provided with a BodyTrace cellular-enabled scale and an iPad tablet computer. Participants will receive a self-efficacy-based orientation designed to develop confidence in the use of each tool, and will practice weighing using the scale and logging their foods and beverages onto a paper food record. They will be asked to place the scale on a hard and even surface and to weigh daily for 7 days. During this same 7-day period they will also be asked to record the type and amount of food and beverages consumed and document the start and stop time of all foods and beverages each day on a paper log. Participants are asked to take a picture of their paper log and email it to the study team after completing their 7th day to help the assessors determine eligibility prior to their next visit. Participants will receive a "frequently asked questions" handout containing key information for each tool and will receive a follow-up call on the first day of the assessment window (i.e., the

day following SV2) to ensure the participant is able to use the technology and food record. Successfully completing the behavioral run-in will be marked by: 1) completing at least five daily weights, 2) completing five full days of food logging as determined by the study staff and 3) eating at least an average of 11 hours each day.

We will assess for any potential adverse events / change in medical history and medications at this visit as well.

All eligibility will be verified before scheduling or conducting Baseline Visit 1.

We will provide the participant with a tablet with 30mg of d3-creatine and instructions on when to take it 72-144 hours prior to their baseline visit 1. Urine is collected with the participant fasting at their baseline visit 1. Deidentified samples will be sent to Dr. Evans's laboratory at University California, Berkeley where labeled creatinine will be assayed.

6.2.3. Baseline Visits 1 and 2. Following confirmation of meeting all eligibility criteria and after approval to participate from the study clinician or his/her designee, there will be two baseline study visits. The two visits will be conducted after approximately 10-15 days, but ideally between 12-14 days apart to allow for the follow-up collection of urine for the TEE measurement.

Baseline Visit 1 (BV1) evaluation procedures include the participant coming in fasting for the following:

- Blood draw (completed after the REE) and urine collection for biomarker assays and biospecimen archive:
    - Venous blood samples will be collected in the morning following a fast of at least 10 hours. Total blood volume collected is estimated at 69.5 ml (~5 Tbsp) at baseline, including:
        - Serum
        - plasma (EDTA and plasma citrate)
        - whole blood in ACD or CPT tubes for cell and DNA isolation
        - blood in RNA stabilizer tube
    - Urine will be collected per doubly-labeled water assessment of energy expenditure as well as for storage (pre-dose urine will be stored) and for the d3cr.
- Biomarker assays. We will measure pre-specified blood-based biomarkers including but not limited to: fasting insulin, interleukin-6 (IL-6), tumor necrosis factor soluble receptor I (TNFRI), cystatin C, and CRP from serum. Additional biomarkers may be measured using serum, plasma, or urine. This panel will be expanded to include additional biomarkers supported by the NCI supplement and includes the Luminex Performance Human XL Cytokine Panel - NEW (25-Plex) FCSTM18B-25
- DNA methylation biomarker. Cells and blood will be collected for DNA/RNA isolation and molecular measures such as DNA methylation. However, there is no plan to use DNA for genome sequencing; the anticipated use is to measure DNA

CpG site methylation for a biomarker of "epigenetic age" and another candidate aging biomarker, telomere length.

- Biospecimen archive. Serum, plasma, citrate plasma, urine, whole blood, and urine will be collected and stored for use in future ancillary studies. After processing, aliquots will be stored at -80ºC or liquid nitrogen until analyses.
- Total Energy Expenditure (TEE) will be assessed using doubly labeled water. This method, which provides the most accurate assessment of free-living daily energy expenditure, is based upon the principle that oxygen atoms in body water and exhaled carbon dioxide are in equilibrium. Oxygen atoms are eliminated from the body as both water (H_2O) and exhaled carbon dioxide (CO_2), whereas hydrogen atoms are eliminated as water only. The difference between the elimination rates of oxygen and hydrogen from body water represents a measure of carbon dioxide flux, which is proportional to total energy expenditure.

  Participants will provide a baseline urine sample after which they will consume a DLW dose which will provide approximately 2.2 g 10% H_2 18O per kilogram total body water and 0.14 g per kilogram total body water of 99% 2H2O. After consuming the DLW dose, participants will be instructed to lay quietly for approximately 20-30 minutes before initiating the resting energy expenditure test after which further urine samples will be collected approximately 4.5 and 5 hours after dosing, while any urine voids before 4.5 hours will be discarded. Two aliquots of each urine sample will be placed in pre-labeled tubes, stored in freezer boxes at -80°C and shipped in batches to Dr. DeLany's lab at the Advent Health Orlando, Translational Research Institute in Florida for analysis.
- Resting energy expenditure (REE) will be measured in the morning after at least a 10-hour fast using indirect calorimetry (MCG Diagnostics, St. Paul, MN).
- Physical activity energy expenditure (PAEE), including light and moderate to vigorous physical activity as well as sedentary behavior, will be objectively assessed over approximately a 10-15-day period using the ActivPAL™ accelerometer (PAL Technologies, Glasgow, Scotland).
- Dietary intake: 24-hour Dietary Recalls (ASA24) - Three 24-hour dietary recalls (two weekdays and one weekend day) will be collected on all participants. Participants will be asked to recall and report their dietary intake (foods and beverages) from the previous day's 24-hour period. Participants will complete the first of their 24-hour dietary recalls during the visit and then be prompted to complete 2 additional 24-hour dietary recalls on their own using the study-provided tablet prior to Baseline Visit 2. Data will be collected and nutrients and food groups analyzed using the publicly available National Cancer Institute's Automated Self-Administered 24-Hour (ASA24) dietary assessment tool (https://epi.grants.cancer.gov/asa24).
- We will assess for any potential adverse events / change in medical history and medications at this visit as well.
- Questionnaires

- Power of Food Scale assesses an individual's drive to consume palatable food in an obesogenic food environment (90).
- Weight Efficacy Lifestyle Questionnaire assesses participants' confidence in their ability to self-regulate eating behavior in the face of common barriers (69).
- Perceived Stress Scale assesses how uncontrollable and stressful life has been over the past week or month (91).
- Walking Self-Efficacy assesses participants' perceived ability to walk certain lengths of time at a moderate pace without stopping (92) .
- Quality of Life will be assessed using the *Short Form-36 Health Survey (SF-36) (93)*.
- Delayed Discounting assesses participants' ability to delay seeking immediate rewards of less value for longer-term rewards of greater value—delay of gratification (94).
- Food Craving Inventory & Emotional & Uncontrolled Eating(95)
    - An abbreviated emotional and uncontrolled eating questionnaire assesses participants' degree of emotional eating and/or eating in which they feel as though they have lost control.
- Three sleep/fatigue questionnaires will be administered: 1) *PROMIS 13a* (FACIT – Functional Assessment of Chronic Illness Therapy) Fatigue Scale (96); 2) *Pittsburgh Fatigability Scale (97); and 3) Pittsburgh Sleep Quality Index (98)*
- Libido will be assessed using the ***PROMIS Interest in Sexual Activity*** questionnaire (99).
- Participants who self-report ≥2 episodes of Night Eating during the 7-day run-in are identified for potential exclusion due to the night eating syndrome (NES). Participants who do self-report ≥2 episodes of night eating, are contacted for phone for additional follow-up. Specifically, participants are told that we would like to verify and expand upon information that was provided via the run-in food record data. Using an interview format, participants are queried about night eating using the Night Eating Questionnaire (NEQ) (116).
- Sleep apnea risk will be assessed using the *STOP Questionnaire* (100).
- Sleepiness will be assessed by using the Epworth Sleepiness Scale that assesses how likely someone is to doze off or fall asleep in different situations (101).

