Enhancing Weight Loss with Financial Incentives in Teens

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Study Protocol and Statistical Analysis Plan dated 2022Apr06

University of Minnesota

Enhancing Weight Loss with Financial Incentives in Teens

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Protocol Change History:	Version 1: March 2, 2017 Version 2: April 11, 2017 blood volumes added, clarification to 6.11.7 Version 3: June 27, 2017 reduction in number of vascular endpoints, elimination of FitBit device, revision of meal replacement therapy (Seattle Sutton food provision) Version 4: November 1, 2017 reduction of physical exams & Tanner staging to baseline only, add Megan Oberle as Co-Investigator Version 5: December 8, 2017 neuromuscular disorder exclusion, substance abuse exclusion Version 6: January 10, 2019 Seattle Sutton Healthy Meals business name change to: Healthy for Life Meals Version 7: Revised the consent process to include consent conducted virtually Version 8: Revised section 11.3 of the protocol to discuss the types of virtual consent that will be utilized and any encryption Version 9: Reduces the sample size to 120 participants. Eliminates the Week 78 visit. Revises the statistical plan. Removes the food diary. Version 10: Clarifies the reporting period for adverse events and serious adverse events now that the protocol has been shortened to 52 weeks. This version also clarifies questionnaires, how blood pressure is being measured, corrects a mention of Seattle Sutton's Healthy Eating, updates the number of iDXA scans, the number of participants, clarifies the monthly phone calls and the total compensation. Version 11: Removes the metabolic rate/energy expenditure testing. We were not allowed to resume this once we were allowed to re-start visits after COVID started. The decision has been made to completely remove it from the protocol at this time. This version also increases enrollment to 130 as a recent batch of recruitment letters has yielded significant interest and we would like to enroll those who are deemed eligible. Version 12: Makes changes to the statistical plan (section 7) of the protocol.

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List of Abbreviations

AE	Adverse Event
AEBQ	Adult Eating Behavior Questionnaire
BIPAP	Bilevel Positive Airway Pressure
BMI	Body mass index
CEBQ	Child Eating Behavior Questionnaire
CES-DC	Depression Scale for Children
CFR	Code of Federal Regulations
CIs	Confidence Intervals
CLIA	Clinical Laboratory Improvement Amendments
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTSI	Clinical Translational Science Institute
DSMB	Data safety and monitoring board
DSM-V	Diagnostic and Statistical Manual of Mental Disorders version 5
ECG	Electrocardiogram
EDE-Q	Eating Disorder Examination Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDL	High density lipoprotein
HIPAA	Health Insurance Portability & Accountability Act of 1996
iDXA	i Dual Energy X-ray Absorptiometry
IWQOL-Kids	Impact of Weight on Quality of Life
IRB	Institutional Review Board
ITT	Intent to Treat
LDL	Low density lipoprotein
MN-POC	Minnesota Pediatric Obesity Consortium
QEWP	Questionnaire of Eating and Weight Patterns-Adolescent
PedsQL™	Young Adult Quality of Life Inventory) Child and Parent
PHI	Personal Health Information
REPA	Report of External Professional Activities
SCARED	Screen for Child Anxiety Related Disorders
SAE	Serious Adverse Event
TC	Total Cholesterol
TG	Triglycerides
UPIRTSO	Unanticipated problems involving risk to subjects or others

Study Summary

Title	Enhancing Weight Loss with Financial Incentives in Teens
Phase	N/A
Methodology	Randomized, controlled clinical trial
Study Duration	5 Years
Study Center	University of Minnesota Center for Pediatric Obesity Medicine in collaboration with the Minnesota Pediatric Obesity Consortium (MN-POC)
Objectives & Hypotheses	**Primary Objective: Evaluate the effect of meal replacement therapy plus financial incentives on weight loss, cardiometabolic risk factors, vascular health, and behavior change among adolescents with severe obesity.** We hypothesize that the use of meal replacement therapy with financial incentives (vs. no financial incentives) will lead to greater percent reduction in BMI (primary endpoint) as well as reduce body fat, blood pressure, triglycerides/HDL ratio, inflammation, oxidative stress, arterial stiffness, and improve heart rate variability at 26 and 52 weeks. **Secondary Objectives: Identify weight loss thresholds associated with significant improvements in cardiometabolic risk factors and vascular health in adolescents with severe obesity.** We hypothesize that a minimum weight loss threshold exists, that when exceeded, will be associated with meaningful improvements in multiple cardiometabolic risk factors and parameters of vascular health.
Number of Participants	130
Diagnosis and Main Inclusion Criteria	**Diagnosis:** Severe obesity **Main Inclusion Criteria:** • BMI ≥1.2 times the 95th percentile (based on sex and age) or BMI ≥35 kg/m^2 • Age 13-17 years
Study Intervention	All participants will engage in 52 weeks of meal replacement therapy. Participants will be randomly assigned to receive financial incentives for weight loss or no financial incentives.
Statistical Methodology	The primary analysis will be conducted using the intent-to-treat population to compare the mean BMI percent change from randomization to 52 weeks (additional analyses will use the 26-week time-point as secondary) of follow-up between the financial incentives and no financial incentives groups, adjusted for BMI at randomization and insurance status (randomization stratification factor) for added precision. Confidence intervals (CIs) and P-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$.

1 Introduction/Summary

Severe obesity, defined as a body mass index (BMI) ≥20% above the 95th percentile or BMI ≥35 kg/m^2, is the fastest growing category of pediatric obesity, with a reported prevalence near 6% in the United States.[1-5] The number and magnitude of cardiometabolic risk factors and co-morbidities, including vascular abnormalities, is much higher in severe obesity vs. overweight or obesity.[2, 6] Severe obesity tracks strongly into adulthood[6] and increases the risk of cardiovascular disease[6] and type 2 diabetes.[7] Initiating effective weight loss interventions prior to adulthood offers the best opportunity to alter the disease trajectory and meaningfully improve long-term health.[8, 9] However, because conventional treatment approaches rarely result in sufficient weight loss in adolescents with severe obesity,[10-13] highly-innovative and effective strategies are desperately needed.

The financial incentive model has been used successfully in adult obesity trials to address suboptimal adherence to lifestyle modification therapy and improves weight loss outcomes.[14-18] Although yet to be investigated as a weight loss intervention among adolescents, financial incentives have been shown to improve many health-related behaviors in teenagers including compliance with wearing physical activity accelerometers,[19] treatment adherence in type 1 diabetes,[20] school attendance in youth at risk for HIV infections,[21] and smoking cessation.[22, 23] Owing to the refractory nature of pediatric severe obesity, financial incentives are more likely to be effective if used in concert with a structured dietary plan such as meal replacement therapy (pre-portioned, calorically defined meals), which has been shown to elicit superior weight reduction compared to conventional diets among adults.[24] Although a relatively new treatment for pediatric obesity, meal replacement therapy has produced promising short-term weight loss (6% BMI reduction at 4 months) in adolescents with severe obesity.[25] However, much of the initial weight lost by participants was regained after 4 months, owing to diminished adherence to the meal replacement regimen over time.[25] Our concept is to capitalize on the potential synergy of meal replacement therapy and financial incentives to optimize weight loss and improve cardiometabolic risk factors and vascular health in teens with severe obesity.

This study will afford a unique opportunity to address another key unanswered question related to the treatment of pediatric severe obesity: how much weight loss is necessary to elicit clinically-meaningful improvements in cardiometabolic risk factors and vascular health? It will be critically important for pediatricians to have evidence-based weight loss targets for their patients with severe obesity since it will better inform the type and intensity of the treatments selected in clinical practice. Although evidence-based benchmarks have been established for adults,[26] no such thresholds have been identified for youth with severe obesity. Therefore, we plan to conduct a 12-month randomized, controlled clinical trial to evaluate the effects of meal replacement therapy plus financial incentives on weight loss and cardiometabolic/vascular outcomes among 142 adolescents (ages 13-17 years old) with severe obesity and to identify thresholds of weight loss required to achieve clinically-meaningful cardiometabolic/vascular improvements in this patient population. Importantly, we will be able to characterize the degree of normalization of risk factors and vascular outcomes according to amount of weight loss and compare post-intervention values to a database of youth with normal weight, overweight, and obesity in the same age-range tested in the same laboratory using identical methods.

