CLINICAL RESEARCH PROTOCOL

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PROTOCOL TITLE:		Food supplementation interventions to improve weight loss for adults with food insecurity and obesity
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PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	National Institute of Nursing Research/National Institutes of Health
STUDY TITLE:	Food supplementation interventions to improve weight loss for adults with food insecurity and obesity
STUDY ID	Pending
PROTOCOL VERSION	V1.1

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name	Ariana M. Chao	Signature	Ariana Chao
Affiliation:	University of Pennsylvania	Date	February 21, 2023

1 STUDY SUMMARY

1.1 Synopsis

Title:	Food supplementation interventions to improve weight loss for adults with food insecurity and obesity
Short Title:	FoodRx for Obesity Treatment
Study Description:	This study is a 3-group, parallel design, randomized controlled trial (RCT) in 105 adults with obesity and food insecurity that will compare BWL-Alone (including standard-of-care referral and connection with community food resources; n=35) to BWL plus food supplementation with either food vouchers (BWL+VOUCHER; n=35) or home-delivered, medically tailored groceries consistent with BWL recommendations (BWL+HOME; n=35). All groups will have BWL treatment provided for 24 weeks per CMS guidelines. Food vouchers and HOME will be provided for 24 weeks of treatment. Assessments will be conducted at baseline, and weeks 12 and 24.
Objectives:	**Primary** **Aim 1:** Test the hypothesis that BWL+VOUCHER and BWL+HOME will result in greater weight loss (percent of initial weight) at 24 weeks than BWL-Alone. **Secondary** **Aim 2:** Test the hypothesis that BWL+HOME will result in greater weight loss (percent of initial weight) at 24 weeks than BWL+VOUCHER. **Aim 3a:** Test the hypothesis that BWL+VOUCHER and BWL+HOME, relative to BWL-Alone, produces greater improvements in health-related quality of life (HRQOL) and dietary quality as assessed by skin carotenoid levels (a fruit and vegetable biomarker) and Healthy Eating Index (HEI) scores from baseline to week 24. **Aim 3b:** Test the hypothesis that BWL+HOME, compared to BWL+VOUCHER, produces greater improvements in HRQOL, skin carotenoid levels and HEI scores from baseline to week 24.
Primary Endpoint:	Percent weight loss at week 24 for BWL+VOUCHER and BWL+HOME vs BWL-Alone
Secondary Endpoints:	Percent weight loss at week 24 for BWL+HOME vs BWL+VOUCHER Health-related quality of life Skin carotenoid levels

	HEI scores
Study Population:	105 adults with obesity (BMI≥30 kg/m^2) and food insecurity
Phase:	II
Description of Sites/Facilities:	Center for Weight and Eating Disorders University of Pennsylvania
Enrolling Sites:	Single-site, Center for Weight and Eating Disorders University of Pennsylvania
Description of Study Intervention:	Participants will have 14 brief, individual lifestyle counseling visits. Visits will be scheduled weekly for the first 4 weeks and every-other week from weeks 6-24. BWL-Alone will have counseling alone. BWL+VOUCHER will be provided with counseling and grocery store gift cards in the amount of $40 every 2 weeks. BWL+HOME will have counseling and receive home-delivered, medically tailored groceries worth approximately $40 every 2 weeks.
Study Duration:	24 months
Participant Duration:	24 weeks

1.3 Schema

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Food insecurity affects 23% of adults with obesity[1] and is a significant barrier to following dietary recommendations prescribed in behavioral weight loss treatment (BWL).[2,3] Compared to participants who are food secure, participants with food insecurity lose significantly less weight during BWL.[4] BWL provides necessary education and skills to lose weight but does not address structural or social detriments of health. Despite the influence of home and neighborhood food environments on dietary habits,[5] standard obesity treatments do not address the ability of patients to *afford* and *access* nutritious foods, which are central to adhering to dietary recommendations needed for weight loss.[4] There is an inverse relationship between energy density and food costs,[5,6] and individuals with food insecurity have more difficulty affording the low-energy density foods often recommended for weight loss (e.g., fruits, vegetables, lean meats).[7,8] Monetary allotments provided by nutrition-assistance program benefits are insufficient to cover the costs of adhering to federal guidelines for healthy diets.[9,10] In addition, neighborhood factors, such as living in a "food desert" and/or "food swamp," limit access to nearby nutritious foods[11] and add additional transportation and time costs.[12,13]

The Centers for Medicaid and Medicare Services (CMS),[14,15] American Diabetes Association,[16] and other organizations[17,18] recommend that healthcare providers screen patients for food insecurity as a "fifth vital sign." However, there is a significant gap in our knowledge of how to best help patients with obesity *and* food insecurity manage their weight. The current standard of care is to provide referrals to community (e.g., food pantries) and federal nutrition assistance programs such as the Supplemental Nutrition Assistance Program (SNAP). Yet, providing referrals for food resources to people with food insecurity results in low resource linkage rates of 0-5%.[19,20] Additionally, food pantries improve access to food, but the majority of choices tend to be nutritionally-poor items.[21] To simultaneously address obesity *and* food insecurity, providers need effective, tailored strategies.

The overarching goal of this application is to reduce socioeconomic disparities in obesity by improving the ability of patients to afford and access nutritious foods during BWL treatment. Previous research in other chronic conditions and preliminary data in patients with obesity have shown two promising approaches that may improve adherence to weight loss dietary prescriptions: food vouchers and home-delivered, medically tailored groceries.[22-25] Food vouchers can reduce cost-related non-adherence to dietary prescriptions by addressing the financial challenges of affording nutritious food. Home-delivered, medically tailored groceries (HOME) can address physical and logistical challenges of accessing nutritious foods. Yet, these promising approaches have not been tested for weight management.

One of the most pressing unmet challenges for preventing and controlling the obesity epidemic is ensuring that socially disadvantaged populations benefit from relevant health interventions. BWL targets individual health behaviors, but it does not consider the broader social and environmental context that creates barriers to treatment adherence. Food insecurity is

recognized as a prevalent and modifiable condition that can impede adherence. The expected outcome of this study is to demonstrate feasible food support interventions that can be used within health care systems to address social determinants of health and achieve better health equity.

2.2 Background

Food insecurity is common among people with obesity. Food insecurity is characterized by a shortage of nutritionally adequate food and a difficulty acquiring sufficient food affects 23% of adults with obesity and 41.5% of individuals with food insecurity also have obesity.[1,26] Food insecurity is closely associated with poverty and contributes to socioeconomic obesity-related health inequities.[27-30] People who are Black or Hispanic are twice as likely as individuals who are White, non-Hispanic to face food insecurity.[31,32] Food insecurity is associated with reduced health-related quality of life[33] and increased risk of depression.[34,35] Historically, food insecurity was associated with underweight due to inadequate *quantity* of food intake. But the relationship between body weight and food insecurity has grown more complex due, in part, to changes in the food environment that promote weight gain. Today, food insecurity increasingly contributes to obesity due to inadequate *quality* of food for optimal health. The episodic nature of food insecurity is characterized by periods of decreased intake when an individual's food supply is low, followed by overconsumption when food is available. Food insecurity is associated with overall low dietary quality,[36] decreased consumption of protein, vegetables and fruits, and higher intake of calories from solid fats, added sugars, and soda.[2,37,38] Cyclic food restriction is associated with preferences for energy-dense foods, binge eating, increased body fat, and decreased lean muscle mass.[39] Food insecurity and resultant negative health outcomes create a vicious cycle that perpetuates health inequities; reliance on cheaper, calorie-dense foods leads to poor nutrition, obesity, and obesity-related diseases such as diabetes and cardiovascular disease. In turn, obesity and related illnesses result in higher healthcare costs and difficulty keeping a job or finding work.[40] These challenges further restrict the household food budget, resulting in fewer resources being allocated to nutrition. Addressing food insecurity is critical to eliminating disparities in obesity, its related conditions, and its treatment.