Baseline Visit 2 (BV2). After approximately 10-15 days, the participant will come to the clinic and will return their ActivPal. Two urine samples will also be collected, at least 30 mins apart, to complete the DLW test for the TEE calculation. At this visit, the participant will be instructed

not to change anything about their diet or exercise behavior prior to the intervention starting. We will also perform the following physical performance/strength tests:

- The Short Physical Performance Battery (SPPB) is a widely used assessment of lower extremity physical function which includes progressively more challenging standing balance tasks held for 10 seconds each (side-by-side, tandem and semi-tandem), the faster of two 4-m walks to assess usual gait speed, and time to complete 5 repeated chair stands. Each of the three performance measures is assigned a score ranging from 0 (inability to do the test) to 4 (the highest level of performance) and summed to create an SPPB summary score ranging from 0 (worst) to 12 (best) (102). We will also administer the components of the ***expanded Short Physical Performance Battery (eSPPB)*** which was modified from the original SPPB to increase the holding time of the semi- and full-tandem stands to 30 seconds and add a single leg stand and a narrow walk test of balance (walking at usual pace within lines of tape spaced 20 cm apart) (103).
- The fast 400 meter walk is a walking-based test of exercise tolerance and aerobic fitness. Participants are instructed to walk 400 m (10 laps of a 20-m course) on a flat indoor surface as quickly as possible at a maintainable pace and the time to complete the walk is recorded in minutes and seconds (103).
- Grip strength will be measured twice in each hand using an isometric hydraulic hand dynamometer (Jamar, Bolingbrook, IL). Participants will be excluded from performing the test if they report hand-pain or recent hand or wrist surgery.

We will assess for any potential adverse events / change in medical history and medications at this visit as well.

6.2.4 Randomization Procedure

Participants will be randomized after attending their Baseline Visit 2 according to the block (by sex) randomization scheme developed by the study statistician. An unblinded study staff member will call the participant and, after reconfirming their willingness to be randomized, will inform them of their group assignment and their planned intervention start date and time. Randomization date will be documented and will occur within approximately 12-16 weeks of the initial Screening Visit, but within approximately 4 weeks of their intervention start date.

6.2.5 Six-month Follow-up Visit 1 (FV1)

There will be one interim follow-up visit after approximately 22-26 weeks of intervention for each group. All assessments during this visit will be conducted by assessors blinded to the randomized group assignment of the participant. Participants will come in fasting and will have the following assessments:

- Vital signs and waist circumference
- Blood for archival storage and the expanded 25 panel biomarker assessment funded through the NCI supplement. Venous blood samples will be

collected in the morning following a fast of at least 10 hours. Total blood volume collected is estimated at 36.5 ml (~2 Tbsp), including:

- serum
- plasma (EDTA and plasma citrate)

- Urine Collection for storage
- Siteman online cancer risk assessment (117) & Cancer Screening Questionnaire (Both may be done at a later visit or by phone for those who have completed all visits).

6.2.6 Nine-month Follow-up Visits 2 and 3

There will be two follow-up evaluation visits after approximately 34-40 weeks of intervention for each group. All assessments during these visits will be conducted by assessors blinded to the randomized group assignment of the participant.

9-Month Follow- Visit 2 (FV2) - Fasting

- Vital signs with waist measurement
- Blood lipids, insulin, HbA1c, CBC, CMP, HbA1c, TSH
- Fasting blood draw and urine collection for biomarker assays, DLW, d3cr and biospecimen archive: see Baseline Visit for detail, but with lower sample volume for archive. Total blood volume collected is estimated at 85.5 ml (~6 Tbsp), including:
  - serum
  - plasma (EDTA and plasma citrate)
  - whole blood in ACD or CPT tubes for cell and DNA isolation
  - blood in RNA stabilizer tube
- Resting Energy Expenditure
- 24-hour Dietary Recalls (ASA24)
- Doubly-labeled water (DLW Dosing) and urine collection for TEE
- Physical activity energy expenditure using ActivPAL
- DXA (Whole Body, Hip & Lumbar Spine)
- CES-D
- MoCA
- Power of Food Scale
- Weight Efficacy Lifestyle Questionnaire
- Perceived Stress Scale
- Delayed Discounting
- Food Craving Inventory & Emotional & Uncontrolled Eating
- Walking Self-Efficacy
- SF-36
- PROMIS 13a (FACIT) Fatigue Scale, Pittsburgh Fatigability Scale, and Pittsburgh Sleep Quality Index
- PROMIS Interest in Sexual Activity questionnaire
- Interim Medical Events / Adverse Events
- STOP Questionnaire

- Epworth Sleepiness Scale

9-Month Follow-up Visit 3 (FV3): Final Evaluation

- Final Medical Events / Medication Updates / Adverse Events
- Doubly-Labelled Water (Final Urine Collections)
- Physical Activity Energy Expenditure (Return of ActivPAL device)
- Short Physical Performance Battery (and expanded SPPB)
- Fast 400 meter walk
- Grip strength
- *Participant evaluations of CR or TRE*. We will ask participants to list any positive or negative outcomes that they associate with either the CR or TRE intervention. Participants are limited to identifying a maximum of 5 outcomes in each category (they can report none). For each outcome listed, they are asked to rate how important each one was to either adhering or not adhering to the goals of the intervention.
- *Participant Satisfaction.* Participants will be asked to rate a series of questions using a Likert scale and complete a series of open-ended questions assessing the acceptability of each key intervention component they received using questions modeled on our previous work and will assess their willingness to continue the intervention for longer durations (i.e., 4yrs).

We may contact some or all participants roughly one year after the end of their participation to ask about their weight and if it's changed in the last year. This will be optional for participants and will not be considered outcome data.

6.2.7 Assessments conducted during intervention:

- *Continuous Glucose Monitoring*. Continuous glucose monitoring (CGM) will assess time in the fasting state in the TRE group using a continuous glucose monitor (G6 Pro, Dexcom) at approximately 3 months (weeks 8-12) and 8 months (weeks 28-32). The CGM records interstitial glucose concentrations every 5 minutes for up to 10 days and will be in blinded mode so the participant cannot see their values. Although it measures glucose levels in the interstitial fluid – and not blood glucose levels – it has been demonstrated to be accurate in the comparison with capillary blood glucose results with the correlation between CGM and capillary blood glucose results of 0.95 (104, 105). The CGM is placed on the lower abdomen using a one-touch applicator by an unblinded study staff member.
- *Ecological Momentary Assessments of Hunger, Desire to eat and Anxiety* (6 assessments during 7 days of months 1, 4 and 7): Within the mHealth *Companion App* we will prompt participants to complete six brief (<60 seconds) ecological momentary assessments (EMAs) each day (waking, late morning, lunch, afternoon, dinner, bedtime) of hunger, desire to eat, and anxiety during 7 days of months 1, 4 and 7. Participants note their hunger in response to the question "to

what extent are you hungry right now?", with responses ranging from "no hunger" to "extreme hunger". Participants note their desire to eat in response to the question "to what extent do you have a desire to eat right now?" with responses ranging from "no desire" to "extreme desire". Anxiety will be rated in response to the question "how anxious do you feel right now?" with responses ranging from "no anxiety" to "extreme anxiety". All responses are provided using a slider with values (which are hidden to the participant) ranging from 0-1000 to simulate a continuous slider.