1.1 Background and Rationale

Severe obesity, defined as a BMI ≥20% above the 95th percentile or BMI ≥35 kg/m^2, is the fastest growing pediatric obesity category, with a reported prevalence of nearly 6% in the United

States.[1-5] The number and magnitude of cardiometabolic risk factors and co-morbidities, including vascular abnormalities, is much higher in severe obesity vs. overweight or obesity.[2, 6] Approximately 85% of children and adolescents with severe obesity have at least 1 cardiovascular risk factor and 60% have 2 or more.[6] Subclinical atherosclerosis and arterial stiffening in the carotid artery is present in youth with severe obesity at levels similar to those with type 2 diabetes.[27] Compared to overweight and obese peers, youth with severe obesity have higher levels of inflammation and oxidative stress,[28] more adverse adipokine profiles,[29] and greater arterial endothelial activation.[30] Moreover, longitudinal data uniformly implicate obesity in childhood as a strong predictor of future risk factor clustering and sub-clinical atherosclerosis in adulthood.[31-33] The risk of developing type 2 diabetes is also high in youth with severe obesity.[7, 34-41] The prevalence of impaired glucose tolerance in children and adolescents with severe obesity is notable, with estimates ranging from 4.5%-25%.[42-44] Perhaps most alarming is the poor prognosis for youth afflicted with severe obesity. Approximately 90% will have a BMI ≥35 kg/m^2 in adulthood;[6] and severe obesity in adulthood reduces life expectancy by 7-14 years.[45] In summary, if left untreated, severe obesity in childhood tracks strongly into adulthood[6] and increases the risk of premature cardiovascular disease[6] and the development of type 2 diabetes.[7]

Initiating effective weight loss interventions during childhood offers the best opportunity to meaningfully alter the disease trajectory and improve long-term health.[8, 9] Early intervention is especially relevant in light of evidence suggesting that duration of obesity is associated with the extent and severity of atherosclerosis.[46] Unfortunately, the lowest-risk and ideal treatment approach, conventional lifestyle modification therapy (diet-, exercise-, behavioral counseling), is relatively ineffective when used alone in terms of BMI reduction and cardiometabolic risk factor improvement in adolescents with severe obesity.[10-13] Indeed, one relatively large study demonstrated that only 2% of adolescents with severe obesity achieved a clinically-meaningful reduction in BMI after 3 years of comprehensive lifestyle modification therapy delivered in a specialty pediatric weight management clinic.[12] The treatment-resistant nature of adolescent severe obesity, at least when conventional approaches are used, has been comprehensively reviewed in a recently-published scientific statement from the American Heart Association.[2] Orlistat is the only weight loss medication approved by the FDA for the treatment of obesity in adolescents but is rarely used owing to minimal effectiveness and notable side effects.[47] Weight loss surgery reduces BMI on the order of 30-40% in adolescents but is not widely available, is associated with greater risk than lifestyle modification therapy or pharmacotherapy, and is often reserved for only those with the most serious co-morbidities.[48-50] Therefore, considering the serious nature of the disease, the poor efficacy of conventional lifestyle modification approaches, and the higher level of risk associated with bariatric surgery, a new direction must be taken in the treatment of severe obesity in adolescents. If the field is to move forward in a meaningful way, highly innovative lifestyle modification strategies and unique combinations of treatments need to be tested in youth who have this difficult-to-treat chronic disease.

The financial incentive model has been used successfully in adult obesity trials to address suboptimal adherence to lifestyle modification therapy and improve weight loss outcomes.[14-18] While probably inappropriate for young children, financial incentives may be an effective tool in teens to address ambivalence, inspire motivation, and improve compliance to obesity interventions, ultimately leading to meaningful behavior change and superior weight loss and risk factor improvement. Indeed, adherence to behavioral targets is a strong predictor of long-term weight loss success among youth.[51] Although yet to be investigated as a weight loss intervention among adolescents, strong rationale supporting this approach can be drawn from evidence demonstrating that financial incentives significantly improved many health-related

behaviors in teens including compliance with wearing physical activity accelerometers,[19] treatment adherence in type 1 diabetes,[20] school attendance in those at risk for HIV infections,[21] and smoking cessation.[22, 23]

Owing to the refractory nature of pediatric severe obesity, financial incentives are more likely to be effective if used in concert with a structured dietary plan such as meal replacement therapy (pre-portioned, calorically defined meals), which has been shown to reduce body weight to a greater extent than the use of conventional dietary regimens among adults.[24] The rationale for the use of meal replacements is that individuals with obesity, including adolescents,[52] often under-estimate caloric intake, and that adherence to a strict, pre-determined meal regimen removes the "guess-work" from eating.

Although a relatively new treatment for pediatric severe obesity, meal replacements elicited promising short-term weight loss (BMI reduction of 6% at 4 months) in a recent study of adolescents with severe obesity[25] and in a separate ongoing trial being conducted by our group (unpublished; data shown in "Preliminary Studies" section). However, in the published trial, much of the initial weight lost was regained by the participants between 4 and 12 months, owing to diminished adherence to the meal replacement regimen over time.[25] Our unique concept is to capitalize on the potential synergy of meal replacement therapy and financial incentives (to optimize adherence), which we believe will lead to clinically-meaningful and sustained weight loss, superior risk factor modification, and vascular health improvement in this difficult-to-treat patient population.

This study will afford a unique opportunity to address another key question related to the treatment of pediatric severe obesity: how much weight loss is necessary to elicit clinically-meaningful improvements in cardiometabolic risk factors, co-morbidities, and vascular health among adolescents with severe obesity? Acknowledging that most teens with severe obesity will opt for non-surgical interventions, it will be critically important for pediatricians to have evidence-based weight loss targets for their patients with severe obesity since it will better inform the type and intensity of the treatments used in clinical practice and may lead to the establishment of future guidelines. Although evidence-based benchmarks have been established for adults,[26] no such thresholds have been investigated in youth with severe obesity.

Therefore, in the current study, we will conduct a clinical trial to determine whether meal replacement therapy plus financial incentives leads to superior weight loss and better health outcomes among adolescents with severe obesity and we will identify the various thresholds of weight loss necessary to achieve specific cardiometabolic risk factor, co-morbidity, and vascular improvements in this unique patient population. Moreover, we will also be able to describe the degree of normalization of cardiometabolic risk factors and vascular outcomes according to varying amounts of weight reduction and compare (in a cross-sectional fashion) post-intervention values to an existing database of youth with normal weight, overweight, and obesity tested in the same facilities/laboratory using the same protocol and methods. Beyond body weight/BMI loss, we will also be able to identify thresholds of reduction in absolute and percent total body fat and absolute and percent visceral fat that are associated with improvements in cardiometabolic risk factors and vascular health.

1.2 Clinical Data to Date

Significance and Preliminary Work

The significance of, and rationale for, the proposed research are that 1) adolescent severe obesity is a prevalent and serious disease that is extremely difficult to successfully treat; 2) conventional lifestyle modification treatment approaches are rarely effective among adolescents

with severe obesity; and 3) although never before evaluated in youth, the combination of meal replacements and financial incentives represents a novel, promising, and relatively low-risk (compared to medications or surgery) treatment approach. The nature of severe obesity demands that appropriately-intensive interventions be initiated earlier in life, not later in adulthood when adiposity and co-morbidities have become entrenched. Indeed, evidence suggests that early interventions targeting adiposity and chronic disease risk factors during childhood is more effective than when instituted in adulthood.[8, 9] Moreover, early weight loss success is associated with better long-term effectiveness and weight loss sustainability.[53] The significance of our study is underscored by the improved outcomes that we expect to deliver (clinically-meaningful and sustained weight loss and risk factor management as well as improved vascular health) in this population in need of safe, effective, and durable treatments. Weight regain has been, and continues to be, a major hurdle in the field of obesity medicine. The use of financial incentives holds strong promise as a tool to encourage long-term adherence to specific dietary and physical activity regimens. Drawing from the adult literature, 12-month control-subtracted body weight reductions with financial incentives have ranged from 4-6%.[17, 18, 54] We expect to observe even greater weight loss efficacy in our trial owing to the concurrent use of meal replacement therapy. Therefore, the magnitude of weight loss and risk factor/vascular improvement with our novel intervention has the potential to exceed all other lifestyle modification treatment approaches studied to date.

