ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance on next page.	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☒ **Yes** ☐ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups each have their own**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu Contact:*	

☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	**application process.**
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☒ **Yes** ☐ **No**	Use data from the Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: ics@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: cdrifka@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

Protocol Title	Lifestyle Counseling and Medication for Adolescent Weight Management
Principal Investigator/Faculty Advisor	Name: Aaron S. Kelly, Ph.D.
	Department: Pediatrics; Center for Pediatric Obesity Medicine
	Telephone Number: (612)626-3492
	Email Address: kelly105@umn.edu
Student Investigator	Name: N/A
	Current Academic Status (Student, Fellow, Resident): N/A
	Department: N/A
	Telephone Number: N/A
	Institutional Email Address: N/A
Scientific Assessment	Nationally-based, federal funding organizations
IND/IDE # (if applicable)	158542
IND/IDE Holder	Aaron S. Kelly, Ph.D.
Investigational Drug Services # (if applicable)	5875
Version Number/Date:	Version 21.0, 12Mar2025

PROTOCOL COVER PAGE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	2.0	Changes the drug being utilized in this study from Liraglutide to Semaglutide and revises the titration schedule and the expected adverse events. Modifies the BMI eligibility criterion by moving down to the 95th percentile. Moved the collection of demographic information to the screening visit. Adds review of GI symptom assessment to each visit. Reorganizes format of secondary outcomes and the statistical analysis section for enhanced clarity. Urine pregnancy tests will now be conducted only at visits where an iDXA will be performed.	Yes
2	3.0	Revision to trial design: reduction of treatment period from two years to one year; reduction in sample size from 140 to 120. Adds details related to safety.	Yes
3	4.0	Addition of monitoring for effects of concomitant oral medications	No
4	5.0	Revises the recruitment section to note the use of social media pages.	No
5	6.0	Adds in neurobehavioral assessments and revises the subject compensation for these assessments.	Yes
6	7.0	Adds in information about the shortage of semaglutide (Wegovy) and our plan to utilize semaglutide (Ozempic) in the titration doses of 0.25, 0.5 and 1.0 mg until the shortage has resolved. There is no supply shortage of semaglutide (Wegovy) at doses above 1.0 mg;	No

		therefore, semaglutide (Ozempic) will only be used at these lower titration doses; participants progressing beyond 1.0 mg will then utilize our stock of semaglutide (Wegovy) for doses >1.0 mg. An information sheet for parents has been created as well as instructions for the use of Ozempic.	
7	8.0	Updates sections 5.3 and 14.6 of the protocol to note Dr. Gross' expanded role in the project now that she has received NIH funding to perform a neurobehavioral substudy that has been embedded into this project.	Yes
8	9.0	Revises the protocol to note how long the research records and HIPAA records will be retained after completion of the research	Yes
9	10.0	Revises section 14.1 risk to participants, revises section 14.5 definition of serious adverse event, adds in section 14.6 definition of adverse reaction, adds in section 14.7 definition of serious adverse reaction, adds in section 14.8 definition of SUSAR, revises section 14.10 to revise the reporting of adverse events, updates the protocol references.	No
10	11.0	Notes that the study medication has now been approved for use in adolescents 12 and older by the FDA.	Yes
11	12.0	Revises Table 3 to update module categories and topics and note that participants randomized to the lifestyle therapy arm will receive items to foster eating changes.	Yes

12	13.0	Corrects the schedule of events (pregnancy testing is no longer done at screening since protocol version 2.0) and updates the notifications to include the NIH when serious adverse events occur.	No
13	14.0	Revises the process for conducting the re-consent process.	No
14	15.0	Revises section 5.1 of the protocol. Adds a hemoglobinA1c to the screening visit. Updates the schedule of events to reflect this and section 9.0 of the protocol. Revises section 12.3 of the protocol to note that we are working with the medical school for a Google ad campaign. Adds a hemoglobin A1c to the screening visit We are submitting the ad text and pictures that will be utilized.	Yes
15	16.0	Clarifies the study exclusion criteria.	
16	17.0	Corrects the footer of the schedule of events with regard to the Hemoglobin A1c	No
17	18.0	Adds the Accessibility survey to the visit at Week 26	Yes
18	19.0	Revises section 13.1 of the protocol to clarify that, in line with the intent-to-treat nature of the study, participants in the medication arm are allowed to stop taking study medication but remain on study and allowed to re-start study medication if they choose. Adds in and EDE-Q questionnaire to ask about eating behaviors.	Yes

19	20.0	Adds in adjusted language about suicidal behavior and suicidal ideation	Yes
20	21.0	Revises section 6.0 of the protocol with regards to exploratory biomarker sampling tests to be undertaken. The study will now use biomarker samples to measure brain inflammation with a test that studies brain derived exomes. The schedule of events has been updated to note this and section 5.3 of the protocol has been updated.	No

Table of Contents

ABBREVIATIONS/DEFINITIONS

AE	Adverse Event
AEBQ	Adult Eating Behavior Questionnaire
AHC	Academic Health Center
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BIS/BAS	Behavioral Avoidance System/Behavioral Approach System Scales
BMI	Body mass index
BRIEF-SR	Behavior Rating Inventory of Executive Functions-Self Report
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDC	Centers for Disease Control
CEBQ	Child Eating Behavior Questionnaire
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CPOM	Center for Pediatric Obesity Medicine
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTSI	Clinical and Translational Science Institute
DEBQ	Dutch Eating Behavior Questionnaire
DCRU	Delaware Clinical Research Unit
DHEAS	Dehydroepiandrosterone Sulfate
DSMB	Data and Safety Monitoring Board
EDE-Q	Eating Disorder Examination Questionnaire
FDA	Food and Drug Administration
FSH	Follicular Stimulating Hormone
GI	Gastrointestinal
GLP1-RA	GLP-1 Receptor Agonist
HIPAA	Health Insurance Portability and Accountability Act
HIPCO	Health Information Privacy and Compliance Office
DXA	Dual Energy X-ray Absorptiometry
IND	Investigational New Drug
ITT	Intention to Treat
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
LDL	Low-density Lipoproteins
LH	Luteinizing Hormone
MCMC	Markov Chain Monte Carlo
MN-POC	Minnesota Pediatric Obesity Consortium
MEN-2	Multiple Endocrine Neoplasia Type 2
mSv	Millisievert
MTC	Medullary Thyroid Carcinoma
NHANES	National Health and Nutrition Examination Survey
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
PAQ-A	Physical Activity Questionnaire for Adolescents
Peds QL	Peds Quality of Life
PHQ-9	Peds Health Questionnaire – 9
PROMIS-29	Patient-Reported Outcomes Measurement Information System
QEWP-A	Questionnaire of Eating and Weight Patterns
QOL	Quality of Life
RED-5	Reward Based Eating Drive Scale X5 (Hedonic Eating)
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
UPIRTSO	Unanticipated Problem Involving Risk to Subjects or Others
TSH	Thyroid Stimulating Hormone
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
WTP	Willingness to Pay