7 SAFETY ASSESSMENTS

The safety of HALLO-P's participants is of paramount importance and will be monitored upon enrollment in the study. Enrollment starts after a participant gives verbal consent to be phone screened. The HALLO-P interventions are generally regarded as safe, as the entry criteria are based on the public health-based indications for weight loss.

Nevertheless, the study's entry criteria are designed to screen-out those for whom CR or TRE may have potentially adverse effects. These include: a history of eating disorders, moderate - severe anemia, uncontrolled hypertension, uncontrolled thyroid disease, osteoporosis, a high risk of fracture, and uncontrolled diabetes.

7.1 Specification of Safety Parameters

Exclusion due to potential safety concerns:

- Osteoporosis (self-report, osteoporosis medication, or DXA t-score ≤ -2.5 on total hip and/or femoral neck scan)
- Self-Report of Type 1 diabetes, use of insulin
- Self-Report of a new diagnosis of Type 2 diabetes (within one year) or newly discovered (elevated HbA1c ≥ 6.5 at screening), use of some medications used to treat diabetes or HbA1c >7.5%

Exclusions for Conditions associated with dietary management that might conflict with a study intervention. These can be rechecked two weeks later if needed to confirm exclusion.

- Uncontrolled hypertension (>160 systolic OR >100 mmHg diastolic)
- Dialysis or abnormal kidney function (eGRF <30 mL/min/1.73 m^2)
- Liver disease or abnormal liver function (ALT levels 2 times above normal)
- Moderate-Severe anemia (Hb <11g/dL)
- Potassium or sodium above or below normal limit
- Uncontrolled thyroid disease (hypo/hyper) or requiring recent (past 3 months) adjustments in thyroid hormone supplementation or TSH <0.45 or >4.5 uIU/mL

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

All participants will be queried for safety events at each assessment visit after the screening visit, and on a monthly basis during intervention at the individual sessions. Both open-ended questions and pre-defined questions of symptoms relevant to common risks of the assessments and

interventions will be asked. All AEs reported to study staff (including those not discovered during the monthly queries) will be recorded using the study's Adverse Event Reporting Form.

AEs and SAEs will be coded and summarized using MedDRA coding and intervention group, with the number of participants and percentage reporting the event. The study investigators, except for Dr. Miller and Ard, will be blinded to review of AEs/SAEs by intervention group. Drs. Miller and Ard will review AEs on a quarterly basis and the study mPIs will review AEs blinded to intervention status.

7.3 Adverse Events and Serious Adverse Events

All participants will be queried at each assessment visit regarding any change in health or physical status using the Health Status Questionnaire and any AEs will be reported using the IRB-approved Adverse Event Reporting form and the running medication log will be updated, as needed. Expected events (signs and symptoms) will be assessed monthly by unblinded interventionist. All AEs reported to study staff, including unsolicited AEs (not including those discovered during the monthly queries) will be recorded using the study's Adverse Event Reporting Form. Study staff will try to match-up unsolicited AEs with events reported per scheduled assessment. Those that do match will be handled through the routine system will be followed and flagged, and reported separately when AEs are summarized. A summary of the expected AEs will be reported from the signs and symptoms questionnaire, but an AE form and evaluation is not required for these common events.

The AE form includes a section for classifying the AEs: 1) Severity, 2) Expectedness (Expected—event is known to be associated with the intervention or assessment activity or Unexpected—not expected or consistent with known information regarding the activity), and 3) Relatedness to the study intervention (Definitely Related, Possibly Related, or Not Related).

Double capture of AEs (e.g., a participant providing an unsolicited report and a second report of the same event at an ascertainment visit) is identified through assigning unique event numbers to AEs, which are then used to link repeated reports within the data capture system. Filtering out of repeated capture of the same event is done during report generation

7.3.1 Adverse Event (AE): Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. These will be assessed at each clinic visit and monthly during intervention

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, qualified medical professional's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

7.3.2 Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Is another condition which investigators judge to represent significant hazards

7.3.3 Unanticipated Problem (UP): Any incident, experience, or outcome that meets all of the following criteria:

- unexpected, in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.4 Severity of Event

All Adverse Events will be classified according to severity according to the following:

• Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

• Moderate: Events that introduce a low level of inconvenience or concern to the participant and may interfere with daily activities but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

• Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

7.3.5 Expectedness

All AEs will be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol and include:

• Unexpected - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.

• Expected - event is known to be associated with the intervention or condition under study.

7.3.6 Relationship to Study Intervention

The study's physician or medical officer will assess the relationship of all AEs to study intervention or study participation. Based on clinical judgement and complete description of the event he will determine if the event is:

- *Definitely Related* – The adverse event is clearly related to the investigational agent/procedure – i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- *Possibly Related* – An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

- *Not Related* – The adverse event is clearly not related to the investigational agent/procedure - i.e., another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

7.4 Reporting Procedures

Any major AE, i.e., any serious injury, including all SAEs, will be recorded and reported to the mPIs immediately after completing any and all actions that are necessary to protect the subject's health and safety. Minor AEs will be recorded and reported to the PIs on at the regular PI meetings. A description of the event, and the date and location of the event will be recorded on the AE Reporting Form, which will be kept in the participant's research file. The mPIs and the Study Physcian (Dr. Ard) will meet quarterly to review all reported events and these will be compiled and reported in aggregate to the DSMB.

Within 48 hours of notification of any SAE that is unexpected and related (death within 24 hours), the contact PI (Dr. Kritchevsky) will report the event to the WFSM Institutional Review Board (IRB), the NIH Program Officer and the Chair of the DSMB through channels specified by the NIH or its contractors.

Any unanticipated problem involving risks to study participants or others will be reported within 48 hours to the NIA and will be forwarded to OHRP within two weeks of the event.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study staff will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation, with follow-up of any active events. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.5 Safety Monitoring

Safety will be monitored by an NIA appointed Data and Safety Monitoring Board (DSMB). The DSMB will act in an advisory capacity to the NIA Director to monitor participant safety, data quality and progress of Nutritional Interventions Planning Project. Meetings of the DSMB will be held regularly (e.g., every six to nine months) at the call of NIA or the DSMB Chair. The NIA staff will be present at every meeting. An emergency meeting of the DSMB may be called at any time by the Chair or the NIA, should participant safety questions or other unanticipated problems arise.
DSMB meetings will consist of open, closed and optional executive sessions, all closed to the public because discussions may address confidential participant data. The study PI and key staff members, DSMB members and authorized NIA staff attend the open sessions. Discussions at these sessions focus on the review of the aggregate data, conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered. Data by treatment group are not presented in the open session.