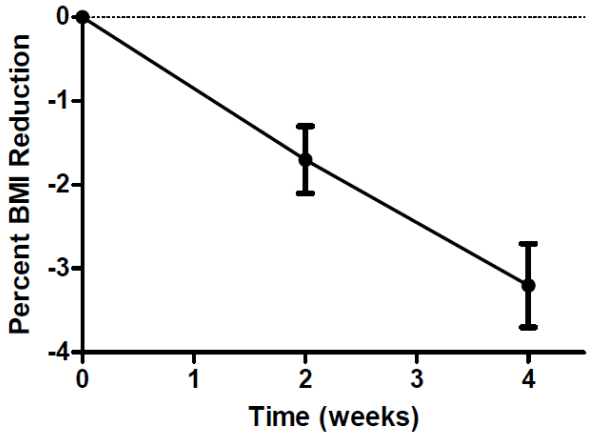
Our second study aim will address an equally significant and highly-relevant unanswered question regarding the treatment of pediatric patients with severe obesity. We will describe for the first time, the thresholds of weight loss required to elicit clinically-meaningful improvements in specific cardiometabolic risk factors and measures of vascular health among youth with severe obesity. Pediatricians need evidence regarding the amount of weight loss they should strive to achieve for their pediatric patients with severe obesity since it will inform the type and intensity of the treatment approach. Although evidence-based benchmarks have been established for adults,[26] no such thresholds have been identified in youth with severe obesity. Owing to the distinct physiological, psychosocial, and demographic features of pediatric severe obesity,[2] it would be inappropriate to assume that the thresholds of weight loss shown to be important for adults also apply to this unique patient population. Therefore, the new knowledge generated from our study will serve as a meaningful advancement in the field of pediatric obesity medicine as it will inform the treatment approach for individual patients and provide an evidence base from which to begin to develop clinical practice guidelines.

The following studies provide the background and rationale for our plans to move forward. Our project is a logical extension of this foundational work, which has informed the basis of the trial detailed in this protocol.

Weight Loss with Meal Replacements in Adolescents with Severe Obesity
Meal replacement therapy is an effective treatment approach for obesity. A meta-analysis of studies among obese adults has shown that meal replacements reduce body weight to a greater extent than conventional diet plans.[24] The rationale for the use of meal replacements is that individuals with obesity, including adolescents,[52] often under-estimate caloric intake and that adherence to a strict, pre-determined meal regimen removes the “guess-work” from eating. A recent study by Berkowitz et al.[25] demonstrated promising short-term weight loss efficacy (BMI reduction of approximately 6%) in adolescents with severe obesity using meal replacements for a period of 4 months. Despite the positive outcome, adherence to the meal replacement regimen was suboptimal even over the short-term (baseline to month 4) and worsened from months 4 to 12 with a parallel trajectory of weight regain.[25] Therefore, meal replacement therapy appears to be a promising weight loss intervention for adolescents with severe obesity;

however, efforts to improve short- and long-term adherence using strategies like financial incentives would likely enhance outcomes.

Figure 1. Weight Loss with Meal Replacement Therapy in Adolescents with Severe Obesity



We are currently conducting a clinical trial that includes a 4-week meal replacement induction period (prior to randomization to topiramate or placebo) and have observed promising BMI reduction in adolescents with severe obesity (N=19). Mean BMI reduction was 3.2% in only four weeks (Figure 1). These data are consistent with the findings of Berkowitz and colleagues[25] and demonstrate the feasibility of meal replacement therapy in our hands. Anecdotally, our participants have had a very positive experience with the meal replacement program and reported high levels of satisfaction with the degree of weight reduction in such a short period of time and with the convenience of the treatment regimen.

Effectiveness of Financial Incentives in Improving Weight Loss and Health Outcomes

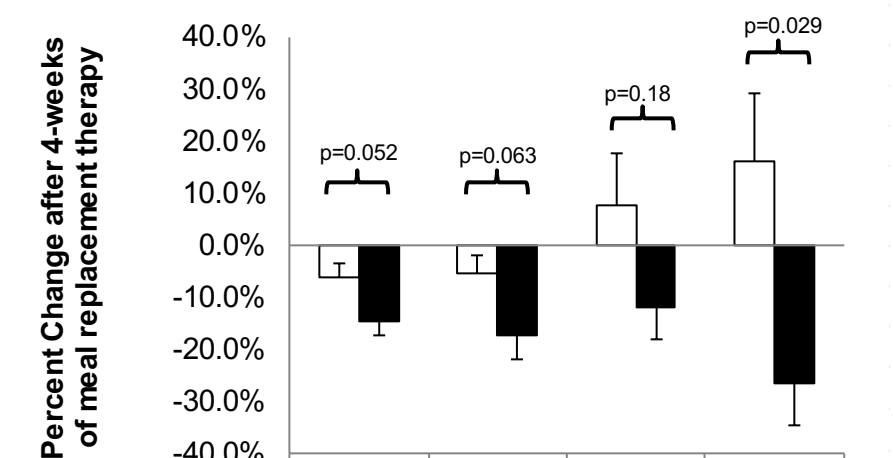
The use of financial incentives to improve health is gaining in popularity among users, employers, and health groups.[14] In particular, the financial incentive model has proven to be an effective weight loss intervention for adults. Adult trials, ranging in length from 4-8 months, have reported weight loss outcomes of between 4-6%.[17, 18, 54] Although yet to be evaluated as a weight loss intervention, financial incentives have been shown to improve other health-related behaviors in adolescents. Compared to a control condition with only 30% compliance with wearing a physical activity accelerometer, teens who received financial incentives had a compliance rate of nearly 55%, almost double that of the controls.[19] In another trial, over 35% of adolescent smokers who received financial incentives were able to quit smoking vs. 0% with cognitive behavior therapy alone.[23] Despite the promising findings demonstrating improvements in health behaviors in both adults and adolescents, the financial incentive model has never been evaluated as a weight loss intervention among adolescents. It is reasonable to hypothesize that money is at least as strong a motivator for teens as for adults[19-23] and could serve as a powerful intervention for addressing severe obesity and its co-morbidities.

Weight Loss Thresholds and Cardiometabolic Risk Factor Improvements in Adolescents with Severe Obesity

Using data from the 19 participants who have completed the 1-month meal replacement period (prior to randomization to drug or placebo) in our ongoing previously-mentioned clinical trial, we compared cardiometabolic risk factor outcomes between those achieving ≥4% (N=7) vs. <4% (N=12) BMI reduction (Figure 2). Note: comparisons of thresholds of 1%, 2%, and 3% BMI reduction did not yield either statistically-significant or clinically-meaningful improvements in risk factors at these lower levels of weight loss. Although a much larger sample size will be required to sufficiently identify important and relevant thresholds of BMI reduction, these preliminary data suggest that 4% BMI reduction elicits significant and clinically-meaningful improvements in multiple cardiometabolic risk factors among teens with severe obesity (>10% improvements in many of the risk factors).

In the context of the much larger proposed study, we will have the flexibility to compare a wide range of BMI reduction thresholds and identify the cutoffs most closely associated with specific cardiometabolic risk factors improvements. Our findings will have an immediate and sustained clinical impact by providing pediatric weight management specialists with critical information regarding weight loss goals for their patients with severe obesity. Beyond body weight/BMI loss, we will also be able to identify thresholds of reduction in absolute and percent total body fat and absolute and percent visceral fat that are associated with improvements in cardiometabolic risk factors and vascular health. Our group has done some of the pioneering work validating the innovative use of iDXA technology to quantify visceral fat in youth.[55]

Figure 2. Cardiometabolic Risk Factor Changes by Degree of BMI Reduction (≥4% vs. <4%)



	TC	LDL-c	TG	Insulin
□ BMI reduction <4%	-5.9%	-5.4%	7.9%	16.4%
■ BMI reduction ≥4%	-14.6%	-17.1%	-11.8%	-26.5%

Importantly, we will be able to not only identify weight loss cutoffs that are associated with improvements in various cardiometabolic risk factors and vascular variables, but will also be able to describe the degree of normalization of these factors by comparing outcomes after weight loss to an existing database of adolescents in the same age-range who underwent identical testing in the same laboratory. Our database, which continues to grow, currently contains data from over 200 adolescents with BMI values ranging from normal weight to severe obesity. In a cross-sectional fashion, we will be able to compare post-weight loss cardiometabolic and vascular outcomes (non-invasively measured arterial stiffness and heart rate variability) of the adolescents with severe obesity in the proposed trial to those in the normal weight, overweight, and obese groups in the database in order to characterize the level of improvement. This analysis will offer a unique perspective, which will enhance our ability to meaningfully interpret the results of the proposed clinical trial and maximize the impact.