Food insecurity is associated with suboptimal treatment outcomes in behavioral weight loss (BWL). Behavioral treatment of obesity can successfully induce losses ≥5% of baseline body weight with clinically significant improvements in obesity-related comorbidities.[3-5] However, people from socioeconomically disadvantaged backgrounds are underrepresented in obesity treatment trials, and, with few exceptions,[41] evidence-based weight loss strategies are less effective in these groups.[42-45] For example, in a trial of 803 patients with obesity, participants randomized to the intensive lifestyle intervention who were food insecure lost approximately 3 kg compared to a 6 kg loss among those who were food secure.[4] Socio-ecological models demonstrate that obesity results from a complex interplay of multiple determinants, operating at individual, interpersonal, organizational, environmental, and public policy levels.[46] Food insecurity is an important socioecological barrier to obesity management, as dietary adherence is core to BWL. However, standard BWL programs do not address social determinants of health that prevent patients' from adhering to dietary recommendations.

Food insecurity creates critical barriers to adhering to dietary prescriptions in BWL. Caloric restriction is the common pathway across all successful dietary strategies for weight management.[47] This reduction is induced and maintained through increases in high-quality foods consistent with federal dietary guidelines.[48] This includes increases in low-energy dense foods such as fruits, vegetables, and lean protein which enhance satiety and reduce overall energy intake,[49] and decreases in low-quality and energy-dense foods that are highly processed and high in calories, saturated fats, and sugar.

Economic. The cost of food is a primary determinant of dietary intake, especially for people with low incomes,[50] but food budgets of lower-income groups are insufficient to support adherence to federal guidelines for healthy diets. Food insecure households spend 24% less on food than a comparable food-secure household of the same size and composition.[51] A diet consistent with the Dietary Guidelines for Americans would cost $8.27/day per person for the Healthy US Style Eating Pattern.[52] The primary source of nutrition assistance for individuals with a low-income, Supplemental Nutrition Assistance Program (SNAP), provides adults with $4.30/day ($1.43 per meal, paid in a monthly sum).[53] SNAP benefits are based on the Thrifty Food Plan, a low-cost meal plan that aligns with the 2005 Dietary Guidelines for Americans and the 2005 MyPyramid Food Guidance System. Of all households, 28.2% exhaust their SNAP benefits within a week of receipt and 53.3% within the first two weeks.[54] SNAP beneficiaries have a significant decline in dietary quality in the final 10 days of the benefit cycle.[55] When benefits run out, individuals often rely on food pantries, which tend to lack fruits and vegetables and have overall low dietary quality.[21] While 84% of individuals who are eligible receive SNAP benefits, one in three people who are food insecure still do not qualify for federal food assistance.[56] Food insecure households are often forced to choose between buying nutritious food and paying for medications, housing, and investment in their long-term economic success, further amplifying structural inequalities.

Access. Characteristics of the built food environment, including the density, distribution and variety of food stores, are important determinants of nutritional intake and weight status.[57-60] Individuals with food insecurity are more likely to live in “food deserts,” defined as low access to outlets selling healthy food such as supermarkets, supercenters, or large grocery stores.[59] At the same time, these individuals are also more likely to live in “food swamps,” characterized by a greater density of stores that sell nutrient-poor, energy-dense food (e.g., fast-food restaurants and convenience stores) than healthy food options.[61,62] Living in a food desert and/or food swamp is associated with lower quality diet, reduced intake of fruits and vegetables, higher consumption of high-energy density snacks and fast food, and increased risk of obesity.[57-60,63-65] These environmental factors make adherence to dietary recommendations more challenging because there is lower availability and quality as well as higher costs of nutritious foods at fast food and convenience stores relative to supermarkets and grocery stores.[66] In addition, for individuals trying to lose weight, a high level of dietary restraint is required when shopping for food at a corner store or fast-food restaurant because these settings offer predominantly high-calorie options.[67] Policy initiatives have tried to address obesogenic environmental issues. For example, the Healthy Food Financing Initiative supports opening full-service grocery stores in food desserts.[68] Quasi-experimental and longitudinal studies evaluating the impact of opening new grocery stores have shown that while perceived access to healthy food improves, diet

quality and body mass index (BMI) do not.[69-72] These findings indicate that while efforts are underway to improve the nutritional environment at policy and community levels, parallel efforts are needed to help the people living in environments that promote obesity.

Healthcare interventions are needed for individuals with food insecurity and obesity. Several professional societies now recommend that healthcare systems integrate food insecurity screening into care.[14-18] The current standard of care for people who screen positive for food insecurity is passive referral to federal and local resources such as SNAP and food pantries. However, provision of written and verbal information about food resources to people with food insecurity results in low resource linkage rates of 0-5%;[19,20] one-third of individuals with food insecurity may not be eligible for SNAP due to income and eligibility guidelines,[73,74] and food pantries often lack foods recommended for weight loss including fresh fruits, vegetables, and lean meats.[75,76] Despite this growing recognition of the importance of food insecurity on weight management, we do not yet have evidence of a rigorous treatment approach to address food insecurity *and* obesity that can target multiple barriers including cost, access, skills, knowledge, and behavior.

Knowledge gap: Do food supplementation interventions improve weight loss, health-related quality of life, and dietary adherence in individuals with obesity *and* food insecurity? A promising strategy to address food insecurity and obesity is food supplementation; however few randomized trials have investigated this approach for individuals with obesity *and* food insecurity.[77] Evidence from individuals with food insecurity and other chronic diseases such as type 2 diabetes, HIV, and hypertension largely supports the notion that food supplementation improves adherence to dietary recommendations, diet quality, and health outcomes[23,24,78-80] by improving affordability and/or access to recommended foods.[12,81] A meta-analysis of 7 trials demonstrated that food supplementation interventions improved quality of life compared to control (SMD=-0.28).[82] Recent systematic reviews have highlighted the lack of randomized controlled trials for individuals with food insecurity as a key barrier to address disparities in chronic diseases such as obesity.[77,83,84] We know of only 3 studies that examined the effects of food supplementation in individuals with overweight/obesity and food insecurity.[23,24,85] These trials have been non-randomized studies, included small samples, and/or lacked examination of the sustainability of the effects after the food supplementation ended.[82] Further, these studies assessed dietary quality using questionnaires or interviews, which are subject to measurement bias and error.[86] Trials have not used objective measures of dietary intake. For example, Berkowitz, Delahanty, et al., 2018 conducted a randomized cross-over clinical trial in 44 adults with type 2 diabetes and food insecurity that compared 12 weeks of home delivered food (10 meals/week) with 12 weeks of usual care, including a Choose My Plate healthy eating brochure.[23] Mean Healthy Eating Index (HEI) score for the food delivery weeks was 71.3 (SD=7.5), which was significantly higher than the mean HEI for the usual care weeks (39.9 (SD=7.8); difference 31.4 points, $p<0.001$). Scores for mental health-related quality of life were significantly improved for the food delivery weeks compared to non-supplemented weeks. BMI did not differ, similar to other studies,[24,85] likely because BWL counseling was not provided. Food provision can improve dietary structure, completion of food monitoring records, and model proper portion size.[87] However, these findings show that simply providing healthy food alone is not adequate to promote the adoption and maintenance of new dietary patterns.