1.0 Objectives

The prevalence of adolescent obesity (defined as BMI ≥95th percentile) is at an all-time high in the U.S. (~20%),[1] and the refractory nature of this disease has led to a serious and challenging conundrum in terms of how to provide effective, safe, scalable, and durable treatments without placing undue strain on the healthcare system. Clinical practice guidelines recommend behavioral interventions as the primary strategy for all ages and classes of obesity – moderate to severe.[2,3] In 2017, the U.S. Preventive Services Task Force (USPSTF) released updated screening recommendations concluding that comprehensive, intensive behavioral interventions with a total of ≥26 contact hours over a period of 2-12 months resulted in weight loss in youth with obesity, with ≥52 contact hours leading to even greater weight loss and improvements in some cardiometabolic risk factors.[4,5]

However, the practicality of delivering these types of intensive behavioral services to the millions of youth with obesity in the U.S. is debatable not only because of the treatment-resistant nature of obesity,[6-10] but also due to the time-commitment, acceptability, and sustainability of this approach for adolescent patients and their families along with the extensive resources required to provide these interventions. Indeed, fewer than 50% of pediatric patients referred for weight management services enroll in treatment, and high attrition rates of up to 50% have been reported in behavioral-based clinical trials and in the clinical setting.[6,10-15] Moreover, adherence to behavioral counseling significantly diminishes over time, which too often erodes early weight loss success and ultimately derails durability.[16] The reality of what most patients/families are able to do and the unique physiological and psychosocial features of obesity in adolescence do not seem to align well with the degree of intensity of behavioral interventions shown to be effective by the USPSTF. Therefore, a critical appraisal of the feasibility, effectiveness, and sustainability of the USPSTF recommendations among adolescents with obesity is warranted.

While behavior change is an indispensable component of any effective weight loss approach, adjunctive strategies such as pharmacotherapy may enhance outcomes in adolescents with obesity. Many maladaptive behaviors attributed to obesity are driven by underlying biological forces, such as increased appetite and food palatability, that are largely beyond the control of the individual.[17] Pharmacotherapy can help facilitate behavior change by disrupting core pathophysiological processes and restoring homeostasis to the energy regulatory system,[18] therein enabling individuals to sustain healthy behavior change. Though underexplored as a treatment for adolescent obesity, pharmacotherapy along with relatively low-intensity behavioral counseling (<26 contact hours) represents a potentially effective, durable, and safe treatment strategy. This approach may be more practical and feasible to implement on a broad scale, be preferred by patients/families, utilize fewer healthcare resources, and cost less to deliver compared to comprehensive, intensive behavioral interventions.

We will conduct a two-arm, randomized clinical trial in adolescents ages 12 to <18 years old with obesity evaluating 56 weeks (one year) of intensive behavioral counseling, aligned with the

USPSTF recommendations (52 contact hours), vs. 56 weeks of medical management with semaglutide 2.4 mg weekly subcutaneous injection (glucagon-like peptide-1 receptor agonist) plus relatively low-intensity behavioral counseling (12 contact hours).

2.0 Background

2.1 Significance of Research Question/Purpose:

The significance of the proposed work is underscored by: 1) the seriousness and prevalence of adolescent obesity; 2) the large treatment gap and paucity of effective non-surgical treatment options for this high-risk patient population; 3) the need for safe and effective medications to aid in obesity management; and 4) the pragmatic alternative treatment approach we plan to investigate.[4,5] The progressive, unrelenting, and recalcitrant nature of obesity demands that appropriately-intensive interventions be initiated earlier in life, not later in adulthood when adiposity and co-morbidities have become entrenched and multisystem physiological decompensation has commenced. Indeed, excess adiposity during childhood is a strong predictor of later development of adverse cardiovascular outcomes and type 2 diabetes; however, remission of obesity prior to adulthood portends favorable health outcomes.[19-23] Moreover, there appears to be a narrow window of opportunity in childhood during which BMI trajectory can be altered to offer a reasonable opportunity for these youth to achieve a healthy BMI in adulthood.[24] Early and effective intervention likely offers the best chance to improve the long-term health outlook for youth with obesity.

There is a need to investigate promising non-surgical treatments that can augment the beneficial effects of behavioral counseling and potentially enhance durability. Indeed, one of the conclusions of the evidence review commissioned by the USPSTF recommendations stated that: "The clinical significance of the small benefit of medication use is unclear."[5] However, in this systematic review/meta-analysis, only metformin and orlistat were examined – both of which have lower weight loss efficacy as compared to semaglutide. Hence, the rationale and significance of our project, aimed at characterizing the effectiveness and safety of pharmacotherapy for youth, is in large part driven by a key unanswered question posed by the USPSTF. Since pharmacotherapy can target the underlying biology of obesity (e.g. reduce appetite), we believe the rationale for investigating its utility is strong and is consistent with treatment approaches for other pediatric chronic diseases. We expect to observe BMI reduction in both groups, but anticipate superior BMI reduction, reasonably equivalent safety, and better participant disposition outcomes and cost-effectiveness in the pharmacotherapy group.