2 Study Objectives

2.1 Primary Objective

Evaluate the effect of meal replacement therapy plus financial incentives on weight loss, cardiometabolic risk factors, vascular health, and behavior change among adolescents with severe obesity. We hypothesize that the use of meal replacement therapy with financial incentives (vs. no financial incentives) will lead to greater percent reduction in BMI (primary endpoint) as well as reduce body fat, blood pressure, triglycerides/HDL ratio, inflammation, oxidative stress, arterial stiffness, and improve heart rate variability at 26 and 52 weeks.

2.2 Secondary Objectives

Identify weight loss thresholds associated with significant improvements in cardiometabolic risk factors and vascular health in adolescents with severe obesity. We hypothesize that a minimum weight loss threshold exists, that when exceeded, will be associated with meaningful improvements in multiple cardiometabolic risk factors and parameters of vascular health.

3 Study Design

3.1 General Design

This will be a 52-week randomized, controlled clinical trial evaluating the effects of meal replacement therapy plus financial incentives on weight loss, cardiometabolic/vascular outcomes, and behavior change among 130 adolescents (ages 13-17 years old) with severe obesity and to identify the various thresholds of weight loss required to achieve cardiometabolic/vascular improvements in this patient population. Randomization will be stratified by health insurance status (public/Medicaid vs. private), which is a highly-quantifiable variable and is closely associated with family income and socioeconomic status. Throughout the entire study, all participants (regardless of financial incentives status) will engage in meal replacement therapy designed to achieve sustained weight loss.

In an effort to maximize the rigor of the study design, we will utilize deception. Upon recruitment, participants will be informed that they will be participating in a trial evaluating the effect of meal replacement therapy on weight loss – we will not mention the financial incentives component. Following randomization, participants allocated to the financial incentives group will be informed of the true nature of the study and asked to sign an addendum assent form (parents will sign the parental consent) detailing the financial incentives protocol. Participants allocated to the control group will remain blinded throughout the trial and will be informed of the true nature of the study once the project is fully completed.

3.2 Primary and Secondary Study Endpoints

The primary analysis will be conducted using the intent-to-treat population to compare the mean BMI percent change from randomization to 52 weeks (additional analyses will use the 26-week time-point as secondary) of follow-up between the financial incentives and no financial incentives groups, adjusted for BMI at randomization and insurance status (randomization stratification factor) for added precision. Confidence intervals (CIs) and P-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$.

Secondary endpoints of body fat, blood pressure, triglycerides/HDL ratio, inflammation, oxidative stress, arterial stiffness, heart rate variability, and adherence to the meal replacement regimen will be characterized at 26 and 52 weeks. The evaluation will be in a similar fashion as

the primary outcome wherein analyses will be adjusted for baseline values and the randomization stratification factor.

We will explore cut-offs of percent change in BMI from randomization that are associated with significant improvement in cardiometabolic risk factors and vascular health. We anticipate a range of values for consideration as the cut-off across the two treatment groups. We also anticipate the cut-off not necessarily being the same across different endpoints. The analyses will be similar to those for continuous outcomes outlined above with adjustment for baseline values, but groups will be determined by candidate cut-offs rather than treatment assignment. This will also allow for quantifying the degree of normalization within each subgroup with point estimates and confidence intervals and also for comparing the post-intervention values against the distribution of values from the existing control database.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- BMI ≥1.2 times the 95th percentile (based on sex and age) or BMI ≥35 kg/m^2
- 13-17 years old

4.2 Exclusion Criteria

- Type 1 or 2 diabetes mellitus
- Previous (within 6 months) or current use of meal replacements
- Previous (within 6 months) or current use of medication(s) prescribed primarily for weight loss (refer to appendix material for comprehensive list)
- If currently using weight altering drug(s) for non-obesity indication(s) (refer to appendix material for comprehensive list), any change in drug(s) or dose within the previous 6 months
- Previous bariatric surgery
- If currently using anti-hypertensive medication(s), lipid medication(s), and/or medication(s) to treat insulin resistance (refer to appendix material for comprehensive list), any change in drug(s) or dose within the previous 6 months
- If currently using CPAP/BIPAP (for sleep apnea), change in frequency of use or settings within the previous 6 months
- History of treatment with growth hormone
- Neurodevelopmental disorder severe enough to impair ability to comply with study protocol
- Clinical diagnosis of bipolar illness, schizophrenia, and/or conduct disorder
- Substance abuse
- Females: currently pregnant or planning to become pregnant
- Tobacco use
- Bulimia nervosa
- Endorsement of vomiting, laxative use, and/or diuretic use for weight control (EDE-Q)
- Binge eating disorder
- Neuromuscular disorder
- Hypothalamic obesity
- Obesity associated with genetic disorder (monogenetic obesity)
- Hyperthyroidism or uncontrolled hypothyroidism
- History of cholelithiasis

Participants will be recruited from the Pediatric Weight Management Clinic at the University of Minnesota Masonic Children's Hospital and referred from the MN-POC member institutions. Additional recruitment strategies may include advertisements, study-specific recruitment letters sent to potentially-eligible patients in the respective health systems of the MN-POC (Fairview for the University of Minnesota), and word of mouth. Appropriate designees will discuss study participation with interested participants and their parents at which time the initial consent and assent discussion will be conducted.

4.3 Early Withdrawal of Participants

4.3.1 When and How to Withdraw Participants

Participants may withdraw from the trial at any time. The study may also be stopped at any time by the principal investigator, medical officer, or IRB for any reason. Participants who discontinue participation and withdraw consent/assent will not complete follow-up visits. However, participants who are not fully compliant with the protocol and/or who choose to stop the intervention altogether but do not withdraw consent will remain in the study for follow-up in order to preserve the ability to perform an ITT analysis. Upon completion of the trial or upon complete withdrawal from the trial, participants will be referred back to their primary care physician, if applicable.

4.3.2 Data Collection and Follow-up for Withdrawn Participants

If a participant withdraws consent to participate in the trial, attempts will be made to obtain permission to record follow-up data. Attempts to follow up will include three phone calls to the participant. A participant will be considered lost to follow-up if no response is obtained after three attempts.

5 Treatment

5.1 Treatment Regimen

All participants will engage in meal replacement therapy throughout the entire 52-week treatment period. Participants will be randomized (1:1) to either financial incentives or no financial incentives.

5.2 Method for Assigning Participants to Treatment Groups

Each participant will be randomly assigned (1:1) to financial incentives or no financial incentives using permuted blocks of size 2, 4, or 6. For eligible participants who are randomized, a randomization number will be assigned starting with R001 and numbered sequentially.

5.3 Prior and Concomitant Therapy

Concomitant medication(s) status will be collected at the baseline visit. Changes in concomitant medication(s) will be assessed during follow-up visits.

6 Study Procedures

Participants will be asked to withhold all medication(s), if applicable, for study visits. Table 1 shows the procedures to be performed and data to be collected at each study visit (please refer to the detailed breakdown of visits following the table for comprehensive list of assessments/procedures). Phone calls will be made monthly to assess adverse events, compliance, and deliver lifestyle/behavioral modification counseling. All participants, regardless of assignment, will receive modest reimbursement for completing study visit assessments (separate from the financial incentive payments described later).