A program of diet, physical activity and behavioral weight loss therapy (BWL) is the first-line treatment for obesity.[3] BWL is central to teaching patients behavioral skills that are core to successful weight management including self-monitoring, adhering to portion sizes, stimulus control, goal setting, problem solving, and relapse prevention.[88] In patients with obesity but without food insecurity, there is strong and consistent evidence that the combination of provision of food and BWL improves weight loss compared to either BWL or food provision alone.[87,89-91] For example, in a randomized trial in patients with obesity, at 6 months, participants in BWL-Alone lost 8.8% of initial weight which was significantly less than the 12.4% for those receiving BWL and food provision.[87] In patients with food insecurity and obesity, the combination of food supplementation and BWL will likely improve dietary self-efficacy and enable patients to act on the lifestyle change advice offered in BWL, resulting in improved dietary adherence, weight loss, and quality of life. Taken together, this body of literature provides strong support for the combination of food supplementation and BWL for individuals with obesity and food insecurity. This study will be the first RCT to assess whether food supplementation, in conjunction with BWL, significantly improves weight loss relative to BWL alone. Such information will help to develop new models of care to help patients access and consume healthier foods.

Knowledge gap: What type of food supplementation intervention is most effective in improving weight loss in individuals with obesity and food insecurity? Several forms of food supplementation have been tested that range in their level of prescription, cost, and the degree to which they address food affordability, availability, access, and acceptability with regard to personal food preferences and cultural food practices.[92] Food supplementation interventions that have been tested for individuals with food insecurity include general food vouchers, produce prescriptions, clinic-based food pharmacies, and home deliveries of medically-tailored groceries, meal kits, or prepared meals.[77] However, few studies have compared different options for food supplementation side by side.

Providing food-focused financial assistance in the form of vouchers can alleviate budget constraints that prevent patients from purchasing nutritious foods.[81] These offer patients flexibility and autonomy over choice of foods based on personal and cultural preferences. Healthcare-based initiatives typically frame this strategy as the healthcare provider giving patients “prescriptions” for nutritious foods. This uses a partnership model of care whereby an authority figure (e.g., healthcare provider) fosters and positively reinforces health-seeking behaviors.[93-95] The use of the term “prescription” helps to reinforce the importance of nutrition and adherence as part of the patient’s treatment plan. Food vouchers have redemption rates of 75-90%.[96-98] Data from natural experiments and randomized controlled trials support that food vouchers improve dietary adherence, diet quality, and health outcomes for individuals with food insecurity and chronic health conditions.[78,96,98,99] Food vouchers have improved weight loss in some[100] but not all studies,[101] most likely because they are typically given without additional counseling. While food vouchers address a patient’s ability to afford healthy foods, several studies have noted that even with these vouchers, individuals with food insecurity continue to face barriers with access and transportation of nutritious foods.[80,102]

Home-delivered, medically tailored groceries (HOME) can help patients overcome barriers to weight management including lack of time, resources, access, and transportation. The use of stock boxes can provide quality food to support chronic disease management, provide more familiarity with diverse fruits and vegetables, and model ingredient selection and portion sizes

congruent with healthier diets, potentially enabling recipients to maintain more healthful diets when supplementation is no longer provided.[81,103-105] Provision of food consistent with dietary recommendations has consistently been shown to improve dietary adherence, decrease snacking, reduce barriers to weight loss, and ultimately improve weight loss and HRQOL in general samples of people with obesity.[89,91,106,107] Yet, this promising strategy has not been well tested in individuals with both food insecurity *and* obesity.

This study will address these critical research and clinical gaps by clarifying effective interventions that address obesity and food insecurity - a modifiable social determinant of health - and improve weight loss, dietary quality and health-related quality of life. There are no large, randomized trials of food supplementation interventions for people with food insecurity and obesity. The proposed study will compare the weight loss efficacy of two different food supplementation interventions which differ in addressing food costs alone (i.e., vouchers) versus food costs and accessibility (i.e., HOME). This study will yield valuable insight into how to design and deliver weight-management interventions to people with food insecurity that also address social determinants of health. This will be one of the first studies to determine whether food supplementation can improve self-reported and objective dietary quality during BWL. The study will provide important evidence of healthcare-based interventions that can reduce socioeconomic disparities in obesity and could contribute to a shift in the current obesity treatment paradigm to integrate social determinants of health within clinical care. The study could lead to personalization of obesity treatment for those with needs related to social determinants of health.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The risks of participating in a behavioral weight loss program are low but do include:

Hypoglycemia. Hypoglycemia may occur during periods of calorie restriction and weight loss.

Risk of gallstones. Rapid weight loss may increase the risk of gallstones. For participants who lose more than 3 pounds per week for 4 consecutive weeks, we will suggest slowing weight loss by increasing calories and participants will be encouraged to have at least 7-10 grams of fat per day to support gallbladder contraction and bile cycling.[108] Participants who lose weight rapidly will not be removed from the study.

Injury due to physical activity. Participants may injure themselves when engaging in physical activity.

Psychological risks. Psychological risks include reduced self-esteem in persons who do not lose weight or regain weight or a sense of shame if not meeting weight loss goals.

Risk of assessments. Some of the questions in the interview that assess history of medical and psychological conditions may be of a personal nature.

Loss of confidentiality risk. Because information about the participant's identity will be collected and stored for research purposes, there is a chance that the information could be viewed by others not associated with the research team; therefore, there is a potential for loss of confidentiality. The study team will work to uphold the privacy of the participants in several ways. Communications made among study staff regarding participants will use ID numbers only and never include names or other personal information. All participant data and recordings will be kept in locked files. Electronic data files will be used when possible. In all data sets, we will use ID numbers only. A separate dataset linking names with ID numbers will be accessible only by the primary study investigators.

Unforeseen risks. If additional risks are identified during the study, study participants will be informed about these risks by the study team.

2.3.2 Known Potential Benefits

Obesity is one of the most common chronic diseases and is associated with an increased risk of health and psychological co-morbidities. All participants who enroll in this study will receive a comprehensive behavioral weight loss program. Based on results of previous studies, we expect participants to lose an average of approximately 5% of their initial weight during the 24-week treatment program and have improvements in their eating behaviors and physical activity. Weight losses of $\geq$5% may be associated with improvements in medical conditions made worse by excess weight including pre-diabetes (high blood sugar), high blood pressure, and high triglyceride levels. Participants will undergo assessment and monitoring of several health factors including weight and blood pressure. These results will be made available to participants. Despite these potential benefits, there is no guarantee that participants will lose weight or get any medical benefits from this study. This study may also benefit society at large by providing information about the effectiveness of a behavioral weight loss program combined with food supplementation on weight, quality of life, and dietary quality in people with food insecurity and obesity.