As noted, weight reduction is expected in both groups. At the same time we expect significant heterogeneity in weight loss response and maintenance to both treatment options. Identifying predictors of response would allow for

matching adolescents to personally effective interventions, thereby optimizing outcomes and minimizing unnecessary exposure to potential risks. Emerging evidence in adolescents shows that aspects of executive functioning, including inhibition, may improve following behavioral interventions/lifestyle modification therapy (LMT) and that enhanced inhibition can predict weight loss response to LMT. Newer anti-obesity medications, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs), decrease activation in reward related regions of the brain in response to food cutes. Currently, it is unclear what neurobehavioral factors predict weight loss maintenance to LMT or pharmacotherapy, which is the ultimate goal of treatment. Identifying neurobehavioral predictors of initial weight loss response *and* weight loss maintenance will stimulate needed progress in the emerging field of precision medicine.

2.2 Preliminary Data:

The following studies from our group, along with evidence from the literature, provide the background and rationale for our proposed project and have informed the design of our clinical trial detailed in this protocol.

Pilot and Feasibility Crossover Trial of GLP-1RA in Adolescents with Severe Obesity

We conducted a pilot/feasibility trial to evaluate the effects of the GLP-1RA exenatide on BMI (primary endpoint), cardiometabolic risk factors, and glucose tolerance in adolescents with severe obesity.[25] Twelve youth (9-16 years old) were enrolled in a six-month, randomized, open-label, crossover, clinical trial consisting of two, three-month phases: 1) a control phase of behavioral counseling and 2) a medication phase of behavioral counseling plus exenatide. Participants were randomized to phase-order (i.e., starting with control or medication) then crossed-over to the other treatment. Outcomes were assessed at baseline, three months, and six months. Results are shown in Table 1. The control-subtracted treatment effect was approximately 5% BMI reduction. Compliance with the injection regimen was excellent (≥94%) and exenatide was generally well-tolerated. The most common adverse event was nausea, which was experienced in 4/11 (all classified as mild). Vomiting (3/11) and headache (3/11) were the second most common adverse events (all categorized as mild).

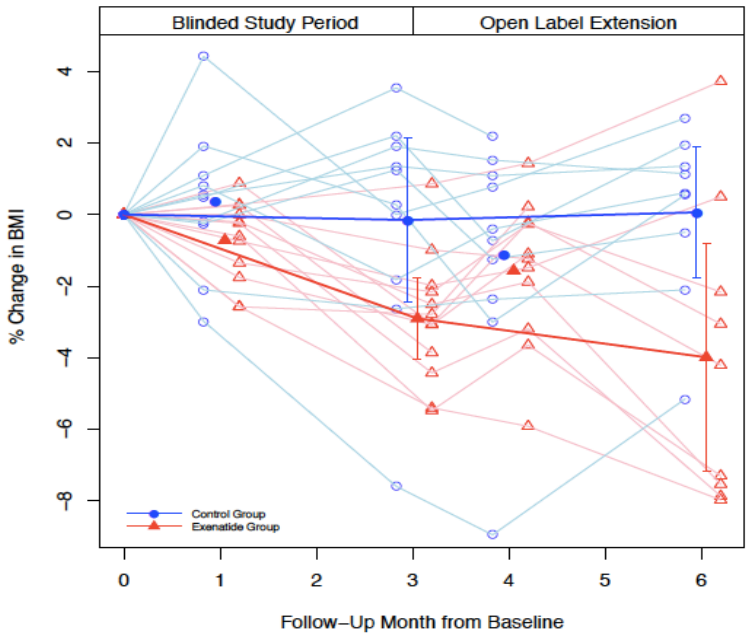
Table 1. Treatment Effects Within and Between Study Arms *(values presented are mean (SD))*

Outcome	Δ Control	Δ Exenatide	Treatment Effect (95% CI)	P-value
BMI (kg/m^2)	0.84 (1.28)	-0.90 (1.22)	-1.71 (-3.01, -0.42)	**0.010**
Percent Change BMI	1.72 (4.19)	-2.57 (3.46)	-4.92 (-8.61, -1.23)	**0.009**
Weight (kg)	2.97 (2.88)	-0.99 (2.90)	-3.90 (-7.11, -0.69)	**0.017**
Body Fat (%)	0.92 (2.75)	-0.36 (3.07)	-1.28 (-4.66, 2.09)	0.457
SBP (mmHg)	3.10 (8.72)	-3.11 (8.51)	-5.31 (-14.89, 4.27)	0.277
HDL (mg/dL)	-0.20 (6.84)	3.44 (3.40)	3.25 (-2.47, 8.97)	0.266
Triglycerides (mg/dL)	-4.22 (37.45)	-9.89 (41.24)	-12.57 (-59.41, 34.28)	0.599
Glucose (mg/dL)	1.60 (6.40)	3.22 (5.85)	1.68 (-3.65, 7.01)	0.537
Glucose AUC (per 100)	11.69 (29.50)	-17.67 (22.98)	-27.96 (-56.51, 0.59)	**0.055**
Insulin (mU/L)	6.00 (5.58)	-1.62 (8.42)	-7.54 (-13.71, -1.37)	**0.017**
Insulin AUC (per 100)	30.29 (98.76)	-38.95 (73.74)	-76.01 (-166.30, 14.28)	**0.099**
WBISI/Matsuda	-2.00 (3.52)	4.12 (7.10)	6.13 (1.01, 11.25)	**0.019**
β-Cell Function	-1.16 (6.33)	14.50 (26.09)	17.97 (1.40, 34.54)	**0.034**

Randomized, Placebo-Controlled Pilot Clinical Trial of GLP-1RA in Adolescents with Severe Obesity

Based on the promising results of our first pilot trial, we performed a larger study with a more rigorous design (randomized, double-blind, placebo-controlled trial with a three-month open label extension) to evaluate the effects of the GLP-1RA exenatide on BMI and cardiometabolic risk factors in adolescents with severe obesity.[26] Twenty-six adolescents (age 12-19 years) were enrolled. All patients received behavioral counseling and were equally randomized to exenatide or placebo injection, twice per day. The primary endpoint was the mean percent change in BMI measured at baseline and three-months. Twenty-two patients completed the trial. We assessed the medium-term durability of the BMI reduction by performing an extension phase during which all participants (regardless of initial assignment) were offered open-label exenatide. BMI trajectories are shown in Figure 1.