Table 1. Measured Variables by Visit

	Baseline	Week 8	Week 17	Week 26	Week 34	Week 43	Week 52
Physical exam	X						
Tanner staging	X						
Safety labs	X						
Fasting labs and blood biomarkers	X			X			X
BMI/anthropometrics	X	X	X	X	X	X	X
iDXA scan (total- and visceral fat)	X			X			X
Vascular assessment	X			X			X
Blood pressure	X	X	X	X	X	X	X
Questionnaires	X			X			X
AE assessment		X	X	X	X	X	X
Lifestyle counseling	X	X	X	X	X	X	X
Financial incentive payment (if eligible)		X	X	X	X	X	X

6.1 Screening Visit or Phone Call

- Informed consent/assent
- Medical record review
- Evaluation against inclusion and exclusion criteria
- Reminder for participant to fast for 8 hours prior to baseline visit

6.2 Baseline Visit (screening and baseline visit may be completed on the same day)

(Visit completed following an 8-hour fast and confirmation that all medications have been withheld on the morning of the study visit)

- Informed consent/assent, if not previously obtained
- Interim medical history review (if screening visit occurred previously)
- Vital signs (heart rate and blood pressure)
- Concomitant medications
- Anthropometric measurements (height, weight, hip/waist circumference, and body mass index)
- iDXA scan
- Physical exam with Tanner (pubertal) stage determination
- Urine pregnancy test for all female subjects
- Questionnaires:
  - PedsQL™ (Young Adult Quality of Life Inventory) Child and Parent
  - Impact of Weight on Quality of Life: IWQOL-Kids
  - Children's Power of Food Scale
  - Child's Eating Behavior Questionnaire (CEBQ)
  - Depression Scale for Children (CES-DC)
  - Screen for Child Anxiety Related Disorders (SCARED)
  - Eating Disorder Examination Questionnaire (EDE-Q)
  - If applicable, additional questionnaires
- Fasting blood draw: complete metabolic panel, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), insulin, and hemoglobin A1c
- Blood draw for frozen plasma and serum storage
- Vascular assessment
- Urine sample collection for frozen storage

- Meal replacement instructions (including food journaling to track compliance)
- Lifestyle/behavioral modification counseling
- Instruction on choosing, ordering, and receiving meals from Healthy for Life Meals

6.3 8-Week Visit (8 weeks ±7 days from baseline visit)

- Anthropometric measurements (height, weight, hip/waist circumference, body mass index)
- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Adverse event assessment
- Eating Disorder Examination Questionnaire (EDE-Q)
- Lifestyle/behavioral modification counseling
- Financial incentive payment (if applicable)
- Review of ordering meals from Healthy for Life Meals

6.4 17-Week Visit (17 weeks ±7 days from baseline visit)

- Anthropometric measurements (height, weight, hip/waist circumference, body mass index)
- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Adverse event assessment
- Eating Disorder Examination Questionnaire (EDE-Q)
- Lifestyle/behavioral modification counseling
- Financial incentive payment (if applicable)
- Review of ordering meals from Healthy for Life Meals

6.5 26-Week Visit (26 weeks ±7 days from baseline visit)

(Visit completed following an 8-hour fast and confirmation that all medications have been withheld on the morning of the study visit)

- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Concomitant medications
- Anthropometric measurements (height, weight, hip/waist circumference, and body mass index)
- iDXA scan
- Urine pregnancy test for all female subjects
- Questionnaires:
  - PedsQL™ (Young Adult Quality of Life Inventory) Child and Parent Questionnaire
  - Impact of Weight on Quality of Life: IWQOL-Kids
  - Children's Power of Food Scale
  - Children's Eating Behavior Questionnaire (CEBQ)
  - Depression Scale for Children (CES-DC)

  - Screen for Child Anxiety Related Disorders (SCARED)
  - Eating Disorder Examination Questionnaire (EDE-Q)
  - If applicable, additional questionnaires
- Fasting blood draw: lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), glucose, insulin, and hemoglobin A1c
- Blood draw for frozen plasma and serum storage
- Vascular assessment
- Urine sample collection for frozen storage
- Adverse event assessment
- Lifestyle/behavioral modification counseling
- Financial incentive payment (if applicable)
- Review of ordering meals from Healthy for Life Meals

6.6 34-Week Visit (34 weeks ±7 days from baseline visit)

- Anthropometric measurements (height, weight, hip/waist circumference, body mass index)
- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Adverse event assessment
- Eating Disorder Examination Questionnaire (EDE-Q)
- Lifestyle/behavioral modification counseling
- Financial incentive payment (if applicable)
- Review of ordering meals from Healthy for Life Meals

6.7 43-Week Visit (43 weeks ±7 days from baseline visit)

- Anthropometric measurements (height, weight, hip/waist circumference, body mass index)
- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Adverse event assessment
- Eating Disorder Examination Questionnaire (EDE-Q)
- Lifestyle/behavioral modification counseling
- Financial incentive payment (if applicable)
- Review of ordering meals from Healthy for Life Meals

6.8 52-Week Visit (52 weeks ±7 days from baseline visit)

(Visit completed following an 8-hour fast and confirmation that all medications have been withheld on the morning of the study visit)

- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Concomitant medications
- Anthropometric measurements (height, weight, hip/waist circumference, and body mass index)
- iDXA scan
- Urine pregnancy test for all female subjects

- Questionnaires:
    - PedsQL™ (Young Adult Quality of Life Inventory) Child and Parent Questionnaire
    - Impact of Weight on Quality of Life: IWQOL-Kids
    - Children's Power of Food Scale
    - Children's Eating Behaviour Questionnaire (CEBQ)
    - Depression Scale for Children (CES-DC)
    - Screen for Child Anxiety Related Disorders (SCARED)
    - Eating Disorder Examination Questionnaire (EDE-Q)
    - If applicable, additional questionnaires
- Fasting blood draw: lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), glucose, insulin, and hemoglobin A1c
- Blood draw for frozen plasma and serum storage
- Vascular assessment
- Urine sample collection for frozen storage
- Adverse event assessment
- Lifestyle/behavioral modification counseling
- Financial incentive payment (if applicable)

6.9 Monthly Phone Call/Email/Text message (completed between in-person study visits)

- Interim current health/medical history review including changes to concomitant medications
- Adverse event assessment
- Lifestyle/behavioral modification counseling

6.10 Detailed Study Procedures

6.10.1 Anthropometric Measurements and Assessment of Pubertal Status

Height and weight will be measured using a calibrated, wall-mounted stadiometer and an electronic scale, respectively. Measurements will be obtained with participants in light clothing, without shoes. Two consecutive height and weight measurements will be obtained and averaged. If the first two values differ by more than 0.5 cm for height and/or 0.3 kg for weight, a third measurement will be obtained and the average of three measurements will be calculated. BMI will be calculated as the weight in kilograms divided by the height in meters, squared. Waist circumference will be measured at end-expiration midway between the base of the rib cage and the superior iliac crest. Hip circumference will be measured at the maximal protuberance of the buttocks. Two consecutive waist and hip measurements will be averaged. If the first two values for either measure differ by more than 0.3 cm, a third measurement will be obtained and the average of three measurements will be calculated. Total percent body fat, visceral fat (novel feature of the iDXA), and lean muscle mass will be determined by dual energy x-ray absorptiometry (iDXA, GE Healthcare). The scanning table accommodates body sizes of up to 204 kg. Tanner stage will be determined by a trained pediatrician or a trained nurse.

6.10.2 Blood Pressure and Heart Rate

Blood pressure measurements will be obtained digitally on the same arm using the same cuff size and equipment. Standardized procedures will be employed as described in previously published standards.[56] Individual cuff size will be determined by measuring the arm circumference midway between the acromial process and the bony olecranon. Sitting blood pressure and heart rate will be measured after the participant has been resting quietly without legs crossed for 10 minutes. Measurements will be made three consecutive times (3-minute intervals). The final two of three independent measurements will be averaged.

6.10.3 Blood Analyses

Fasting (≥8 hours) blood (approximately 2 tablespoons) will be collected for the measurement of lipids (total-, LDL-, HDL-cholesterol, and triglycerides), glucose, and insulin (to be assayed in Fairview Diagnostics Laboratories, Fairview-University Medical Center, Minneapolis, MN - a Center for Disease Control and Prevention certified laboratory). Fasting samples for C-reactive protein and oxidized LDL cholesterol will be processed and stored at -80 degrees C for a batched analysis in the University of Minnesota Cytokine Reference Laboratory (CLIA licensed).