The closed session will be attended by unmasked study staff, the DSMB members and the NIA PO or designee, but not by the NIA Project Scientist(s). The NIA PO attends the closed and open sessions as an observer, not as a DSMB member, to answer any policy or administrative questions the DSMB members may have. The primary objective of the closed sessions is to review data by study group. To ensure participants safety and well-being, DSMBs for NIA-funded trials are usually required to review safety data by the actual treatment group. The timing of unmasking of the treatment groups is determined by the DSMB. In many instances, safety data could also be the outcome data. Therefore, the unmasked Boards no longer review and provide recommendations to NIA on any, but safety-related protocol changes. All other protocol modifications are subject to review by the masked working groups of the DSMBs. DSMBs' working groups are appointed by NIA and provide their recommendations to NIA Director who makes decisions about whether to approve or decline proposed modifications.

If necessary, an executive session may be requested by the DSMB and will be attended only by voting DSMB members. The NIA Program Officer or designee is not permitted to attend the executive sessions.

8 INTERVENTION DISCONTINUATION

There are no specific events that would lead to intervention discontinuation.

Participants may temporarily discontinue participation due to intercurrent illnesses. In this case, participants will be asked to restart the intervention upon clearance from their primary care provider.

Participants may withdraw voluntarily from participation in the study at any time and for any reason. Participants will continue to be followed, with their permission, even if the study intervention is discontinued. These participants will be invited to participate in the 6-month and 9-month visits.

Participant who drop from the study after randomization will not be replaced.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

As suggested by multiple authors (106-108), the design and sample sizes for our HALLO pilot study have been chosen to focus on the feasibility of the design of the targeted full-scale study, rather than on power for hypothesis testing between groups.

During the HALLO pilot, we target the enrollment of approximately 100 participants meeting the inclusion/exclusion criteria to one of three intervention arms 1) 20% CR delivered in-person; 2) 20% CR delivered remotely via video conferencing; and 3) 8-hour TRE with *ad libitum* calorie intake for the first 3 waves (66pts) and the fourth wave will randomize ~24 pp to one of two intervention arms including 20% CR delivered remotely and 8-hour TRE groups. We anticipate randomizing 22:34:34 participants with fewer participants being in the in-person CR group since our group (and others) has more experience with that intervention. From those randomized, we anticipate approximately 20:30:30 participants to complete both pre-and post-measures at 9 months. Data from the enrollment process will be used to refine recruitment criteria, estimate recruitment yields, and test and refine intervention approaches. The pilot will inform three design benchmarks: **a)** The degree of sustained CR **(Benchmark 1):** CR > 10% at 9 months; **b)** TRE sustainability **(Benchmark 2):** At least 75% of participants eating within window on >80% of days; and **c) Benchmark 3**: Retention > 85% at 9 months.

9.2 Sample Size and Randomization

Sample sizes for each group in the pilot study were determined by focusing on the width of 90%, one-sided confidence intervals, as used previously for pilot projects (109). For **Benchmark 1**, the 20% CR interventions will be considered successful if the mean reduction in DLW-assessed weight-maintaining energy intake (EI) provides evidence that the %CR is >10% of the baseline mean (e.g., >200 kcal/day reduction from 2000 kcal/day). This level was chosen because it is approximately the lower end of the range of CR associated with benefits in animal models. Our **primary outcome** will be absolute rather than relative EI change to avoid the loss of efficiency and power from the direct modeling of ratio measures (110, 111). Analyses will be based on constrained, mixed linear models described in Section 9.5. The primary quantity of interest is whether each group's least squares mean EI one-sided 90% lower confidence interval excludes the mean value for an average 10% reduction in caloric intake based on the mean baseline EI.

Benchmark 1. Within the remote CR group with ~30 paired observation (i.e., 10% LTFU), and a conservative SD of 250 kcal/day for change in EI, as calculated from CALERIE, we project a 90%, one-sided confidence intervals will have a lower bound excluding 200 kcal/day (a 10% reduction from a baseline mean of 2000 kcal/day) if we observe a 260 kcal/day or greater reduction (a 13% reduction). In a case where the baseline mean intake is 2500 kcal/day, a 310 kcal/day reduction (12.4%) would result in a confidence interval that excludes a 10% reduction in EI (112). With 20 evaluable participants in the in-person CR group, these percentages increase to 13.7% (for a baseline mean of 2000 kcal/day) and 13% (for a baseline mean of 2500 kcal/day). Note that these calculations assume the ICC capturing the dependence of change in EI resulting from group-based interventions is zero. Should the ICC arising from group-based intervention delivery be large enough to inflate the variance of the within-group mean by as much as 10%, a slightly larger observed decrease in EI will be needed to rule out a 10%

reduction. If the target is met for both CR groups, practical and economic considerations will be considered in developing the intervention for the larger trial.

Benchmark 2. We will estimate the proportion of individuals consuming calories within the 8-hour window (+/- 30 min) on 80% of days (i.e., each participant will receive a yes/no categorization as to whether they consumed calories within the window on > 80% of days) based on participants' self-report of first and last meal/snack times. If feasible, this calculation will also be performed using data from continuous glucose monitors. If ≥75% of individuals are compliant at this level, we consider it reasonable to consider that TRE within the window chosen could be sustained for a longer-term trial. With N=30 participants in this group, if the observed sample proportion is 87% or above, the lower bound on the Clopper-Pearson exact 90%, one-sided confidence interval will exclude retention values of 75% or below (112). Here again, in the presence of a positive ICC for TRE 8-hour adherence, there will be an inflation in variance of the mean which will translate into needing observed sample proportions > 87% to exclude a value of 75% or below.

For **Benchmark 3**, we target ≥85% retention in each intervention group based on completion of the 9-month follow-up exam. If the observed sample proportion is 90% or higher (N=81/90), Clopper-Pearson exact 90%, one-sided confidence interval will exclude retention values of 85% or below. In the presence of a large, positive ICC for dropout, there will be an inflation in variance of the mean which will translate into needing an observed proportion > 90% to exclude values of ~85% or below.

9.2.1 Treatment Assignment Procedures

The randomization protocol and the randomization process are prepared and executed by investigators from the Biostatistics and Design Team through the secure web-based data management system, so that eligibility is automatically confirmed, and records are current. The study statisticians have developed the randomization protocol to ensure that sufficient baseline and eligibility data are entered and validated before participants are randomized into the study.

Randomization will be performed stratified on sex, and will use blocked randomizations. Recruitment will target equal numbers of men and women and 23% minority participation. All study personnel, except for the Biostatistics Team will be blinded to the randomization table. We do not anticipate the need to break the randomization code with any urgency, but should it be necessary, it will be decided by the four PIs, with input from the NIH Project Officer. The Study Physician and/or Medical Safety Officer will review descriptions of safety events in an un-blinded manner.

9.3 Interim analyses and Stopping Rules

No formal stopping rules are planned for this pilot study. Interim analyses on data quality and safety will be provided to the DSMB. Safety data will be provided by randomized group to the DSMB in a closed session.

9.4 Outcomes

9.4.1 Primary feasibility outcomes

a) Degree of sustained CR **(Benchmark 1):** CR > 10% at 9 months;

b) TRE sustainability **(Benchmark 2):** At least 75% of participants eating within window on >80% of days; and
c) Retention of study participants **(Benchmark 3)**: Retention > 85% at 9 months.