Figure 1. Percent Change in BMI during the Randomized, Placebo-Controlled and Open Label Phase



Compared to placebo, GLP-1RA treatment reduced BMI by approximately 3% at three months (see Table 2). Of note, during the open label extension, BMI continued to decrease in participants initially randomized to exenatide (cumulative BMI reduction of 4%). Compliance was excellent and ranged from 85-100% of the required doses; mean = 95%. The most common adverse events (all mild-moderate and transient) were nausea (placebo 31%, exenatide 62%), abdominal pain (placebo 23%, exenatide 15%), diarrhea (placebo 31%, exenatide 8%), headache (placebo 46%, exenatide 23%), and vomiting (placebo 8%, exenatide 31%). The findings of this pilot trial provided additional evidence supporting the feasibility, safety, and efficacy of GLP-1RA treatment in adolescents with severe obesity.

Table 2. Change from Baseline to Three Months for the Primary and Secondary Endpoints (values presented are mean (SD))

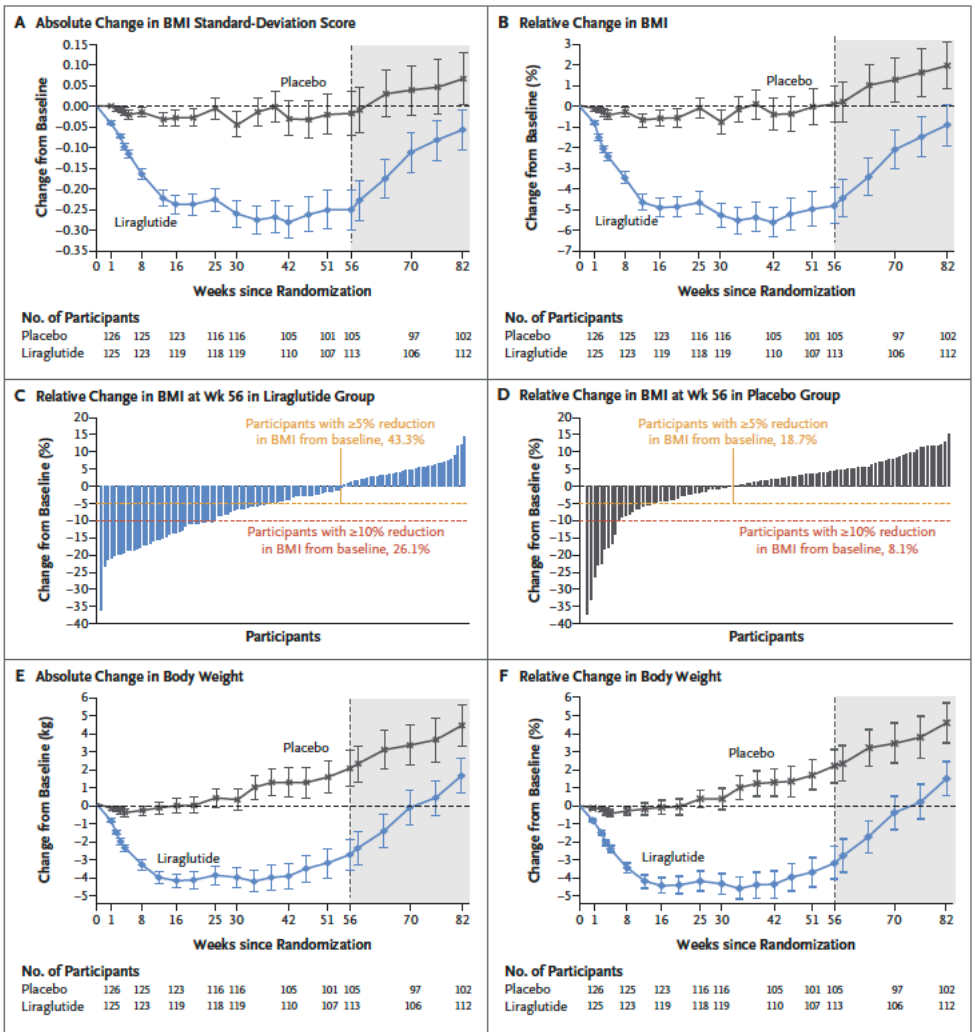
Covariate	N	Exenatide Δ	Control Δ	Estimate (95% CI)	P-value
Percent Change BMI	22	-2.90 (1.80)	-0.15 (3.20)	-2.70 (-5.02, -0.37)	**0.025**
BMI (kg/m^2)	22	-1.18 (0.67)	-0.04 (1.23)	-1.13 (-2.03, -0.24)	**0.015**
Weight (kg)	22	-2.93 (2.48)	0.32 (3.21)	-3.26 (-5.87, -0.66)	**0.017**
Waist (cm)	22	-2.04 (2.62)	-1.01 (5.57)	-0.98 (-4.60, 2.64)	0.579
Total Tissue Fat (kg)	15	-1.69 (2.41)	-0.65 (2.50)	-0.72 (-3.66, 2.23)	0.610
Visceral Fat Area (cm^2)	14	-97.00 (191.22)	-18.17 (178.62)	-78.15 (-309.55, 153.25)	0.473
SBP (mmHg)	22	-5.50 (9.13)	2.00 (13.43)	-6.36 (-13.46, 0.73)	**0.076**
HDL-cholesterol (mg/dL)	22	-0.42 (4.08)	-3.00 (5.12)	2.08 (-1.82, 5.99)	0.278
Triglycerides (mg/dL)	22	2.83 (53.69)	3.90 (44.41)	-4.71 (-45.14, 35.72)	0.810
Glucose (mg/dL)	22	1.17 (8.19)	4.60 (9.51)	-3.33 (-9.71, 3.05)	0.288
Insulin (mU/L)	22	-8.33 (18.81)	0.67 (7.43)	-2.91 (-10.91, 5.10)	0.455
HbA1c (%)	22	-0.12 (0.16)	-0.01 (0.14)	-0.11 (-0.23, 0.01)	**0.072**