6.10.4 Lifestyle/Behavioral Modification Counseling

All participants, regardless of group assignment, will receive the same lifestyle/behavioral modification counseling monthly throughout the entire study: delivered at each in-person study visit and on the phone for months when there is no study visit. The lifestyle/behavioral modification curriculum has been adapted from the NIDDK-sponsored TODAY study lifestyle modification program materials[57] and utilized by our group in a previous[58] and ongoing trial. Trained study coordinators will deliver the lifestyle/behavioral modification counseling, which will focus on small, successive changes in dietary (after meal replacement induction period) and physical activity behaviors through the use of evidence-based behavior change strategies such as self-monitoring, goal setting, reinforcement for goal achievement, stimulus control, social support, problem solving, and motivational techniques. The educational materials will be given to subjects and parents at the first study visit and selected sections will be reviewed and discussed at each face-to-face and phone-based lifestyle modification counseling session. We have previously demonstrated the effectiveness of this lifestyle modification protocol in a randomized, placebo-controlled trial among adolescents with severe obesity.[58] The intensity of the lifestyle modification is designed to be practical and feasible in the clinic setting.

6.10.5 Meal Replacement Therapy

All participants, regardless of assignment to the financial incentives group or control group, will engage in meal replacement therapy throughout the entire 52-week trial. Participants will be asked to strictly follow the prescribed eating regimen, which will include provision (home delivery) of pre-packaged meals from Healthy for Life (1,200 kcals per day). Meals will be provided free of charge. Guidance will be provided regarding the use of the meals at school, and participants will be encouraged to engage in family meal sessions despite eating different foods.

6.10.6 Financial Incentives

With the intent of utilizing a straight-forward process with clear goals for the participants, financial incentives will be tied to individual percent reduction in body weight (changes in

body weight and BMI can differ slightly based on growth but are highly correlated). We believe the complexity of basing incentives on BMI reduction would create confusion and frustration for the participants owing to the interplay between changes in height and weight ultimately making it difficult to effectively communicate goals to the participants. Moreover, change in height is obviously beyond the domain of control for participants and offering higher payouts to individuals who experience greater increases in height will be viewed as unfair. Using the baseline body weight as the reference for all subsequent study visits (to avoid offering incentives for weight cycling – gain and subsequent loss), participants will receive $20 (in the form of a gift card) for every 0.5% reduction in body weight from baseline. To make goals clear for participants, individual tables will be created displaying the amount of weight loss (in pounds) corresponding to each half percentage-point reduction in body weight. Financial incentive payments, if earned, will be made to participants in the financial incentives group at all study visits. Even if unsuccessful in earning a payment at a preceding visit, participants will remain eligible for the incentives at all subsequent visits (i.e., if weight is gained or remains stable, participants will be have the opportunity to get back on track; again, in relation to the baseline body weight). No payment will be made for partial goal attainment (i.e., full 0.5% weight reduction increments must be achieved).

6.10.7 Assessment of Motivation, and Other Behavioral and Psychosocial Factors

Questionnaires to be utilized at the same time points will measure quality of life (PedsQL Child and Parent questionnaire; Impact of Weight on Quality of Life: IWQOL-Kids), anxiety (Screen for Child Anxiety Related Disorders: SCARED questionnaire) and depression (Depression Scale for Children: CES-DC questionnaire). Weight reduction will be measured at all study visits.

6.10.8 Vascular Measurements

Vascular testing will be performed in the morning in a quiet room of constant temperature (22º C – 23º C). Participants will be fasting and will be instructed to refrain from caffeine and medications prior to the study.

Carotid-radial, carotid-femoral, and/or carotid-foot augmentation index and pulse wave velocity will be measured by the SphygmoCor® MM3 system (AtCor Medical, Sydney, Australia). Augmentation index is a measure of the relative magnitude of the reflected (or retrograde) pulse wave early in the cardiac cycle. Higher values represent increased arterial stiffening. Pulse wave velocity will be calculated as distance divided by transit time. Higher values of pulse wave velocity represent increased arterial stiffness. Resting heart rate variability will be measured with the SphygmoCor® MM3 system.

7 Statistical Plan

7.1 Participant Populations for Analysis

The primary analysis will be on an intent-to-treat population where all randomized participants will be evaluated according to their treatment assignment (financial incentives vs. no financial incentives). The analysis will be conducted with multiple imputation techniques, if necessary. A secondary per protocol analysis will include participants who are without major protocol violations. Safety assessments will include all participants who receive any treatment according to the treatment they receive. Randomization will be stratified by health insurance status

(public/Medicaid vs. private), which is highly-quantifiable, clinically-relevant, and closely associated with family income and socioeconomic status.

- Intent-to-treat (ITT): All participants randomized according to the treatment assignment received.
- Per-Protocol (PP): All participants randomized without major protocol violations and who were compliant (at least 80%) with the treatment assignment received. Major protocol violations include: cessation of study meals.
- Safety Population: All participants who receive any amount of treatment according to the treatment they receive.

7.2 Sample Size Determination

Based on results of adult clinical trials of financial incentives for weight loss, we anticipate a control-subtracted treatment effect (BMI reduction, our primary endpoint) of 5% at 52 weeks.[17, 18, 54] We estimate having a dropout rate of no more than 20% (our previous clinical trial experience with this population has been 10-15%).[58, 61] We do not expect to observe differential attrition by treatment arm based on results of adult financial incentives trials demonstrating nearly identical study completion rates among the control and treatment groups.[17, 18, 54] Using BMI variability estimates from a previous trial using meal replacements over 12 months[25] suggesting a standard deviation of approximately 8.8 and using a conservative correlation between baseline and follow-up scores of 0.6, we present in Table 2 the power associated with a clinically-meaningful control-subtracted BMI reduction of 5% based on an overall sample size of 130 (60 in each treatment arm) and a range of degrees of attrition (including rows reflecting scenarios of higher than expected levels).

Table 2. Conservative Estimates of Power for a Range of Potential Treatment Effects at 52 Weeks

Difference in BMI Percent Change	5%
Two-sided Unadjusted	97.18%
Two-sided with 10% attrition	95.67%
Two-sided with 15% attrition	94.5%
Two-sided with 20% attrition	93.25%

7.3 Statistical Methods

Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations for continuous variables and frequencies for categorical variables. Treatment compliance will also be evaluated. Safety analyses will use the Safety analysis population and will be primarily descriptive, reporting the number and percentage of adverse events.

7.3.1 Specific Aim #1 (Primary and Secondary Endpoints)

The primary analysis will be conducted using the intent-to-treat population to compare the mean BMI percent change from randomization to 52 weeks (additional analyses will use the 26-week time-point as secondary) of follow-up between the financial incentives and no financial incentives groups, adjusted for BMI at randomization and insurance status (randomization stratification factor) for added precision. Confidence intervals (CIs) and P-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$. Supportive analyses using the per-protocol population will

also be conducted along with consideration of adjustment for residual imbalances between treatment groups after randomization (e.g., in sex).

Secondary endpoints of body fat (total, visceral, and subcutaneous), blood pressure, triglycerides/HDL ratio, inflammation, oxidative stress, arterial stiffness, heart rate variability, and adherence to the meal replacement regimen will be characterized at 26 and 52 weeks. The evaluation will be in a similar fashion as the primary outcome wherein analyses will be adjusted for baseline values and the randomization stratification factor. Longitudinal analyses will also be conducted, incorporating the variables that are measured at multiple time points (e.g., blood pressure, adherence). Supportive analyses using the PP population will also be conducted. We also recognize there is always the possibility of subgroups with differential treatment effect. We do not a priori have a particular subgroup of interest the study is designed to evaluate, though exploratory analyses would be able to investigate such.

7.3.2 Specific Aim #2

We will explore cut-offs of percent change in BMI from randomization that are associated with significant improvement in cardiometabolic risk factors and vascular health. We anticipate a range of values for consideration as the cut-off across the two treatment groups. We also anticipate the cut-off not necessarily being the same across different endpoints. The analyses will be similar to those for continuous outcomes outlined above with adjustment for baseline values, but groups will be determined by candidate cut-offs rather than treatment assignment. This will also allow for quantifying the degree of normalization within each subgroup with point estimates and confidence intervals and also for comparing the post-intervention values against the distribution of values from the existing control database (normal weight, overweight, and obese groups).