9.4.2 Secondary outcomes

Secondary

- Body weight change assessed using home scales at baseline, 6 and 9 months
- Changes in fat and lean body mass assessed by DXA at baseline and 9 months
- Change in bone mineral density assessed by DXA at baseline and 9 months
- Change in resting energy expenditure assessed by indirect calorimetry at baseline and 9 months
- Change in physical activity energy expenditure assessed by ActivPAL at baseline and 9 months
- Change in energy intake assessed at baseline and 9 months using doubly-labeled water
- Change in total muscle mass at baseline and 9 months assessed by d3 creatine (d3cr)
- Change in self-reported energy intake assessed using the ASA24 at baseline and 9 months
- Change in physical and cognitive function assessed at baseline and 9 months
- Change in age-related biomarkers at baseline and 9 months

HALLO-P will also collect the following information to guide the design of a longer-term study.

HALLO-P Feasibility Benchmarks

- Community Interest – Response rates to mailings and other outreach
- Recruitment Yields – Ratio of initial contacts to randomizations
- Participants with Inter-current Health Events – Health events that suspend intervention participation
- Intervention Delivery Costs – fixed and variable costs associated with each intervention arm

9.5 Data Analyses

9.5.1 Primary Feasibility Analyses.

Our **primary feasibility outcome (Benchmark 1)** will be absolute rather than relative Energy Intake change to avoid the loss of efficiency and power that has been criticized relative to the direct modeling of ratio measures (110, 111). The primary analyses of DLW-based EI will use constrained mixed linear models (cLDA), with both baseline and follow-up values as model outcomes, to estimate within-group pre-post changes in EI, with group assignment as the primary variable of interest, adjusted for sex (113). We note that the constrained, linear mixed model is extremely flexible, constrains pre-randomization group means to be equal, allows for both intent-to-treat analyses by including participants with incomplete data, and permits inclusion of random effects related to group-based interventions; the traditional ANCOVA can be shown to be one specific parameterization of this model. Kenward et al. (114) note that with proper use of REML

estimation, the constrained, mixed model and ANCOVA are equally efficient (115). Lu (2010) notes that for within group estimation, which is a focus of this pilot study analyses, the ability to include participants with partial data can have advantages relative to reducing bias due to missing data (113).

From these models, the primary finding of interest is whether each group's least squares mean EI one-sided 90% (80%) lower confidence interval excludes the mean value for an average 10% reduction in caloric intake at 9-months based on the mean baseline EI. In addition, using results from this model, we will estimate percent change in EI with a bootstrapped 90% (80%) one-sided confidence interval to provide direct estimates of the relative reduction. Because participants are "grouped" for a component of each intervention, intra-class correlations will be estimated to characterize the dependence of response within intervention groups. Sensitivity analyses will be performed to determine how the width of confidence intervals may depend on the ICC and these analyses will be performed within all randomized groups.

For **Benchmark 2**, we will use Clopper-Pearson 90% (80%), one-sided confidence intervals to provide a lower limit on the estimate of the proportion of individuals consuming calories within the 8-hour (+/- 30 min) window on 80% of days (i.e., each participant will receive a yes/no categorization as to whether they consumed calories within the window on > 80% of days) based on self-report. Marginal models for binary outcomes will also be used to explore the magnitude of the ICC for this outcome. This calculation will also be performed using proportion of days as a continuous outcome based on self-report or data from continuous glucose monitors (TRE group). When considered a continuous outcome, methods identical to those outlined for Benchmark 1 can be used.

For **Benchmark 3**, the primary outcome will be the proportion of participants that complete the 9-month follow-up exam. As for Benchmark 2, Clopper-Pearson exact 90%, one-sided confidence intervals will be used to put lower limits on these estimates. Marginal models for binary outcomes will also be used to explore the magnitude of the ICC for this outcome.

Supporting analyses will also be carried out within subgroups defined by sex and race/ethnicity.

9.5.2 Analysis of Secondary Outcomes

The secondary outcomes listed in Section 9.4.2 have continuous distributions. Accordingly, we will use linear, mixed effects models to explore both between and within-group effects. Longitudinal trends will be investigated for measures such as: in-home body weights, patterns CGM, self-reported daily energy intake, and steps per day. Other important secondary analyses will focus on daily access to the intervention app and trajectories of adherence and engagement in the app as it relates to change in body weight and biomarker endpoints. Residuals will be examined for each outcome and should distributions be deemed not to be normal, appropriate transformations to normality will be sought.

9.5.3 Safety Analyses.

In general, between-group differences in the proportion of participants with AEs will be compared between groups using either chi-square or Exact Tests (when expected cell counts are small). The proportion of participants with other adverse experiences are estimated within intervention groups and expressed as relative effects via risk ratios (95% CIs), or as absolute effects (95% CIs) for between-treatment differences in proportions. Continuous safety measures

will be compared among groups using analysis of variance and 95% CIs. Withdrawals due to SAEs will be summarized by MedDRA code by intervention group.

The exact presentation of analysis results for safety are developed in collaboration with the DSMB. No adjustment for multiplicity is planned for pre-specified safety endpoints.

9.5.4. Other analyses helpful in planning future longer term studies.

Additional exploratory analyses will use a variety of analytical techniques to examine: (a) the distribution of changes over time in potential outcomes that may be used as part of a composite outcome in the larger study, (b) how adherence characteristics of TRE are associated with weight change, (c) agreement and potential biases between energy intake targets obtained by initially estimating energy intake necessary for a 20% CR through use of DLW versus based upon using REE and an activity level factor specific to sedentary older adults (or based on observed baseline ActivPAL data) (d) associations between actual weights and expected weights based on the trajectory-based model of the relationship of weight loss to energy intake restriction, and factors associated with discrepancies, and (e) measurement properties (e.g., test-retest reliability, variability in time-course within controls) of selected biomarkers (e.g., of IL6, CRP, TNFR1, Cystatin C, insulin levels).

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data on eligibility, study outcomes and other clinical assessments will be collected by the clinical research staff of the Sticht Center for Health Aging and Alzheimer's Prevention as overseen by the clinical research team. This staff will be blinded to group assignments. Data collection forms can be found in the study MOP. Participant contact information and other PHI will be stored in a secure location that is separate from study data.

10.2 Data Management

HALLO-P will use the World Wide Web to enter participant data.

10.2.1 Clinical Site Responsibilities. The single clinical site will maintain appropriate medical and research records for this study, in compliance with federal regulatory and institutional requirements for the protection of confidentiality of participants. The clinical site will also maintain documentation that all members of the research team have completed training requirements. Data collection is the responsibility of the clinical site staff under the supervision of Dr. Nicklas, who will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data are collected in multiple ways at all participant contacts, including electronic CRFs (**eCRF**) or hard copy CRFs, mHealth app, and automatically generated device data. Clinical site staff are expected to review hard copy CRFs for accuracy and completeness and resolve any data issues prior to data entry. Clinical data (including AEs, concomitant medications) are entered into the website, a 21 CFR Part 11-compliant data capture system. Each clinical site staff member is

authorized before being given a username, password, and staff ID to use the data system on the website.