2.3.3 Assessment of Potential Risks and Benefits

The benefits of this research to the participants studied, and to society at large, surpass the risks. We believe that this study poses minimal risk to participants, while providing potential benefit to people with obesity. The known risk of receiving behavioral obesity treatment, food supplementation interventions, and completing the study assessments are minimal. Numerous clinical trials have demonstrated the safety of behavioral weight loss programs for obesity. Research staff will monitor subjects closely during their participation. Every effort has been made to provide a study in which the safety and privacy of research participants is protected. We anticipate that after the weight loss treatment, participants will have improvements in their eating, physical activity, and weight. Results of this study hold promise of significantly improving the management of obesity and its associated complications.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
Test the hypothesis that BWL+VOUCHER and BWL+HOME will result in greater weight loss (percent of initial weight) at 24 weeks than BWL-Alone.	P initial weight loss at week 24
Secondary	
Test the hypothesis that BWL+HOME will result in greater weight loss (percent of initial weight) at 24 weeks than BWL+VOUCHER.	P initial weight loss at week 24
Test the hypothesis that BWL+VOUCHER and BWL+HOME, relative to BWL-Alone, produces greater improvements from baseline to week 24 in: General health-related quality of life (QOL) Weight-related QOL Dietary quality as assessed by skin carotenoid levels (a fruit and vegetable biomarker) Healthy Eating Index (HEI) scores	 Change from baseline to week 24 in general health-related quality of life as assessed with the Short Form (SF)-36 Change from baseline to week 24 in weight-related quality of life as assessed with the Impact of Weight on Quality of Life(IWQOL)-Lite Change from baseline to week 24 in skin carotenoid levels Change from baseline to week 24 in Healthy Eating Index scores as measured with the ASA24
Test the hypothesis that BWL+HOME, compared to BWL+VOUCHER, produces greater improvements from baseline to week 24 in: General health-related QOL	 Change from baseline to week 24 in general health-related quality of life as assessed with the Short Form (SF)-36

OBJECTIVES	ENDPOINTS
Weight-related QOL	Change from baseline to week 24 in weight-related quality of life as assessed with the Impact of Weight on Quality of Life (IWQOL)-Lite
Skin carotenoid levels	Change from baseline to week 24 in skin carotenoid levels
HEI scores	Change from baseline to week 24 in Healthy Eating Index scores as measured with the ASA24
Tertiary	
Test the hypothesis that BWL+VOUCHER and BWL+HOME, relative to BWL-Alone, produces greater improvements from baseline to week 24 in:	
Food security scores	Change from baseline to week 24 in food security scores as assessed by the USDA Food Security Measure
Binge eating and eating disorder psychopathology	Change from baseline to week 24 in binge eating and global eating disorder psychopathology as measured by the Eating Disorder Examination Questionnaire
Depressive symptoms	Change from baseline to week 24 in depressive symptoms as measured by the Patient Health Questionnaire 8
Weight-loss-related behaviors	Change from baseline to week 24 in weight-loss-related behaviors as measured by the Eating Behavior Inventory
Eating self-efficacy	Change from baseline to week 24 in eating self-efficacy

4 STUDY PLAN

4.1 Study Design

The single-site, open-label, phase 2, three-arm RCT will enroll 105 participants recruited from the community who will be randomly assigned to one of three groups, all of which will receive BWL. Groups include: BWL-Alone (including standard-of-care referral and connection with community food resources); BWL combined with food vouchers (BWL+VOUCHER); and BWL combined with home-delivered, medically tailored groceries (BWL+HOME). Each intervention will be provided for 24 weeks. We hypothesize that participants in BWL+VOUCHER and BWL+HOME will achieve greater improvements in weight, self-reported and objective markers of dietary quality, and health-related quality of life relative to BWL-Alone. Further, we predict that participants in BWL+HOME will experience greater improvements in weight, dietary quality, and quality of life than BWL+VOUCHER. Assessments will occur at weeks 0, 12, and 24.

4.2 Scientific Rationale for Study Design

The BWL-Alone condition is included because we believe it is necessary to determine the added value of food supplementation above the standard treatment. We elected to use a multi-arm design, rather than sequential 2-arm trials, because it makes better use of resources and offers participants a higher probability of being allocated to a food supplementation intervention.[89]

4.3 End of Study Definition

A participant is considered to have completed the study if he or she has completed all parts of the study including the last visit and the last scheduled procedure.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Age $\geq$18 years
4. BMI $\geq$30 kg/m^2 at screening visit
5. Screening positive for food insecurity using a score of $\geq$3 on the 10-item US Adult Food Security Survey Module[109]
6. Completion of baseline assessments
7. Ability to engage in physical activity (i.e., can walk at least 2 blocks)
8. Willing and able to provide pictures of food receipts to study team (or mail actual receipts)
9. Ability to reliably receive packages at a consistent location in a timely manner
10. Telephone or internet service to communicate with study staff

11. For females of reproductive potential: agreement to use of highly effective contraception for during study participation

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Serious medical conditions (e.g., type 1 or type 2 diabetes, renal failure) that may pose a risk to the participant during intervention, cause a change in weight, or limit ability to adhere to the program's behavioral recommendations
2. Significant psychiatric conditions (e.g., active substance abuse, schizophrenia) that may pose a risk to the participant during intervention, cause a change in weight, or limit ability to adhere to the program's behavioral recommendations
3. Breastfeeding, pregnant or planning pregnancy in the next 6 months (because weight loss is typically discouraged during pregnancy and there is minimal literature on the safety of dietary restrictions necessary for intentional weight loss during gestation; and guidelines, such as those from the IOM, recommend *weight gain* (though weight gain targets are lower) for pregnant people with obesity)[110]
4. Planned move from the Philadelphia area in the next 6 months
5. Weight loss of >5 kg in the previous 90 days
6. Recently began a course of or changed the dosage of medication that can cause significant weight change (±5 kg)
7. Previous or planned obesity treatment with surgery (excluding lap band if removed for >1 year) or a weight-loss device
8. Use of prescription or over the counter medications for chronic weight management in the past 3 months
9. Household member already participating in study due to potential contamination effects
10. Lack of stable residence and ability to store and prepare food

11. Lifestyle Considerations

During this study, participants will be asked to not seek any other lifestyle, pharmacologic, or surgical treatments for obesity.

5.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened after 3 months. Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 Strategies for Recruitment and Retention

Participants will be recruited utilizing a multimodal strategy. Participants will be recruited using advertisements and flyers in print, newspaper, radio, and social media outlets. We will also recruit participants in collaboration with community partners, referrals from primary care practices at the University of Pennsylvania Health Care System, and food pantries. We will be recruiting from the university-based website, iConnect, which allows access to their volunteer registry data of potential participants. We will use study condition terms such as obesity. Recruitment may also use Penn media services (e.g., communications) and social media (e.g., Facebook, Twitter). Social media recruitment will be limited to one-way advertisements.

Retention during follow-up will be promoted with strategies such as: providing reimbursement for travel; conducting assessment visits at convenient times for participants (e.g., early morning, weekends); emphasizing the clinical and research obligations of the study; and addressing potential participant disappointment with being assigned to a particular study condition.

5.5 Measures to Minimize Bias: Randomization and Blinding

A permuted block randomization method will be used to assign participants to one of the three intervention groups in a 1:1:1 ratio. Once eligibility is confirmed, intervention assignment will be made by a pre-programmed randomization scheme. Block sizes will be varied to minimize potential bias, and randomization will be stratified by baseline SNAP/WIC receipt (vs no receipt). All participants who are randomized will be entered into the study database and analyzed according to Consolidated Standards of Reporting Trials guidelines for multi-arm parallel-group randomized trials.[111] This is an open-labelled randomized trial.