Other scales will also be explored, e.g., absolute BMI, percent of the 95th BMI percentile, BMI z-score, total body fat, percent body fat, total visceral fat, and percent visceral fat at follow-up, in addition to percent change in BMI from randomization. Results of these analyses will be considered exploratory, interpreted as suggestive, requiring confirmation. It is also possible thresholds may differ for different types of participants, e.g., based on sex. Such interactions will be explored to the extent there are sufficient numbers of individuals within subgroups and sufficient variability over which to explore thresholds. In addition, these results will be used to aid in the interpretation of the clinical meaningfulness of the treatment effect from aim #1. For example, if a cutoff of 4% BMI reduction is associated with clinically meaningful improvements in at least some of the cardiometabolic risk factors, we will examine how many participants met this threshold in each group. In an exploratory fashion, we will utilize the receiver operating characteristic (ROC) analysis to describe the sensitivity and specificity of various BMI reductions cut-points associated with remission of dichotomous co-morbidities at baseline such as dyslipidemia, pre-hypertension/hypertension, pre-diabetes, etc. (in the subset of participants with these conditions at baseline).

7.3.3 Safety Analyses

The safety profile will be evaluated using the Safety analysis population and evaluated using data collected throughout follow-up. Analyses will be primarily descriptive reporting the number and percentage of adverse events along with categorizations of seriousness, severity, frequency (within a subject), and perceived relatedness to the

intervention. In addition, incidence of disordered eating behaviors will be evaluated between groups and monitored by the data and safety monitoring board (DSMB) throughout the trial.

7.4 Missing Data

Despite best efforts, it is possible that some data will be missing, which could limit the interpretation and generalizability of results. If the missing data is missing completely at random, the consequence will merely be lost precision. Based upon attrition rates in our previous trials,[58, 61] we anticipate that no more than 20% of the participants will be lost to follow-up. Taking this into account, the planned enrollment of 130 is inflated to account for potential drop out. As such, in the 'worst case' situation of observing missing data as high as 20%, we will still have >85% and >95% power to detect a 4% and 5%, respectively, control-subtracted percent change in BMI from randomization to 52 weeks (primary endpoint). If the data are missing at random, conditioned on measured covariates, then supplementary analyses adjusting for these covariates will produce unbiased results. For potential missing data mechanisms beyond measured covariates, we will examine the extent to which results may be affected. Imputation techniques will be considered for missing data issues (e.g., multiple imputation). Secondary endpoints will be handled similarly. We do not expect to observe differential attrition by treatment arm based on results of adult financial incentives trials demonstrating nearly identical study completion rates among the control and treatment groups.[17, 18, 54] But, it is possible we may observe differential attrition. Sensitivity analyses will include differential imputed values to examine the degree of robustness of the results. We will also collect data on why participants decide to discontinue, enabling us to examine differences between study arms and in participant characteristics between completers and dropouts.

8 Safety and Adverse Events

8.1 Potential Risks

As with any research study, there may be unforeseen risks. A trained interdisciplinary research staff comprised of physicians, scientists, nurses, and coordinators carefully guard against all potential risks.

8.1.1 Dual-energy X-ray Absorptiometry (iDXA) Scan

The iDXA is painless and involves exposure to a very low dose of radiation. As part of this study, participants will undergo a total of three iDXA scans.

8.1.2 Blood Sampling

There is minimal risk of bruising and infection associated with the blood draw.

8.1.3 Questionnaires

There are no risks associated with the questionnaires to be used in the study. Participants may refuse to answer any questions or stop participating at any time.

8.2 Definitions

8.2.1 Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Inter-current illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Adverse events relationship to the study will be based on the following scale:

- Unrelated: Clearly not related to study
- Unlikely: Unlikely to be related to study
- Possible: May be related to study
- Probable: Likely to be related to study
- Definite: Clearly related to study

8.2.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that 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

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.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

8.2.3 Adverse Event Reporting Period

Adverse events will be followed from the initiation of any study procedures until the Week 52 visit. Serious adverse events will be followed from the initiation of any study procedures until resolution.

All serious adverse events will be followed from the initiation of any study procedures until the events are resolved, the participant is lost to follow-up, or the serious adverse event is otherwise explained. At the final visit, if there is an ongoing serious adverse event, the participant and the parent/guardian will be instructed to report any subsequent event(s) that they, or their personal physician, believe might be reasonably related to participation in this study.

8.2.4 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will only be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.2.5 General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will be recorded and documented as an adverse event.

8.2.6 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

8.2.7 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.3 Recording of Adverse Events

At each contact with the participant and their parent/guardian, adverse events will be assessed by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event form. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, although they should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.4 Reporting of Serious Adverse Events

8.4.1 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) will be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.5 Stopping Rules

In the event that a participant has a serious adverse event that is deemed study-related by the lead-investigator for medical safety, the participant will be required to immediately withdraw from the study. The overall study may be stopped at any time at the request of the DSMB, principal investigator, and/or lead-investigator for medical safety. The main adverse effect that we expect to observe is excessive weight loss during the meal replacement period. In the context of this trial, we will define excessive weight loss as 2 consecutive weeks during which ≥5 pounds are lost per week for those with a BMI <40 kg/m2 and ≥7 pounds are lost per week for those with a BMI ≥40 kg/m2. Individuals endorsing vomiting, laxative use, and/or diuretic use for weight control at the baseline visit will be excluded. We will also monitor for the incidence of disordered eating behaviors using the EDE-Q questionnaire, which will be administered at all in-person study visits. Any participant endorsing vomiting, laxative use, and/or diuretic use for weight control (via the EDE-Q) at any time during the trial will be interviewed using the Eating Disorders Module of the Structured Clinical Interview for DSM-5. If disordered eating is present upon clinical interview, the participant will be removed from the trial and referred to an eating behavior specialist for clinical follow-up. If no eating disorder is present, the participant may continue in the trial. The DSMB will be given the authority to stop the trial if the occurrence of excessive weight loss and/or incidence of disordered eating are deemed to be at an unacceptably high level. Participants will be instructed that they may withdraw from the study at any time and for any reason.

8.6 Medical Monitoring

Safety monitoring will include individual participant comprehensive assessment and appropriate reporting of adverse events as they occur. Adverse events will be monitored closely and participants will be provided with information about the risks of the study intervention and provided with phone numbers to reach the principal investigator/study coordinator in case of emergencies.

8.7 Data and Safety Monitoring Board

A DSMB will be established, which will include a pediatrician with obesity expertise, a pediatric psychologist or psychiatrist with eating disorders expertise, and a biostatistician. DSMB members will not be affiliated with the study. The DSMB will meet regularly (frequency to be determined by DSMB members) during the trial to review data and evaluate participant safety. A charter for the DSMB to outline the responsibilities and procedures for the conduct of the monitoring board will be developed and approved by its members along with a plan for frequency of data review prior to the commencement of the trial. Review materials for the DSMB will be prepared and presented by the study biostatistician. A report from each meeting will be sent to the principal investigator and co-investigators advising on the continuation of the study.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents and Case Report Forms

All data will be collected and transcribed onto source documents. These source documents will act as the CRF.

9.3 Records Retention

The investigator will retain study essential documents for at least 6 years after the conclusion of the study.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The study will undergo regular monitoring (annually during the enrollment and follow up period) of the facility, staff, and study documents by clinical research associates in the University of Minnesota Clinical Trials Monitoring Service, which specializes in regulatory compliance for clinical trials associated with the Food and Drug Administration. This service provides regular monitoring of all research-related activities and is offered free of charge through the University of Minnesota CTSI. Monitoring staff will present a summary report to the PI after each site visit.

If necessary, corrective action plans will be devised and implemented by the PI to address deficiencies.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the 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, CTSI, etc.).