10.2.2 Biostatistics and Design Team Responsibilities. During data entry, a variety of programmed error checks are performed for key variables, such as automatic range checks and logical consistency checks, to identify data that are inconsistent, incomplete, or inaccurate. When these edit checks fail, data may be flagged for further review or prevented from becoming part of the study database. At regular intervals, data queries are carried out on the computerized databases to perform consistency checks on key variables and other data. Metadata of the date, person, programmed edit check results, as well as the creation, modification, deletion, transfer, aggregation, and derivation of data are collected and documented.

Clinical site-generated measurements utilizing instrumentation (e.g., wearable devices measuring activity or glucose levels) will be transmitted to the Data Management Team through Application Programmer Interfaces (APIs). Metadata from these devices is captured and each data type is evaluated for proper storage. Data are archived through the end of the study and/or as required by local and national regulations.

Data security in the web-based data system uses 2048-bit encryption and SSL. Once data are received, recovery from disasters such as natural phenomenon (water, fire, or electrical) is possible through the ability to reconstruct both the database management system and the data up to the last back-up using nightly backups. This process ensures optimal recovery of data systems in the event of a disaster.

Access to the website, privileges to various areas of the website, and to the data on the website is managed by the Biostatistics and Data Management Project Managers in consultation with the clinical site coordinator.

Confidentiality of information is protected through a variety of procedures and facilities:

1. The confidential nature of the data collected, processed, and stored is explained to all new personnel.
2. All access to office space containing data is controlled through a single door, which is locked and only accessible by key or security badge.
3. All participant data are encrypted as described above.
4. All participant data stored on the WFBMC computers are likewise encrypted. In addition, all such databases are protected by passwords that must be supplied before the data can be accessed. Passwords are released only to Biostatistics and Data Management Team staff with a need to use the particular file and are changed on a regular schedule.
5. All printouts, plots, and reports containing individually identifiable data are produced on printers and plotters within the Biostatistics and Data Management Team secure office space.

PHI such as participant name, addresses, contact information and other identifiers of concern, if collected and data entered, are securely stored separately from the main clinical data on eCRFs. Access to these data is limited to a few primary people in the Biostatistics and Design Team and only the PID number connects these data, if required.

Documents pertaining to the study will be maintained for at least until 5 years after the final visit of the last HALLO-P participant.

10.3 Quality Assurance

10.3.1. Training

Study training will entail didactic and hands-on training. All study staff will be required to read the protocol, the informed consent form and the study manual of procedures. In a series of didactic sessions, the study investigators will explain the rationale of the study, provide an overview of study procedures and measurements, and discuss how to identify and report adverse events. The training will also include a discussion of the ethical conduct of research and the primacy of safety and privacy of study participants. Trainees take a test to make sure the most important training points are retained.

Following this session senior Sticht Center for Health Aging and Alzheimer's prevention staff will demonstrate specific study procedures, ask the staff to practice these procedures, and then observe and certify the examiner on the proper conduct of the measurement and procedure. Study staff will run through practice visits with non-study volunteers to gain experience with each assessment.

The interventionist will be trained under the supervision of Dr. Jack Rejeski and Dr. Jason Fanning.

10.3.2 Metrics

Quality will be monitored by evaluating missing data on study forms and tracking the percent of visits that are within protocol-specified windows.

10.3.3 Protocol Deviations

Protocol deviations will be identified in several ways: staff report, missing data on study forms, and documentation of missed, or out-of-window visits. The investigators will identify whether the deviation could have been prevented and discuss potential protocol or procedure changes with the Steering Committee. These deviations and pursuant protocol changes will be described in written communications with both the IRB and the DSMB.

10.3.4 Monitoring

Monitoring for data completeness will be tracked by the data management system. Senior staff will periodically review study binders to make sure informed consent has been appropriately obtained and documented.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB and study DSMB.

11.2 Informed Consent Forms

Participants who are eligible after the phone screen will be scheduled for an in-person screening visit. A trained study examiner will obtain full study consent as the first part of the visit. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The examiner will describe the study and the requirements for participation, review the informed consent form in detail with the participant, and address any participant questions. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice, and that the quality of their medical care will not be adversely affected if they decline to participate in this study. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will be given a copy of the ICF so that they may discuss the study with their family or surrogates or think about it prior to agreeing to participate. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. A copy of the signed informed consent document will be given to the participants for their records.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (PID) to maintain confidentiality. All written records will be kept in locked file cabinets. All electronic data will be housed in password protected files with access limited to only study personnel. All computer entry and networking programs will be done using PIDs only. Identifiable information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the NIA, and the OHRP.

11.4 Study Discontinuation

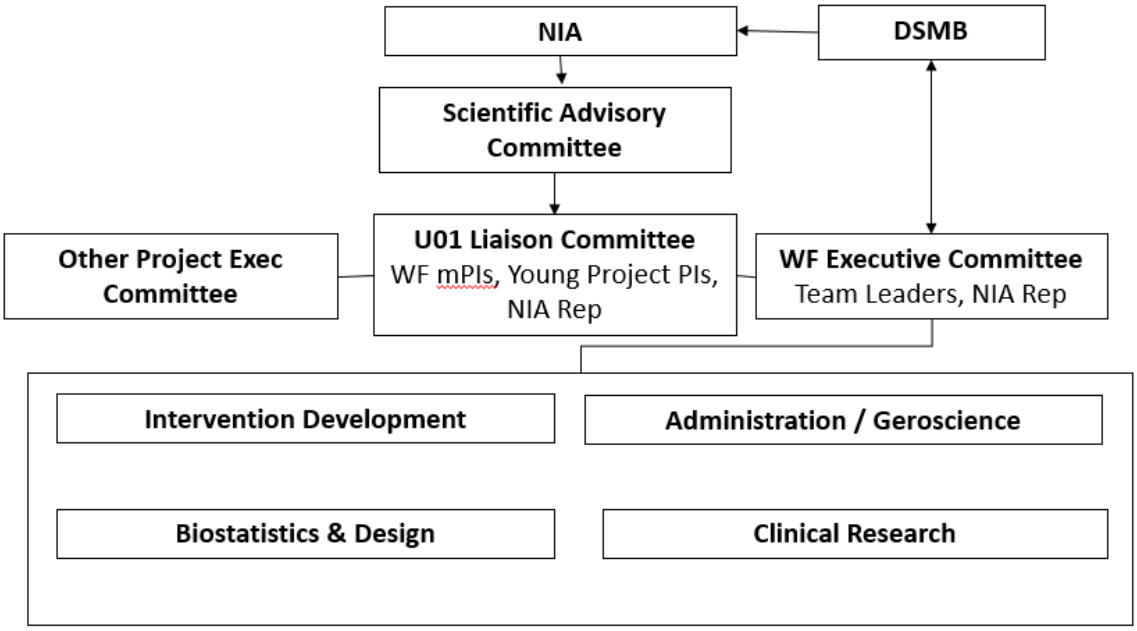
Given the short duration of the intervention and the low inherent risk of the intervention, there are no statistical rules that would lead to an early termination of the study. The study may be discontinued at any time by the IRB, the NIA, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

The HALLO-P study will be conducted following the principles guiding human clinical research as laid out in the Belmont Report, the Declaration of Helsinki and aligned with the 7 specific tenets promulgated by NIH's own Clinical Research Center 1) HALLO-P has social and clinical value providing important information to fully understand the implications of CR in older adults. 2) It will be conducted with high rigor to yield scientifically valid results. 3) It will fairly select subjects in a way that aligns with the goals of the study. 4) The study has a favorable risk to benefit ratio. The risks of participation are low, and the participants will be coached in ways to eat more healthfully and be more active. 5) Study activities will be independently reviewed by an NIA appointed Data and Safety Monitoring Board. 6) We will provide a complete description of

the study so that participant volunteers will be informed about what their participation would entail, and to make clear that their participation is entirely voluntary. 7) Potential and enrolled participants will be fully respected by keeping their information confidential, respecting their right to change their mind about participation without penalty, inform them of new information that might change their assessment of risks and benefits of participation, monitoring their welfare and adverse events to ensure appropriate medical responses, and to ensure that the safety of their continued participation, and providing a summary of results to participants after the study's completion.