Large Safety and Efficacy Trial of GLP-1RA in Adolescents with Obesity

In this randomized, double-blind trial, which consisted of a 56-week treatment period and a 26-week follow-up period, adolescents (12 to <18 years of age) with obesity and a suboptimal response to lifestyle therapy alone were enrolled.[27] Participants were randomly assigned (1:1) to receive either liraglutide (3.0 mg) or placebo subcutaneously once daily, in addition to lifestyle therapy. The primary end point was the change from baseline in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) standard-deviation score at week 56. A total of 125 participants were assigned to the liraglutide group and 126 to the placebo group. BMI and weight-related outcomes are shown in Figure 2. Liraglutide was superior to placebo with regard to the change from baseline in the BMI standard-deviation score at week 56 (estimated difference, −0.22; 95% confidence interval [CI], −0.37 to −0.08; P = 0.002). A reduction in BMI of at least 5% was observed in 51 of 113 participants in the liraglutide group and in 20 of 105 participants in the placebo group (estimated percentage, 43.3% vs. 18.7%), and a reduction in BMI of at least 10% was observed in 33 and 9, respectively (estimated percentage, 26.1% vs. 8.1%). A greater reduction was observed with liraglutide than with placebo for BMI (estimated difference, −4.64 percentage points) and for body weight (estimated difference, −4.50 kg [for absolute change] and −5.01 percentage points [for relative change]). After discontinuation, a greater increase in the BMI standard-deviation score was observed with liraglutide than with placebo (estimated difference, 0.15; 95% CI, 0.07 to 0.23). More participants in the liraglutide group than in the placebo group had gastrointestinal adverse events (81 of 125 [64.8%] vs. 46 of 126 [36.5%]) and adverse events that led to discontinuation of the trial treatment (13 [10.4%] vs. 0). Few participants in either group had serious adverse events (3 [2.4%] vs. 5 [4.0%]). One suicide, which occurred in the liraglutide

group, was assessed by the investigator as unlikely to be related to the trial treatment. In adolescents with obesity, the use of liraglutide (3.0 mg) plus lifestyle therapy led to a significantly greater reduction in the BMI standard-deviation score than placebo plus lifestyle therapy.

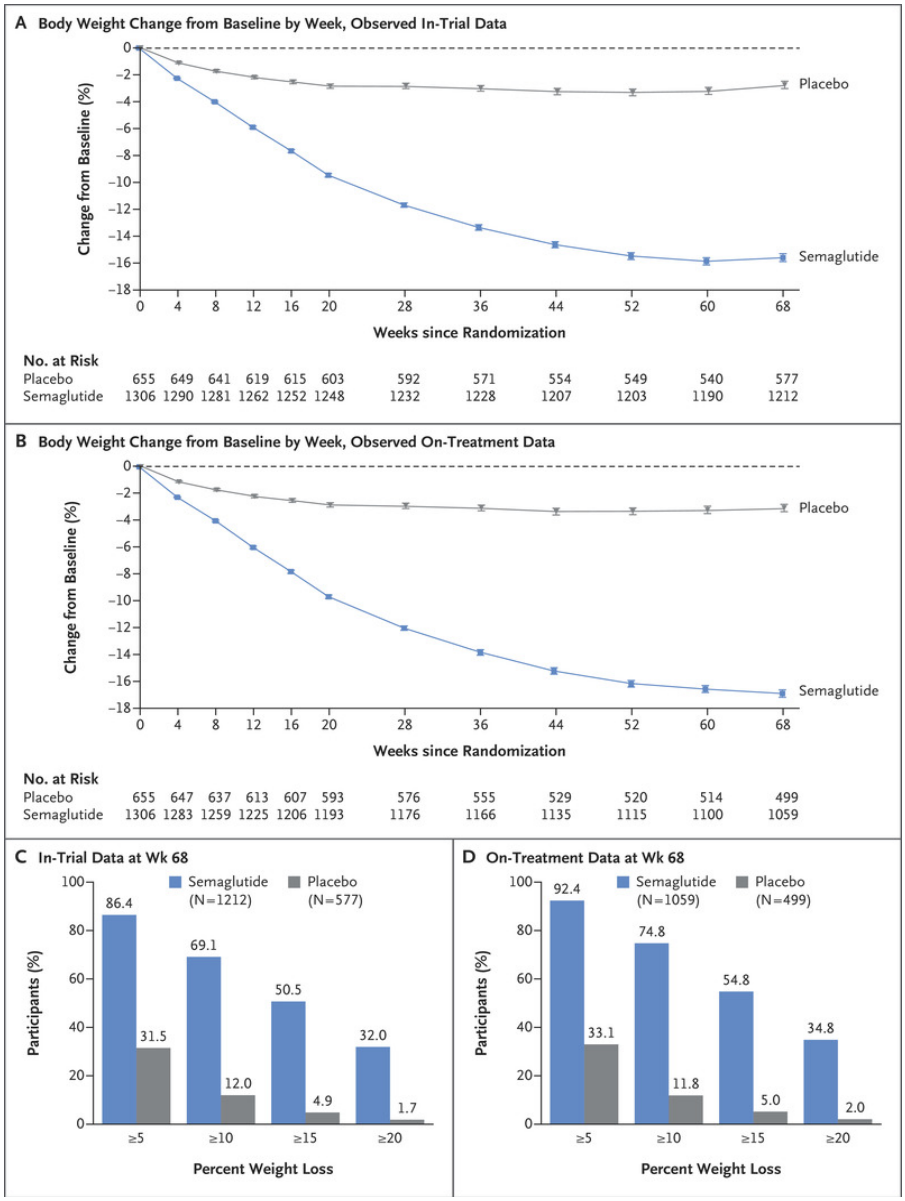
Figure 2. BMI and Weight-Related Outcomes with Liraglutide in Adolescents with Obesity



Safety and Efficacy of GLP-1RA in Adults

One of the largest phase III clinical trials of semaglutide 2.4 mg weekly in adults (N=1,961) demonstrated a mean placebo-subtracted body weight reduction of 12.4% at 68 weeks.[28] Figure 3 shows the body weight trajectories and the percent achieving 5%, 10%, 15%, and 20% weight loss of the placebo and semaglutide groups, both of which received behavioral counseling.