6 ASSESSMENT AND PROCEDURES

Phone screen. Interested participants will be consented verbally over the phone by study staff to participate in the initial telephone screening. Study staff will describe the study, explain that the research is completely voluntary, and conduct a brief screening of candidates who express an interest in proceeding (e.g., self-reported height and weight to calculate BMI and food insecurity eligibility). We request a waiver of written documentation of consent for the telephone and questionnaire screen. Those who appear eligible will attend an in-person screening visit where they will receive detailed information about the study, eligibility will be verified, informed consent obtained, and baseline assessments completed. Based on our previous studies, we expect to screen 40 participants per month who respond to our advertisements and enroll 8-10 participants each month.

Screening and intake visit. After the phone screen, eligible subjects will be forwarded a modified version of the Weight and Lifestyle Inventory (WALI),[25] an inventory that assesses general eating and lifestyle behaviors, the screening for food insecurity using the 10-item US Adult Food Security Survey Module, and the Patient Health Questionnaire-8 via REDCap. The surveys will be completed by participants prior to their screening/informed consent visit. (All patients and subjects at our Center complete the WALI and a depression symptom screening to facilitate their initial interview.)

Eligible participants will attend a 1.5-hour, in-person screening visit. At this intake visit, candidates will meet individually with study staff, who will explain the study and obtain participants' informed consent. The in-person interview will be conducted by study staff, who will obtain informed consent and evaluate subjects' behavioral eligibility (i.e., willingness and appropriateness to participate). This will include our assessment of the applicant's mood (as measured by interview and the PHQ-8) and dietary quality (as assessed by a 24-hour dietary recall). Individuals who remain interested and pass this portion of the assessment will be asked about their medical history to determine medical eligibility. The following procedures will be completed at the screening visit:

- Informed consent
- Behavioral evaluations
- Review of modified version of the Weight and Lifestyle Inventory[25]
- Contact information
- Height and weight to assess BMI
- Routine medical history
- Review of medications
- Waist circumference
- Blood pressure and heart rate
- Urine pregnancy test (if unsure about pregnancy status)
- Questionnaires
    - Demographic data
    - Short Form-36 (SF-36)
    - Impact of Weight on Quality of Life-Lite (IWQOL-Lite)
    - US Adult Food Security Survey, 10 item
    - Eating Disorder Examination Questionnaire (EDE-Q)
    - Patient Health Questionnaire 8 (PHQ-8)
    - Eating Behavior Inventory (EBI)
    - Eating Self-Efficacy Survey
    - Perceived Nutrition Environment
    - Neighborhood Environment Walkability Scale
- 24-hour dietary recall interview
- Skin carotenoid assessment
- A second 24-hour dietary recall will be scheduled within 7 days and will need to be completed before the participant is randomized.

Randomization visit. The randomization visit will occur within two weeks of the second dietary recall (scheduled within 7 days after the baseline assessment visit). For randomized participants, the first BWL visit will also occur at this visit.

7 STUDY INTERVENTIONS

7.1 Study Intervention Description

BWL-All Groups

Participants in all groups will receive the same lifestyle modification program consisting of behavioral, physical activity, and dietary counseling.[112] Participants will have 14 brief, individual, telehealth (15 to 20 minute) lifestyle counseling sessions with visits scheduled weekly for the first 4 weeks (weeks 1, 2, 3, and 4) and every-other week from weeks 6-24 (weeks 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24). This is the schedule and duration of counseling visits recommended by CMS[2] (and as now assessed by our research team in three randomized trials[113-115]). Counseling sessions will be delivered by trained interventionists. Interventionists will complete a 10-hour initial training and every-other-week supervision provided by Dr. Chao. They also will receive specific training in how to adhere to the intervention protocol.[112] Telehealth visits (delivered by telephone or videoconference) will be used to reduce time and transportation barriers of in-person visits. Previous research supports that weight loss is similar with remote and in-person visits.[116,117] If participants do not have access to a telephone or videoconference, they will be allowed to have visits on-site as needed.

Behavioral. The behavioral treatment will be adapted from the MODEL Program developed by our team, with tailoring for individuals with food insecurity.[112-114] The program represents an abbreviated version of the Diabetes Prevention Program protocol (with 15-minute rather than 30-minute visits).[11,17,97-99] Core behavioral skills include self-monitoring calorie intake, physical activity, and weight; reducing portion sizes of high-calorie foods and increasing portions of low energy-density foods (e.g., fruits and vegetables); stimulus control; identifying triggers for overeating; setting goals; problem solving; and social support. The participants will be encouraged to weigh themselves at home daily in light clothing without shoes (all participants will be provided with a digital body weight scale); daily weighing is associated with greater weight loss compared to less frequent self-weighing.[100] The 15-minute intervention visits in the three treatment groups will be conducted using a similar format employed in our previous studies.[112-114]

At each visit, the participant and interventionist will discuss the weight change from the prior session and whether it meets expectations. They will then review the participant's food and activity records for the prior week to determine the number of days records were kept and the total number of calories consumed and minutes of activity completed for the week. Problem solving will be used to address any difficulties encountered. The provider will then review a new topic in weight management, from the treatment protocol, and discuss the participant's accompanying homework assignments for the next session. Participant handouts, which summarize the key learning points and homework assignments for the next session, will be provided for each session. Session content will be tailored to individuals with food insecurity using strategies from ongoing trials by Delahanty and as described below. Missed visits will be rescheduled when possible, within a visit window of $\pm$4 days.

Diet. Participants across groups will be given calorie goals based on weight, in accordance with standard guidelines (e.g., 1200-1500 for those <250 lbs and 1500-1800 for those $\geq$250 lbs, with approximately 15% to 20% kcal from protein, 20% to 35% from fat, and the remainder from carbohydrate).[101] Emphasis will be placed on increasing intake of low-energy dense foods (e.g., fruits, vegetables, and lean meats) and decreasing consumption of high-calorie foods. Participants will be instructed to record their food and calorie intake daily, using paper-and-pencil diaries or on-line trackers including MyFitnessPal, a publicly available and free app for dietary self-monitoring. They will be encouraged to record what they eat and drink directly after consumption. All participants will be provided with low-cost meal plans, menus, and recipes (which offer breakfast, lunch, and dinner options for the week) that were provided in the Diabetes Prevention Program[18] and POWER-UP studies.[20] In addition, content will include strategies about shopping and eating healthily on a limited budget.

Physical activity. Participants will be instructed to gradually increase their physical activity to ≥180 minutes/week by week 24, primarily through walking or other exercises. Participants will also be instructed to record their minutes of physical activity each day. In addition, participants will be instructed to increase their daily steps by 250 a week, until they reach a goal >10,000 steps per day. Each participant will be provided with a pedometer. The physical activity prescription is based on that used in the MODEL,[112] Look AHEAD[118] and POWER-UP studies.[119] Participants will be instructed to record their activity daily. Participants who live in areas with high violent crime and those who have safety concerns face additional barriers to engaging in physical activity.[120,121] Unsafe neighborhoods may hinder outdoor activity such as walking and reduce access to neighborhood parks and other places to walk. We have made several adaptations to our program for individuals who may not feel comfortable walking outside including providing at-home workout videos, low-cost exercise equipment for home use such as jump ropes, and maps of no- and low-cost recreational facilitates.