13 COMMITTEES



The above diagram shows the HALLO-P study organization. The roles and responsibilities of the committees / teams are:

Executive Committee: This Committee is comprised of the four mPIs and the NIA representatives and is responsible for the coordination and overall progress of the Wake Project, budgetary issues and reallocations and sets the Agenda for the Steering Committee.

Steering Committee: The Executive Committee and the members of all work teams comprise the Steering Committee which is responsible for coordinating all aspects of the HALLO-P project, and discusses and approves protocol changes, ancillary study proposals, publications and presentation activities, feedback from oversight and regulatory bodies. Each paid investigator and the NIA scientific officer each have one vote if a decision cannot be made by consensus.

U01 Liaison Committee: This committee is a forum for the Wake and Pennington projects to compare progress, align measures and technologies.

Scientific Advisory Board: This Board is made up of scientists external to the HALLO-P. It is advisory to the Executive Committee and gives advice on the scientific aspects of the study as well as serving to identify opportunities for improving the conduct and scientific impact of the study.

Data and Safety Monitoring Board: The DSMB is advisory to the NIA which is responsible for its constitution. It provides the NIA feedback on the conduct of the study, participant safety and burden.

Administrative / Geroscience Team: This team is responsible for the administrative and regulatory aspects of HALLO-P including the preparation of budgets, correspondence with the NIA, arranging meetings, and interactions with the IRB and DSMB. It is also responsible for the Geroscience aspects of the study including formulating a biobanking and specimen collection strategy, and selecting, measuring and interpreting biomarker results from the study.

Intervention Development Team: This team is responsible for the development and implementation of HALLO-P's behavioral interventions.

Biostatistics and Design Team: This team oversees the development of data collection / management systems for the study, and the analysis and interpretation of study data.

Clinical Research Team: This team is responsible for the recruitment and management of study participants, and the collection of participant data related to eligibility, safety and study outcomes.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. All publications include an acknowledgement of the supporting grants including U01 AG073240 along with administrative supplements including one from the National Cancer Institute, UL TR001420 and P30 AG021332.

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16 APPENDICES

A. Abbreviations Used

B. Protocol Updates / Revisions

Appendix A. Abbreviations Used

AE - Adverse Event

ACD – Acid Citrate Dextrose

ADL – Activity of Daily Living

ALS – Amyotrophic Lateral Sclerosis / Lou Gehrig's disease

ALT – Alanine Transaminase

AMPK - AMP-activated protein kinase

ANCOVA - Analysis of Covariance

API – Application Programming Interface

App - Application

ASA24 – Automated Self-Administered 24-hour Dietary Assessment Tool

BEDS-7 – Binge Eating Disorder Screener – 7

BMD – Body Mineral Density

BMI – Body Mass Index

BP – Blood Pressure

BV1 – Baseline Visit 1

BV2 – Baseline Visit 2

CALERIE – Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy

CBC – Complete Blood Count

CES-D – Center for Epidemiologic Studies Depression Scale

CFR – Code of federal Regulations

CGM – Continuous Glucose Monitoring

CI – Confidence Interval

CLIP- Cooperating Lifestyle Intervention Program

cm – Centimeter

CMP – Comprehensive Metabolic Panel

CO2 – Carbon Dioxide

COPD – Chronic Obstructive Pulmonary Disease

CPT – Cell Preparation Tube

CR – Caloric Restriction

CRF – Case Report Form

CRP – C-Reactive Protein

CRU – Clinical Research Unit

d – Day

dL – Deciliter

DLW – Doubly-Labeled Water

DNA – Deoxyribonucleic Acid

DSE- Education Program

DSMB – Data and Safety Monitoring Board

DXA- Dual-energy X-ray absorptiometry

eCRF – Electronic Case Report Form

EDTA – Ethylenediaminetetraacetic acid

e.g. – Exempli Gratia (for example)

eGFR – Estimated Glomerular Filtration Rate

EI – Energy Intake

EMA – Ecological Momentary Assessment

eSPPB - Expanded Short Physical Performance Battery

FACIT – Functional Assessment of Chronic Illness Therapy

FV1 – Follow-up visit 1 (~ 6 mos)

FV2 – Follow-up visit 2 (~ 9 mos)

FV3 – Follow-up visit 3 (~ 9 mos)

g – Gram

h – Hour

H – Hydrogen

H2O – Water

HALLO-P - Health, Aging and Later-Life Outcomes Pilot Trial

Hb – Hemoglobin

HbA1c – Hemoglobin A1c

HIPAA – Health Insurance Portability and Accountability Act

HMR – Health Management Resources Caloric System©

ICC – Intraclass Correlation Coefficient

ICF – Informed Consent Form

IIS- Insulin-like growth factor-1 signaling

Il6 – Interleukin 6

ILI – Intensive weight loss and exercise

INFINITE – Investigating Fitness Interventions in the Elderly

IRB – Institutional Review Board

IU – International Units

kcal – Kilocalorie

kg – Kilogram

Look AHEAD – Look Action for Health in Diabetes Study

LTFU – Lost to Follow-up

m – Meter

MedDRA – Medical Dictionary for Regulatory Activities

ml – Milliliter

mg – Milligram

MI- Myocardial Infarction

mins – Minutes

mmHg – Millimeters of Mercury

MoCA – Montreal Cognitive Assessment Tool

MOP – Manual of Procedures

mPI – Multiple Principal Investigator

MS – Multiple Sclerosis

mTOR – Mammalian target of Rapamycin

NAD+ - Nicotinamide adenine dinucleotide

NC – North Carolina

NCI - National Cancer Institute

NIA – National Institute on Aging

NIH – National Institutes of Health

OHRP – Office for Human Research Protections

PAD – Peripheral Arterial Disease

PAEE – Physical Activity Energy Expenditure

PHI – Protected Health Information

PI – Principal Investigator

PID – Participant Identification (Number)

PO –Program Officer

PROMIS – Patient-Reported Outcomes Measurement Information System

RD – Registered Dietitian

REE – Resting Energy Expenditure

REML – Restricted Maximum Likelihood

RNA – Ribonucleic Acid

SAE –Serious Adverse Event

SD - Standard Deviation

SF-36 – Short Form 36-item Health Survey

SPPB – Short Physical Performance Battery

SSL – Secure Sockets Layer

SV1 – Screening Visit 1

SV2 – Screening Visit 2

TBSP – Tablespoon

TEE – Total Energy Expenditure

TNFRI – Tumor Necrosis Factor Soluble Receptor I

TRE- Time Restricted Eating

TSH – Thyroid Stimulating Hormone

tv – Television

uIU/mL – Micro-international Units per Milliliter

UP – Unanticipated Problem

VITAL – Volunteers in Touch With Aging and Life

WF – Wake Forest

WFBMC – Wake Forest Baptist Medical Center

wks – Weeks

yrs - Years

Appendix B. Protocol Updates / Revisions

Version Number: 2.1
Version Date: 11/30/2023
Summary of Revisions Made:

- Removed Jamie Justice as a CoI as she is no longer at Wake Forest.
- Added the National Cancer Institute as a sponsor from recent administrative supplement.
- Added the online Siteman Cancer Center risk assessment, cancer screening questionnaire and expanded biomarker panel at baseline and 6mo as requested by the NCI.