Figure 3. Weight Outcomes in Adults Treated with Semaglutide 2.4 mg Weekly or Placebo[42]



The most frequently-reported adverse events with semaglutide were gastrointestinal in nature - mild or moderate nausea and diarrhea were predominantly experienced in the up-titration period.[28] Serious adverse events occurred in 9.8% of the participants receiving semaglutide and 6.4% in those receiving placebo.[28] These data support our hypothesis that, other than GI symptoms, side effects will be similar between groups.

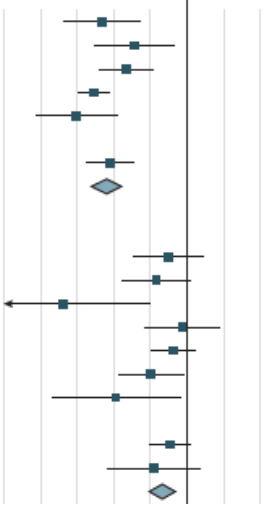
Outcomes of Behavioral Interventions in Youth with Obesity

In 2017, the USPSTF released updated screening recommendations concluding that comprehensive, intensive behavioral interventions with a total of ≥26 contact hours over a period of 2-12 months resulted in weight loss in youth with obesity, with ≥52 contact hours leading to even greater weight loss and improvements in some cardiometabolic risk factors.[4,5] Figure 4 shows the change in BMI in various trials summarized in the USPSTF report.[5] Results from these trials have informed our anticipated treatment effect estimates presented in the statistical analysis plan elsewhere in the protocol.

Figure 4. BMI Reduction with Behavioral Intervention

Figure 4. Change in Weight (BMI *z* Score, BMI, Weight in Kilograms, or BMI Percentile) in Behavior-Based Weight Loss Intervention Trials, by Estimated Hours of Contact, Showing DerSimonian and Laird Pooled Estimates (Key Question 4)

Source	Estimated Contact Hours Through 12 mo	Months Since Randomization (Months Since End of Treatment)	Intervention No.	Intervention Change From Baseline, Mean (SD)	Control No.	Control Change From Baseline, Mean (SD)	Standardized Mean Difference in Change From Baseline (95% CI)
Estimated contact ≥52 h							
Outcome: BMI *z* score							
Weigel et al,[64] 2008	114	12 (0)	36	-0.34 (0.48)	30	0.26 (0.57)	-1.15 (-1.68 to -0.63)
Savoye et al,[51] 2014	78	6 (0)	31	-0.05 (0.13)	27	0.04 (0.12)	-0.72 (-1.25 to -0.19)
Reinehr et al,[45] 2006	78	12 (0)	174	-0.30 (0.35)	37	0 (0.41)	-0.83 (-1.19 to -0.47)
Reinehr et al,[46] 2009	78	12 (0)	288	-0.22 (0.35)	186	0.15 (0.17)	-1.27 (-1.47 to -1.07)
Reinehr et al,[47] 2010	67	6 (0)	34	-0.26 (0.22)	32	0.05 (0.19)	-1.50 (-2.05 to -0.96)
Outcome: BMI							
Savoye et al,[52] 2007	82	12 (0)	105	-1.7 (3.1)	69	1.6 (3.2)	-1.05 (-1.37 to -0.72)
Subtotal (I^2=43.4%; P=.12)							-1.10 (-1.30 to -0.89)
Estimated contact 26-51 h							
Outcome: BMI *z* score							
Vos et al,[61] 2011[a]	45	12 (NA[b])	32	-0.40 (1.3)	35	-0.1 (1.1)	-0.25 (-0.73 to 0.23)
Kalavainen et al,[34] 2007	44	12 (6)	35	-0.30 (0.15)	35	-0.20 (0.30)	-0.42 (-0.89 to 0.05)
Stark et al,[54] 2011	38	12 (6)	7	-0.37 (0.41)	9	0.40 (0.49)	-1.68 (-2.85 to -0.52)
Croker et al,[26] 2012	38	6 (0)	31	-0.11 (0.16)	27	-0.10 (0.16)	-0.06 (-0.58 to 0.45)
DeBar et al,[29] 2012[a]	37	12 (7)	90	-0.15 (0.41)	83	-0.08 (0.36)	-0.18 (-0.48 to 0.12)
Sacher et al,[49] 2010	36	6 (3.75)	37	-0.30 (0.51)	45	-0.01 (0.65)	-0.49 (-0.94 to -0.05)
Stark et al,[53] 2014	30	12 (16)	11	-0.59 (0.75)	12	-0.03 (0.36)	-0.97 (-1.84 to -0.10)
Outcome: BMI							
Kalarchian et al,[33] 2009	44	12 (0)	97	0.50 (3.0)	95	1.1 (2.2)	-0.23 (-0.52 to 0.05)
Nemet et al,[42] 2005[a]	33	12 (9)	20	-1.6 (4.3)	20	0.60 (5.5)	-0.45 (-1.07 to 0.18)
Subtotal (I^2=24.0%; P=.23)							-0.34 (-0.52 to -0.16)



Frequency of Contact in Multidisciplinary Pediatric Weight Management Programs

The frequency of contact for the semaglutide plus low-intensity behavioral counseling group (12 contact hours) was chosen to reflect what is generally considered practical in the real-world clinical setting. Data collected on program profiles from over 30 multidisciplinary pediatric weight management clinics throughout the U.S. reported that most (52%) programs offered <25 contact hours; only 17% offered contact hours between 25-75 hours.[29] Results from the large registry study stemming from this collaborative network demonstrated that there was a dose-dependent relationship in BMI reduction (expressed as change in BMI percent of the 95th percentile) such that outcomes were best in patients who received ≥7 contact hours.[10] Many programs offer approximately monthly

provider-patient contact averaging 12 hours per year. Therefore, we have chosen to mimic the approximate number of contact hours that are commonly offered in multidisciplinary pediatric weight management programs.