Referral. As per standard of care, participants will receive passive referrals to external, community and federal resources.[14-16,122,123] All participants will be provided verbal and written information about food resources. This will include referrals to external, community, and federal resources including federal nutrition programs and local food pantries, soup kitchens, and free dining rooms in the Philadelphia area. Referrals will be provided after outcome assessments are completed at baseline, and weeks 12 and 24.

BWL-Alone. The intervention for participants assigned to BWL-Alone is described above. There are no additions or alterations to this treatment plan.

BWL+VOUCHER. Participants randomized to this group will receive the BWL program as detailed above as well as food vouchers, in the form of grocery store gift cards. Participants will be allowed to select to receive gift cards to a grocery store or supermarket from a pre-determined list of stores in the Philadelphia area. Gift cards worth $40 will be emailed (preferred) or, if necessary, mailed to participants every 2 weeks after their BWL session. At each BWL session, the counselor will provide the patient with a nutrition prescription for low-energy dense foods (i.e., fruits, vegetables, lean proteins[49]). Participants will also receive personalized meal plans and menus congruent with their calorie goals and focused on increasing intake of low-energy density foods *while* decreasing high-calorie food intake. Increased intake of low-energy density foods allows patients to consume satisfying portions while also avoiding hunger and improving dietary quality.[49,124] However, reductions in high-calorie foods also must occur for weight loss.[49,124] Counselors will verbally encourage participants to use the vouchers to purchase foods congruent with their weight loss meal plan and to spend the voucher within two weeks. A copy of the prescription, meal plan, and menus with portion size information will also be emailed/mailed to the participant.

Only gift cards to supermarkets or grocery stores, as defined by the USDA store type definitions, will be eligible.[125] Provision of the gift cards will be contingent on attending BWL sessions and providing pictures of receipts for purchases made with the voucher in the previous 2 weeks. (Participants will be permitted 3 lost or missing receipts. In these instances, participants will still be provided with a voucher, and purchases will be reviewed verbally. If participants are not able to send a picture of their receipts, we will provide them pre-paid envelopes that they can use to return their receipts.) Review of receipts will also provide an opportunity for participants to get personalized feedback and counseling regarding food choices. If participants do not spend the full voucher amount, staff will record any unspent amount, and participants will be encouraged to redeem it in subsequent weeks. Individuals will not be prevented from obtaining food or food-related resources from other programs such as WIC,

SNAP, or food pantries. The dollar amount was selected as this seems to be the minimal level of subsidy required to induce a meaningful increase in healthier food purchases and consumption. Previous research has shown that low-income households spend about $20 less on food per week than food-secure households, and this amount was selected to closely bridge the gap in food spending between these two groups.[53] This led to the voucher value of $20 per week (i.e., $40 every 2 weeks).

Gift cards were selected to ensure discreetness and minimize stigmatization of participants. We decided not to limit the food choices for our vouchers due to concerns about the effectiveness and feasibility of placing restrictions on the types of foods that can be purchased. We considered using produce vouchers for farmers' markets. However, we decided it would be most feasible and translatable to use grocery store vouchers. Some farmers' markets are seasonal and geographically limited, which may create time and transportation barriers. In a randomized, community-based experiment, fruit and vegetable intake, overall dietary quality, and food insecurity did not different between vouchers redeemable for only fruits and vegetables versus unrestricted food vouchers.[126] However, we will provide participants with a prescription with recommended foods (e.g., fruits, vegetables, lean meats) and detailed meal plans, reinforcing selection of these foods at each BWL session. The supplementation from the intervention will not be increased to cover family size. This decision was based on the need to ensure an equivalent intervention cost across participants given the individual basis of the study design. Family size will be measured within the patient demographics to allow further investigation of the influence of this factor.

BWL+HOME. Participants randomized to this group will receive home-delivered, medically tailored groceries in addition to BWL, as detailed above. In Philadelphia, only 19% of all retail foods stores have high produce supply (e.g., grocery stores).[127] Lower income neighborhoods have disproportionately high numbers of fast-food restaurants and low-produce supply stores (e.g., corner stores, convenience stores, dollar stores), with low-produce supply stores often representing more than 90% of stores in a neighborhood.[127] This makes it harder to find healthy food, and fresh produce and lean meats are often expensive and low quality in stores in lower-income neighborhoods.[128] The HOME intervention is designed to increase dietary adherence and quality by addressing affordability as well as accessibility and convenience, which we hypothesize will allow participants to consume low-energy density foods congruent with the patient's meal plan and caloric prescription. In addition, receiving grocery items can help decrease purchases of unhealthy, impulse sensitive-food purchases such as candy and desserts.[129]

The boxes will contain low-energy density foods conducive to weight management guidelines[49,124] and meal plans we have used previously[112,118] including shelf-stable and perishable products like lean meats, fresh vegetables, and fruits. Selection of items for the boxes will also be informed from data from food basket studies that have identified commonly consumed and culturally acceptable foods that meet current dietary recommendations.[130,131] Only canned products low in sodium and added sugars will be eligible. Every 2 weeks, participants will be allowed to select a choice of one of 4 boxes with slightly varied contents, though each box will be sufficient to last two weeks and to provide 600-700 kcals/day (~50% of daily calories for weight loss), with recommended participant purchased and obtained additions to make up the balance. A partial rather than a full subsidy treatment will be provided based on a previous study showing similar weight losses between conditions and partial subsidies are more cost-effective than full subsidies.[132] The contents of each box will be approximately $40 ($20/week), not including delivery and service fees.

At each BWL session, participants will receive personalized meal plans, menus, and recipes corresponding with their calorie goals and with the content of the grocery box they selected integrated into the meal plans, menus, and recipes. As with the other groups, participants will be encouraged to increase intake of low-energy density foods and decrease high-calorie food intake. Interventionists will encourage participants to consume the food provided within two weeks. Like the voucher intervention, participants will be eligible to receive food packages every 2 weeks, contingent on their attending their BWL session. Participants will be asked to self-report items they consumed from their stock box at each BWL session using a standardized checklist. Participants will be instructed not to share the meals with others in their household. As in the BWL+VOUCHER arm, individuals will not be prevented from obtaining food from other programs such as WIC, SNAP, or food pantries. While we considered using medically tailored meals (e.g., home delivered prepared meals), we decided not to use these for the current study. Medically tailored meals are typically costly, may not provide additional skills related to cooking, and are logistically more challenging to disseminate as most need to be kept frozen, which may prohibit widespread policy use.

7.2 Study Intervention Adherence

All staff and clinicians will be trained in the protocol by an experienced staff member. To ensure provider skill acquisition we will use role playing. Fidelity to the treatment protocols, content, information, and delivery will be assessed using observation checklists. To minimize provider and intervention 'drift', we will meet every-other-week to discuss intervention strategies and problem solve challenges including adherence with the use of vouchers and grocery boxes. We will have weekly team meetings to discuss participant progress and protocol adherence.

Attendance of intervention sessions will be used to assess adherence to the BWL treatment. Redemption rates of vouchers will be assessed using receipts collected every 2 weeks. Data will be extracted on date of purchase, grocery items purchased and grocery items' price. Each food item will be coded into broader categories of food (e.g., fruits, vegetables) based on the USDA food guidelines. Consumption of items from food boxes will be reviewed with a standardized checklist. Food resource connection and enrollment will be assessed with a questionnaire at each outcome assessment.

7.3 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Concomitant medications will be assessed at baseline, weeks 12 and 24.