Version Number: 2.0
Version Date: 7/17/2023
Summary of Revisions Made:

- Reduced sample size from 120 to approximately 100.
- Discontinued the in-person CR group for the last wave and updated the statistical considerations as applicable.

Version Number: 1.9
Version Date: 5/3/2023
Summary of Revisions Made:

- Further expanded the BMI range from 27 - $\leq$ 37 kg/m2 to 27 - $\leq$40 kg/m2.
- Revised the 5% weight change to 3 months instead of 6 months.
- Clarified how night eating is addressed and added in correct reference.
- Revised one-on-one intervention sessions to be in person, by phone or by video to allow for flexibility.

Version Number: 1.8
Version Date: 2/2/2023
Summary of Revisions Made:

- Added CPT tubes as an option for whole blood collection.

Version Number: 1.7
Version Date: 1/3/2023

Summary of Revisions Made:

- Updated the run-in to include a paper log instead of tracking using the fitbit app.
- Revised the CGM collection to only 2 time points at ~3 and ~8 months.
- Updated the visit window of the 9 month follow-ups to occur after 34-40 weeks of intervention instead of 36-40.
- Updated the exclusion criteria for Osteoporosis to also include the femoral neck (t-score ≤ -2.5 on total hip and/or femoral neck scan)
- Revised the timing of the EMA assessments to occur 1 week out of months 1, 4 and 7 instead of the first week of every month

Version Number: 1.6
Version Date: 11/29/2022
Summary of Revisions Made:

- Expanded the BMI range from 27 - < 35 kg/m2 to 27 - ≤37 kg/m2.
- Revised that randomization can occur after the participant arrives for the BV2 visit and doesn't need to complete the visit first.

Version Number: 1.5
Version Date: 9/22/2022
Summary of Revisions Made:

- Modified how randomizations will occur being blocked randomizations stratified by sex instead of a permuted block scheme with blocks of various sizes.
- Changed the amount of time from 3 months to 4 weeks to wait before enrolling someone who had Covid, the flu or other acute respiratory illness.

Version Number: 1.4
Version Date: 8/19/2022
Summary of Revisions Made:

- Removed the use of home scales for weights at baseline, 6 and 9 month
- Removed 6 month biomarkers from the secondary outcomes as blood will be banked but no planned biomarkers at that visit.
- Modified how the ActivPal data will be reviewed at baseline averaging all days, not just 5-7 days
- Modified the inclusion/exclusion criteria to reduce the amount of time participants need to already be eating/drinking during the day from 12 to 11 to help aid in recruitment and other updates to further clarify the criteria.
- Updated the participants receiving a paper log at SV2 to track their start and stop times of eating and drinking and that participants should email this log on day 7 to help study staff determine eligibility prior to the visit.
- Added 2 new sleep questionnaires (STOP and Epworth) to BV1 and FV2.
- Updated the EMA assessment from Hunger, Cravings, Affect, and Sleep to Hunger, Desire to eat and Anxiety
- Minor editorial changes throughout.

Version Number: 1.3
Version Date: 7/13/2022
Summary of Revisions Made:

- Added TSH and tube for blood for biomarker QC to SV1 labs and TSH to FV2
- Removed congenital birth defects as possible SAE

Version Number: 1.2
Version Date: 5/16/2022
Summary of Revisions Made:

- Provided clarification regarding the 20% increase in step count from baseline throughout the document
- Removed Daniel Beavers as a Co-I and add Fang Chi Hsu as his replacement.
- Removed DXA and ASA from the 6 month visit outcomes, assessment table and visit descriptions.
- Revised the inclusion/exclusion criteria to be more inclusive; main changes include:
    - Use of regular cane is ok, quad cane or walker is not.
    - Revised that persons with type 2 diabetes can participate as long as they've been diagnosed at least one year and their HbA1c is <7.5% and not on insulin or any medication that could interfere with study. Anyone presenting with a HbA1c of ≥6.5% and not already diagnosed as a diabetic will be excluded.
    - Removed multiple psychiatric exclusions but will continue to screen for depression at screening.
    - Removed "Evidence of severely disturbed sleep/wake cycle"
    - Revised the anemia cutoff to <11 g/dL for both men and women.
- Updated the assessment table to accurately reflect assessment of medication updates, health status changes and common signs and symptoms and described the collection and reporting of each in the applicable adverse event section.
- Updating the timing of the DLW measurement from 9-12 days to 10-15 days to allow for more flexibility around scheduling visits
- Updated the amount of blood being collected and stored as its less than originally planned.
- Updated one of the questionnaires from the Barriers Self-Efficacy to Walking Self-Efficacy.
- Added a night eating assessment at baseline visit 1.
- Provided an update on the Safety Monitoring now that we have a DSMB charter and removed the names of committee members at the request of the NIA. The study organization chart was revised and the DSMB listing was removed.
- Minor editorial changes throughout.

Version Number: 1.1
Version Date: 4/4/2022
Summary of Revisions Made:

- Added d3 creatine dilution protocol at baseline and 9 months to assess change in total muscle mass. Added to secondary outcomes, assessment table, visit details and associated references.

- Removed the use of prepared meals for the first 3 weeks of intervention. There were a number of logistical concerns we couldn't work out with the metabolic kitchen so instead during the first three weeks of the intervention, the RD will spend significant time reviewing and providing hands-on experience with both portion control and planning/preparation of meals.
- Revised the target to aim to recruit up to 50% men, with the expectation we will likely enroll between 35%-45% based on our demographics.
- Updated section 6.1 Schedule of Evaluations to note when the health status form (adverse event query) will be administered to avoid duplicate reporting between blinded and unblinded assessors.
- Removed PAEE (ActivPAL) assessment at 6 month visit as it was only intended to be done at baseline and follow-up.
- Moved the physical performance testing from BV1 and FV2 visits to BV2 and FV3 visits to avoid activity during the DLW initial collection and to fill time during the follow-up visits to allow enough time for 2 urine collections at BV2 and FV3.
- Reordered the listing of some of the assessments to fall in line with the order of preference, especially for the fasting visits.
- Added that we may contact participants roughly one year after the end of their participation to ask if their weight but will be optional and not considered outcome data.
- Minor editorial changes throughout.