In summary, this portfolio of preliminary work: 1) demonstrates our Center's experience and leadership role in the field of pediatric obesity medicine, and the GLP-1RA class in particular; 2) highlights the refractory nature of adolescent obesity; 3) demonstrates heterogeneity in treatment response; 4) provides evidence of the safety/efficacy of GLP-1RAs in adolescents and in adults; and 5) sets the stage for taking this next important step.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Compare the effectiveness of intensive behavioral counseling vs. medical management plus low-intensity behavioral counseling on mean percent change in BMI from baseline to 56 weeks of follow-up in adolescents with obesity. We hypothesize that semaglutide 2.4 mg weekly plus low-intensity behavioral counseling will elicit superior reductions in BMI (primary efficacy endpoint) compared to intensive behavioral counseling at 56 weeks (primary outcome assessment timepoint).

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

3.2.1 Compare the effectiveness of intensive behavioral counseling vs. medical management plus low-intensity behavioral counseling on body fat, cardiometabolic risk factors, and quality of life in adolescents with obesity. We hypothesize that semaglutide 2.4 mg weekly plus low-intensity behavioral counseling will elicit superior reductions in body fat and greater improvements in cardiometabolic risk factors and quality of life compared to intensive behavioral counseling at 56 weeks (primary outcome assessment timepoint).

3.2.3 Compare the number of adverse events (AEs) and safety outcomes for intensive behavioral counseling vs. medical management plus low-intensity behavioral counseling in adolescents with obesity. We hypothesize that the number of gastrointestinal-related AEs will be higher in those randomized to semaglutide, but that changes in other safety outcomes will be approximately equal between the groups.

3.2.4 Evaluate the implementation feasibility of the strategies by assessing acceptability, adherence, rate of attrition, and cost-effectiveness. We hypothesize that the semaglutide plus low-intensity behavioral counseling will have a higher rate of acceptability and adherence, lower rate of attrition, and will be more cost-effective as compared to intensive behavioral counseling.

3.3 Tertiary Endpoint(s): Neurobehavioral Predictors of Response

3.3.1 Identify baseline neurobehavioral predictors of weight loss response in adolescents with obesity undergoing intervention.

3.3.2 For participants achieving >5% BMI reduction at 6 months (i.e., initial responders), identify neurobehavioral predictors of weight loss maintenance at 12 months.

3.3.3 Evaluate differences in predictors of response between intensive LMT and GLP-1RA therapy.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

Behavioral Intervention

The comprehensive behavioral intervention for both groups (intensive behavior group and medication group) will be designed and delivered according to the principles and components detailed in the evidence report and systematic review commissioned by the USPSTF.[5] Participants assigned to the *intensive behavioral intervention group* will engage in weekly sessions for a total of 52 contact hours including biweekly (twice per month) in-person group sessions plus bi-weekly virtual sessions consisting of a self-paced online module with an accompanying individual counseling virtual/phone session, for a total of one hour of contact every week. Participants assigned to the *medication group* will also receive behavioral counseling, with the same content and structure as that of the intensive group, but delivered with lower frequency. Participants will receive a total of 12 contact hours including six in-person group sessions plus six online modules accompanied by an individual virtual/phone counseling session, for a total of one hour of contact every four weeks. The rationale for the frequency of contact in both groups is that obesity, as a chronic and relapsing disease, necessitates a chronic care model.[30, 31]

In the spirit of generalizability and in consideration of cost-effectiveness and implementation feasibility, almost all in-person sessions will be group-based and include only the participants. It should be noted that the USPSTF recommendations encompass both group and individual session strategies (i.e., the recommendations apply to either of the two approaches). In-person sessions will involve the adolescent participants only (without a parent/guardian/caretaker). However, acknowledging the potential for meaningful developmental differences in younger participants, and the variable role of parents in creating the proper conditions for aiding in weight management, we will encourage all parents/guardians/caretakers for both groups to complete a parent-specific self-paced virtual session at the beginning of each module that will specifically address how to be supportive with the current topic. All parents/guardians/caretakers will also attend the first in-person session with their

child at the time of their child's enrollment and will receive regular communication regarding programming and content of the in-person sessions. Parents/guardians/caretakers will only be required to attend the virtual/phone sessions with their child if he/she is 13 years old or younger.

The behavioral program will be based on state-of-the-art interventions conducted by members of the study team[8, 32-36] and others.[37-41] Curriculum will incorporate evidence-based behavior change principles, which will include four macro components: dietary modification, energy expenditure modification, behavior modification, and family involvement and support. The intervention focuses on: 1) dietary intake changes; 2) increases in physical activity and reductions in sedentary behavior; and 3) behavior change strategies to facilitate adherence to the diet and activity change recommendations. The core intervention is based on a behavioral conceptualization of effective weight management that emphasizes: 1) identifying behaviors in need of change; 2) setting goals for change; 3) monitoring progress; 4) modifying environmental cues to facilitate change; and 5) modifying consequences to motivate change. The intervention will incorporate core behavior change strategies including self-monitoring, stimulus control, modeling, goal setting, and positive reinforcement. Each session will follow a general format including a review of progress, new material, supervised interactive activities, and a summary/plan for the upcoming week. By design, the intensive group will have repetition and overlap of curriculum. Owing to the reduced contact time for the medication group, less of the content will be repeated. Therefore, curriculum for the medication group will include the same principles and components as outlined below, but will be delivered in a distilled and less-redundant fashion.

Sample details of curriculum components along with the frequency of delivery for the intensive group are shown in Table 3. Although USPSTF recommendations were written to encompass all ages, we will tailor session curriculum components to address the unique developmental needs of teens. For example, topics will include shared-decision making among parents and adolescents and fostering independence with appropriate oversight. Topics related to social support and problem-solving will include examples of maintaining healthy goals and how to resist peer pressure.