7.3.1 Rescue Medicine

The study site will not supply rescue medications. During this study, participants will be asked to refrain from joining another structured weight loss program, starting a weight loss medication, or receiving bariatric surgery. If participants do begin a weight loss medication or have bariatric surgery, they will be allowed to continue in the study treatment and assessments, and it will be documented in participant forms and analyzed using sensitivity analyses.

8 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Intervention

Discontinuation from the study intervention does not mean discontinuation from the study. If participants are willing, we will ask them to complete study assessments as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Follow-up assessment measures
- Follow-up questionnaires
- Reason for discontinuation

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- If any clinical adverse event (AE) or other condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Participants who sign the informed consent form and are randomized but do not attend the randomization visit may be replaced. Participants who sign the informed consent form and are randomized and receive the study intervention (i.e., attend the first BWL visit after the randomization visit), and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

For participants that may discontinue or withdraw early, we will capture the rationale during the final visit.

8.3 Lost To Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for the week 24 assessment (+4 weeks) and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study assessment visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.

Should the participant continue to be unreachable for their week 24 assessment, he or she will be considered to have withdrawn from the study with the primary reason of lost to follow-up.

9 STUDY ASSESSMENTS

9.1 Efficacy Assessments

Research staff will conduct assessments at our Center at weeks 0 (baseline), 12 and 24. All measures will be administered at all timepoints. Assessment staff will receive training in adherence to the data collection protocol. Questionnaires will be completed on REDCap, a secure, web-based program (if requested, participants can completed questionnaires on paper). To provide compensation for time and travel, participants will be paid $40 per assessment. We will provide participants with ClinCards, which are similar to debit cards, that we have used for other studies. This form of payment allows us to load money remotely, enabling us to compensate participants soon after they complete study tasks.

Demographic and neighborhood data. Standard questionnaires will be administered to collect data on demographics at week 0 including age, biological sex, gender, race/ethnicity, income, street address, zip code, receipt of SNAP and/or WIC, household size, disabilities, marital status, and highest education level. We will recollect these data at weeks 12 and 24 to account for changes in status. We will also collect descriptive data at each timepoint on neighborhood food and physical activity environment including the Perceived Nutrition Environment Measures Survey[133] and Neighborhood Environment Walkability scale.[134]

Weight and height. Weight will be measured in light clothes and no shoes, after an 8-hour fast, using a standardized scale calibrated monthly and accurate to 0.1 kg. Weight will be measured in duplicate. Height will be assessed in duplicate with a wall-mounted stadiometer at baseline.

Quality of life. General health-related quality of life (HRQOL) will be assessed by the Short Form (SF)-36, which contains 36 items that measure subjective health status.[119] The scale forms two summary measures—a physical and mental component summary. Scores are transformed using a 0 to 100 scale, with higher scores indicating better HRQOL. Weight-related quality of life will be measured with the 31-item IWQOL-Lite scale.[120] The measure generates a total score ranging from 0 (worst) to 100 (best).

Diet. Participants will complete two 24-hour dietary recalls at each assessment point. During each assessment, one 24-hour recall will be conducted during an in-person study visit, and one will be conducted over the telephone within 7 days of the primary assessment. We will use the version of the assessment that includes questions about portion sizes. The assessments will be

performed by a trained assessor interactively using the Nutrition Data System program (University of Minnesota).[135] A standard 5-step, multiple-pass method will be used to improve accuracy. Diet information will be summarized into calorie intake and macronutrient composition.

Skin carotenoid levels. Skin carotenoid levels will be measured with the Veggie Meter® (Longevity Link Corporation, Salt Lake City, Utah). The Veggie Meter® is a noninvasive research-grade instrument that detects and quantifies the optical density of skin carotenoids using reflection spectroscopy.[136] The measure has been validated against plasma carotenoid levels[137] and is reflective of intake from the past 8 weeks.[138] The measure is unaffected by an individual's skin melanin concentration.[139] We will follow the standardized protocol for assessments including using the fingertip three times sequentially and averaging the three scores.[139-141] The same fingertip will be used at all assessment points with preference for the non-dominant ring finger. Scores range from 0 to 800 with higher scores indicating higher skin carotenoid stores. Participants will be told that this is measuring general health and will not be told the specific biomarker being assessed as this may influence intake of these foods.

Cardiometabolic risk factors will be assessed using blood pressure, waist circumference, and pulse. Blood pressure and pulse will be measured on each occasion using an automated monitor. Two readings will be taken on each occasion (at 1-minute intervals), after participants have been seated for at least 5 minutes. Waist circumference (measured horizontally halfway between the lowest rib and the top of the hipbone) to the nearest 0.1 cm will be assessed. Two waist measurements will be obtained at each assessment visit.

Exploratory endpoints. In addition, we will collect exploratory data on mediators and surrogate endpoints. Food insecurity status will be assessed with the 10-item US Adult Food Security Survey Module.[109] At follow-up assessments, we will ask about food insecurity over the past 30 days. Depressive symptoms will be assessed with the Patient Health Questionnaire-8 (PHQ-8),[142] a clinically validated measure (that does not include the suicidality question contained in the PHQ-9). Weight control behaviors will be assessed with the Eating Behavior Inventory (EBI).[121] The EBI is a 26-item measure of behaviors conducive to weight control (e.g., "I carefully watch the quantity of food that I eat.") Scores range from 26 to 130. Higher EBI scores indicate a greater use of weight control behaviors. Psychometric measures of eating behavior will include the Eating Disorder Examination Questionnaire (EDE-Q). The EDE-Q evaluates binge eating episode frequency as well as associated features of disordered eating. Dietary self-efficacy will be measured using the Self-Efficacy for Diet Scale.[143] Satisfaction with the interventions will be assessed using Likert scales and open-ended questions.

9.2 Safety and Other Assessments

Safety evaluations include adverse events (AEs) and assessment of blood pressure and heart rate. In the event of adverse mental health events, participants will be referred to a psychologist or psychiatrist for further evaluation, if required. For all non-study-related medical events, participants will be referred to their own primary care provider.

9.3 Adverse Events and Serious Adverse Events

9.3.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

9.3.2 Definition of Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance they may jeopardize the participant and may require intervention to prevent one of the other serious outcomes noted above.

9.3.3 Classification of an Adverse Event

9.3.3.1 Severity of Event

For adverse events (AEs), the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

9.3.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to the study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Unrelated – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.3.3.3 Expectedness

The study team will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9.3.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse effects using the protocol defined grading system at each assessment visit. Participants will be monitored by medical histories. The severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each assessment visit (baseline, weeks 12 and 24) study staff will seek information on adverse events by non-directive questioning. Adverse events may also be detected when they are volunteered by the participant during the screening process or between assessment visits. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade
2. Duration (start and end dates)
3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process
5. Action taken with respect to study or investigational treatment or process (none, treatment adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether the event is serious

Once an adverse event is detected, it will be followed until its resolution during the trial or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

9.3.5 Adverse Event Reporting

Reporting Period

Adverse events will be reported from the time of informed consent until study completion.

Investigator Reporting: Notifying the Study Sponsor

Every SAE, regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the sponsor within **24 hours** of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

9.3.6 Serious Adverse Event Reporting

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

9.4 Unanticipated Problems

9.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all 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 Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("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); and
- 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.

9.4.2 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as:

- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

should be reported by the investigator to the National Institutes of Health and reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.
- Any other UP will be reported to the Sponsor, IRB and to the DCC/study sponsor within 1 week of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 7 days of the IRB's receipt of the report of the problem from the investigator.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

Primary Efficacy Endpoint(s):

Aim 1: BWL+VOUCHER and BWL+HOME will result in greater weight loss (percent of initial weight) at 24 weeks than BWL-Alone.