11 Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All participants and parents/guardians for this study will be provided an assent and consent form, respectively, describing this study and providing sufficient information for participants/families to make an informed decision about participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal assent of a participant and consent of the parent/guardian, using the IRB-approved assent and consent forms, must be obtained before that subject is submitted to any study procedure. This consent form will be signed by the participant or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Based upon guidance provided in 45 CFR 46, subpart D sections 401-409 regarding research in children, we believe that the proposed study poses greater than minimal risk but provides the prospect of direct benefit to the participants. The risk lies mainly in the use of a low calorie diet in the form of meal replacements (shakes and entrees of known caloric content) to elicit weight loss among adolescents (ages 13-17 years old) with severe obesity.

Claudia Fox, M.D., M.P.H. (lead-study investigator for medical safety), a pediatric obesity medicine specialist with experience conducting pediatric obesity clinical trials, will be responsible for the medical safety aspects of this trial. Dr. Fox is board-certified in Obesity Medicine by the American Board of Obesity Medicine. The study will undergo regular monitoring by clinical research associates employed by the University of Minnesota Clinical Trials Monitoring Service, which specializes in regulatory issues related to studies monitored by the Food and Drug Administration. The following sections detail how each subpart D criterion will be satisfied: a) the risk is justified by the anticipated benefits to participants; b) the relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternate approaches; and c) adequate provisions are made for soliciting the assent of the adolescents and permission of their parents or guardians.

11.1 Human Subjects Involvement and Characteristics

One-hundred, twenty (130) adolescents (ages 13-17 years old) with severe obesity (BMI ≥ 1.2 times the 95th percentile or BMI ≥35 kg/m^2) will be recruited from the University of Minnesota Masonic Children's Hospital, Pediatric Weight Management Clinic and Minnesota Pediatric Obesity Consortium (MN-POC) sites and by recruitment letters through various health systems. Adolescents are typically referred to these clinics to address issues related to excess body weight and adverse cardiometabolic risk factors. Participants in this study will undergo a series of clinical measurements, which will require blood draws. All costs of testing will be covered by the research study and subjects will be reimbursed for study participation.

11.2 Source of Research Materials

The following types of research material will be obtained from the participants: blood specimens, anthropometric data, blood pressure data, and other clinical variables. This material will be used exclusively for research. Pre-existing chart information will be used. Data obtained will be stored in a confidential database without direct subject identifiers. The principal investigator and designated study staff will have access to the participant linkages, which will be stored in a separate, secured location. Hard copies of data, including source documents with patient identifiers, will be kept in locked file cabinets in a locked office until the completion and publication of the study, at which point any patient identifiers will be removed and data will be stored at a secure storage facility for 6 years. Access to the locked file cabinet will be given to the study coordinators and principal investigator only. Any study files that will be shared with the University of Minnesota will remove patient identifying information.

11.3 Recruitment and Informed Consent

Participants will be recruited from the University of Minnesota Masonic Children's Hospital, Pediatric Weight Management Clinic and MN-POC sites and through various health systems. Appropriate designees will discuss study participation with interested participants and their parents at which time the initial consent and assent discussion will be conducted. Assent and consent will be obtained by the study coordinator after explaining the entire study in detail, asking the participant and the parent(s)/guardian(s) to explain the purpose, risk and benefits, and other details of the study, and giving the participant and parent(s)/guardian(s) an opportunity to ask questions. A copy of the assent and consent form will be given to the participants and parent(s)/guardian(s).

In an effort to minimize participant face-to-face time due to COVID-19 concerns, the consent discussion and process may be done virtually. This will be offered to be conducted via Zoom for families with a computer and an internet connection and the Zoom connection will be encrypted so that it will be private. For families where this is not an option, we would ask that the parent and the participant discuss the project over the phone. The study coordinator will mail two copies of the parental consent, assent and HIPAA forms and will review the study, review the documents and address any concerns that the parent or participant may have. If the participant and parent agree to enroll in the study, they will be asked to sign both copies of each of the forms and return one set of originals via mail to the study coordinator for placement in the participant file. We anticipate that there will be a date discrepancy between when the participant and parent sign the forms and the date the form is returned to the study coordinator and a notation will be made about the discrepancy.

11.4 Potential Risks to Participants

As with any research study, there may be unforeseen risks. A trained interdisciplinary research staff comprised of physicians, scientists, nurses, and study coordinators carefully guard against all potential risks.

Blood Sampling (fasting and during meal test)
There is minimal risk of bruising and infection associated with the blood draw.

Meal Replacements and Monitoring for Excessive Weight Loss and Disordered Eating Behaviors
Adverse events will be comprehensively documented at all study visits and during each monthly phone call. Participants will be instructed to contact study staff immediately if any adverse event is experienced. All participants will receive counseling regarding avoidance of unhealthy weight loss behaviors such as use of diuretics, diet pills, purging, or excessive exercise. However, this message will be delivered conscientiously so as not to provide participants with ideas they may not already have. We will serially assess multiple domains of unhealthy weight loss behaviors using the EDE-Q. The EDE-Q identifies disordered eating behaviors and unhealthy attitudes about weight such as purging, unhealthy obsession with dieting and/or body weight, prolonged fasting/starvation, use of laxatives to control weight, and excessive exercise. The EDE-Q has been validated and used extensively in the adolescent population and normative values and cut-points have been established for this age group. Participants will be asked to weigh themselves regularly, and monthly phone calls will be performed. We will use the in person visits to monitor for excessive weight loss defined as ≥5 pounds per week for those with a BMI <40 kg/m^2 and ≥7 pounds per week for those with a BMI ≥40 kg/m^2. Participants reporting excessive weight loss will be given supplemental counseling regarding unhealthy weight loss behaviors and removed from the trial if excessive weight loss is noted for 2 consecutive visits.

11.5 Protections Against Risk

Claudia Fox, M.D., M.P.H. (lead-study investigator for medical safety) will be responsible for the medical safety aspects of this trial. Dr. Fox is board-certified in Obesity Medicine by the American Board of Obesity Medicine and has experience conducting pediatric obesity clinical trials in collaboration with Dr. Kelly. Participants will be evaluated at each visit for potential adverse effects. At each contact with the participant and their parent/guardian, adverse events will be assessed by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event form. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document and will be grouped under one diagnosis. All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

Females will undergo pregnancy tests at each study visit requiring a DXA scan. Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Blood samples sent to other laboratories will be

identified only by study identification number, never by name. Data to be used in scientific presentations or publications will not contain participant identifiers.

11.6 Potential Benefits of the Proposed Research to the Participants and Others

The investigators believe the potential benefits to the participants outweigh the risks in this study. Since data from clinical trials in adults and one relatively large study in adolescents have demonstrated reduction in weight and improvements in co-morbidities and cardiometabolic risk factors with the use of meal replacements, it is reasonable to expect similar results in this trial of adolescents with severe obesity. The alternative treatment approach is standard-of-care lifestyle modification therapy.

11.7 Importance of the Knowledge to be Gained

Lifestyle modification, focusing on weight loss and increased physical activity, should be the foundational approach to treating severe obesity in adolescents. However, most adolescents with severe obesity are unable to reduce their weight to an acceptable level with standard approaches to lifestyle modification and may benefit from adjunctive treatment strategies to reduce weight and improve the cardiometabolic risk factor profile. Novel approaches such as meal replacements plus financial incentives should be explored. Data obtained from this study will determine whether combining these approaches is a promising weight loss strategy for adolescents with severe obesity.

11.8 Data and Regulatory Monitoring Plan

Medical Monitoring
Safety monitoring will include careful assessment and appropriate reporting of adverse events. Adverse events will be monitored closely and participants will be provided with information about the risks of the study intervention and provided with phone numbers to reach the principal investigator/study coordinator in case of emergencies.

12 Study Finances

12.1 Funding Source

The study is funded by the National Institutes of Health (NIH) through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

12.3 Participant Stipends or Payments

Participants will receive $100 (in the form of a gift card) for completing each study visit – in total, participants may receive $700 if they complete all study visits (7 visits total). In addition, if applicable, hotel, parking and/or meal vouchers will be provided at each visit. Participants who are withdrawn early from study participation will be paid for the visits completed to that point.

13 Publication Plan

Data from this trial may be published. Dr. Aaron Kelly holds the primary responsibility for the publication of these data.

14 Reference List

Reference List

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