Secondary Efficacy Endpoint(s):

Aim 2: BWL+HOME will result in greater weight loss (percent of initial weight) at 24 weeks than BWL+VOUCHER.

Aim 3a: BWL+VOUCHER and BWL+HOME, relative to BWL-Alone, produces greater improvements in health-related quality of life (HRQOL) and dietary quality as assessed by skin carotenoid levels (a fruit and vegetable biomarker) and Healthy Eating Index (HEI) scores from baseline to week 24.

Aim 3b: BWL+HOME, compared to BWL+VOUCHER, produces greater improvements in HRQOL, skin carotenoid levels and HEI scores from baseline to week 24.

10.2 Sample Size Determination

This is an exploratory study. The sample size should be sufficient to provide us with effect size estimates for a larger randomized controlled trial.

10.3 Populations for Analyses

Populations for analyses will include:

- Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)
- Per-Protocol Analysis Dataset: subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants attended at least 80% of study intervention visits; participants reported consuming at least 50% of food purchased with food vouchers (BWL+VOUCHER) or 50% of food they received from food boxes (BWL+HOME))

10.4 Statistical Analyses

10.4.1 General Approach

Descriptive statistics and exploratory plots will be generated for all variables of interest. We will conduct initial exploratory data analyses to identify outliers and to assess the distribution of data. Data summaries will be produced both the combined sample, and separately by treatment arm. Continuous variables will be transformed if they are skewed. Categorical variables will be summarized as proportions. Baseline characteristics will be compared among the treatment arms using ANOVAs for continuous variables and chi-square tests for categorical variables. Key baseline variables that differ by treatment arm will be considered for use as covariates in the

analyses described below. Patterns of missing data will be examined. If the missingness mechanism is related to the missing outcome itself, we will use sensitivity analyses to explore how robust our findings are with respect to a range of assumptions regarding missing data.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The two primary outcomes are to test the hypotheses that each of the BWL+VOUCHER and BWL+HOME interventions will result in better weight loss at week 24 compared to BWL-Alone. The primary analysis is an intention-to-treat, between-group comparison of the mean change from baseline (randomization) to week 24 using a linear mixed model. Specifically, we will regress the mean change from baseline on the treatment indicator and baseline weight loss. Significance will be determined using an α cutoff of 0.05. The primary analysis will be an intent-to-treat analysis. The model will include each participant as a random intercept to adjust for within-patient correlation of the repeated measures, fixed predictors of study arm indicators, time indicators, and time by study arm interactions. In addition, sensitivity analyses will be conducted adjusting the model by including baseline variables that either had between-group differences at baseline or that were associated with the likelihood of missing outcomes at a 0.20 significance level.

10.4.3 Analysis of the Secondary and Exploratory Endpoint(s)

For non-primary comparisons, an α level of 0.05 will be used for significance. We will test the main effects of treatment condition on percent initial weight change at skin carotenoid levels, general health and weight-related quality of life as well as exploratory endpoints using linear mixed models and similar methods as described above. Analyses will use intention-to-treat analyses and will be conducted with and without adjustment for baseline differences in characteristics. We plan to assess for differential effects of the interventions based on sex/gender and race/ethnicity. Separate analyses will be performed for men and women and based on self-identified race/ethnicity, although these will be considered exploratory as there is no strong reason to hypothesize a difference in efficacy based on these characteristics.

10.4.4 Safety Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA)). Each AE will be counted once only for a given participant and presented using the severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings. Information that will be reported about each AE will include duration (from start date and stop date) severity, relationship, expectedness, outcome, and duration. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a table or a listing.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory, Ethical, and Study Oversight Considerations

11.1.1 Informed Consent Process

11.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Informed consent document
- Printed and web-based materials
- Phone screening scripts

11.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. 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 have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. 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. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.1.1.3 Informed Consent Process / HIPAA Authorization

Following the screening telephone call, trained clinical assessors will meet in person with all potential participants to describe the study, its requirements, and its likely risks and benefits. Participants will be provided a written copy of the Consent Form/HIPAA Authorization at this meeting and will be given an opportunity to read it and have all of their questions answered. Persons who wish to participate in the study will be asked to give their written consent at the

time of consent discussion and will then continue with the screening visit. Participants will also be permitted to discuss the consent form and procedures and return the signed form and continue with the screening at a later date (within 2 weeks), if they prefer. Participants will be told that they can contact the Principal Investigator at any time if they have questions about the study. The study team member who reviews the consent document will emphasize that participation in the study is voluntary and that medical care will not be influenced by the participants decision to participate or not. The f process will take place in a private office or exam room to help protect subject privacy. Subject comprehension of the nature of the study will be assessed using interactive conservation methods (e.g., asking the potential subject to paraphrase different points of discussion, asking open-ended questions, encouraging questions).

11.1.1.4 Waiver of Written Documentation of Consent

We are requesting a waiver of the requirement to obtain a signed consent form for the phone screening. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

11.1.2 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, research records for the participants in this study. The clinical study site will permit access to such records.

The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be securely stored. At the end of the study, all study databases will be de-identified and archived.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

11.1.3 Future Use of Stored Data

Data collected for this study will be analyzed and stored. After the study is completed, the de-identified, archived data will be transmitted to and stored, for use by other researchers including those outside of the study. Permission to store data will be included in the informed consent.

11.1.4 Safety Oversight

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis and for reporting Serious Adverse Events and Unanticipated Problems to the Institutional Review Board (IRB).

11.1.5 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).
- The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. diagnostic laboratory, etc.).
- Monitoring will be conducted virtually/on-site throughout the study and through a targeted or random review of certain data.
- Independent audits may be conducted to ensure monitoring practices are performed consistently at the clinical site.

11.1.6 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6(R2).

Our site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. Quality control (QC) procedures will be

implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be investigated for clarification/resolution. The checks will verify that the clinical trial is conducted and data are generated, and specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.1.7 Data Handling and Record Keeping

11.1.7.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data and follow ALCOAC standards (attributable, legible, contemporaneous, original, accurate, and complete).

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCAP, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Clinical and laboratory data will be entered into a 21 CFR Part 11-compliant electronic data capture system (EDC) that includes individual user account level password protection. This EDC (Velos version 9) supports programmable data entry validation rules and edit checks to identify data entry errors.]

11.1.7.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if

applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.1.8 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect subject safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

11.1.9 Publication and Data Sharing Policy

This study will comply with the data sharing agreement.

The Sponsor must approve all sharing of information/data prior to its occurrence.

11.1.10 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

11.2 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
2.0	12/20/22	Finger used in taking skin caroteinoid measurement changed from "right index finger" to "non-dominant ring finger."	Per: Radtke, M. D., Poe, M., Stookey, J., Jilcott Pitts, S., Moran, N. E., Landry, M. J., Rubin, L. P., Stage, V. C., & Scherr, R. E. (2021). Recommendations for the Use of the Veggie Meter® for Spectroscopy-Based Skin Carotenoid Measurements in the Research Setting. *Current developments in nutrition*, *5*(8), nzab104. https://doi.org/10.1093/cdn/nzab104
3.0	2/21/23	Removed: "A hard copy of the meal plan, menus, and recipes with portion size information will also be mailed with the groceries"	Feasibility.

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