Participants will be asked to track their food intake and share this information with the study staff.

Table 3. Overview of Comprehensive Behavioral Intervention Curriculum

Table 3*		Intense Lifestyle ARM	Meds ARM	Parent
Module 1: Kickstarter Build Your Knowledge				
WEEK	**TOPIC**			
1-wk	Getting Started, Energy Balance	In-person Individual	In-person Group	In-person Individual
2-wk	Keeping Track	Virtual Session + Call		
3-wk	Learning About Food	In-person Individual		
4-wk	What Should I Eat?	Virtual Session + Call		
Module 2: Rethink your drink				
5-wk	What Do You Drink?	In-person Group	In-person Group	Virtual Session
6-wk	Hydration	Virtual Session + Call		
7-wk	Quench Your Thirst, Problem Solving	In-person Group		
8-wk	Rethink Your Drink	Virtual Session + Call		
Module 3: Let's Be active				
9-wk	Why Be Active?	In-person Group	In-person Group	Virtual Session
10-wk	How hard is your body working?	Virtual Session + Call		
11-wk	Burn Calories through Exercise	In-person Group		
12-wk	What Are you Doing to Be Active?	Virtual Session + Call		
Module 4: It's All in the Planning				
13-wk	Plan Your Day	In-person Group	In-person Group	Virtual Session
14-wk	Plan What You Need, What's in Your kitchen	Virtual Session + Call		
15-wk	Plan What You Buy	In-person Group		
16-wk	Plan How Much You Have	Virtual Session + Call		
Module 5: High Quality vs Low Quality Foods				
17-wk	High Quality vs Low Quality Foods	In-person Group	Virtual Session + Call	Virtual Session
18-wk	You are what you eat	Virtual Session + Call		
19-wk	Snacks	In-person Group		
20-wk	Food Makeover	Virtual Session + Call		
Module 6: Mindfulness				
21-wk	Acceptance of Food-Related Internal Experiences	In-person Group	Virtual Session + Call	Virtual Session
22-wk	Strategies to Increase Willingness	Virtual Session + Call		
23-wk	Mindful-Decision Making	In-person Group		
24-wk	Clarification and Commitment to Core Values	Virtual Session + Call		
Module 7: Let's be Balanced				
25-wk	Being Healthy is Being in Balance	In-person Group	In-person Group	Virtual Session
26-wk	Portion Distortion	Virtual Session + Call		
27-wk	After-School Snacks	In-person Group		
28-wk	Q and A about sports nutrition, fad diets…	Virtual Session + Call		
Module: 8 Outside Influences (media, food advertising, food cues, body image, teasing…)				
29-wk	Effects of Social Media	In-person Group	Virtual Session + Call	Virtual Session
30-wk	Food Cues (Vignette)	Virtual Session + Call		
31-wk	Aaron Kelly: What is research, why is it important + Q&A	In-person Group		
32-wk	Influence of advertising: Are you falling for it? (Vignette)	Virtual Session + Call		
Module 9: Eating Away from Home (fast food, with friends, social support, saying No)				
33-wk	Eating Away from Home Challenges	In-person Group	Virtual Session + Call	Virtual Session
34-wk	Social Support	Virtual Session + Call		
35-wk	Time Crunch Meal and Snack Ideas	In-person Group		
36-wk	Tips and Tricks	Virtual Session + Call		
Module 10: Boost Your Activity, Lessen Your Sedentary Activity				
37-wk	Increasing Your Steps	In-person Group	In-person Group	Virtual Session
38-wk	Move More, Sit Less	Virtual Session + Call		
39-wk	Media Messages	In-person Group		
40-wk	Activity In a Normal Week	Virtual Session + Call		
Module 11: Thoughts and Feelings (unhelpful thoughts, emotional eating)				
41-wk	Learning to Eat When You're Hungry— and Not When You're Not	In-person Group	Virtual Session + Call	Virtual Session
42-wk	Managing Emotions the Healthy Way	Virtual Session + Call		
43-wk	Unhelpful Thoughts	In-person Group		
44-wk	High Risk Situations	Virtual Session + Call		
Module 12: Self Care				
45-wk	Mindful Eating	In-person Group	Virtual Session + Call	Virtual Session
46-wk	Label Claims (Vignette)	Virtual Session + Call		

47-wk	Amy Gross: Managing Stress	In-person Group		
48-wk	Sleep (Vignette)	Virtual Session + Call		
Module 13: Staying the Course (motivation, overcoming mistakes, focus on positive results, tracking, relapse)				
49-wk	Motivation	In-person Group	In-person Group	Virtual Session
50-wk	Building Healthy Habits	Virtual Session + Call		
51-wk	Keeping Old, Unhealthy Habits Away	In-person Group		
52-wk	Positive Results	Virtual Session + Call		

*Items to foster change will be distributed during class to intensive lifestyle arm – water bottle, overnight oats kit, crystal light packets, portion-control zip-lock bags.

A multidisciplinary team will supervise the delivery of the intervention including a researcher with extensive experience in designing and delivering comprehensive behavioral interventions (Dr. Sherwood), a pediatrician with specialized training in obesity medicine and experience delivering behavioral therapy in the clinical setting (Dr. Fox), exercise physiologists (Drs. Kelly and Ryder), registered dietitians and/or nutritionist staff members with extensive experience delivering comprehensive, intensive behavioral therapy curriculum, behavioral psychologist with experience in clinical behavioral management of obesity (Dr. Gross), and specially-trained study coordinators that will assist in staffing the sessions. Dr. Marcus, a researcher and clinician with expertise in behavioral interventions for youth with severe obesity, will provide consultation regarding the design, implementation, and ongoing fidelity monitoring of the behavioral intervention via regularly-scheduled conference calls. Notably, Dr. Marcus was the principal investigator of an NIH-funded clinical trial evaluating behavioral therapy for weight management in youth with severe obesity and served as an investigator for the NIDDK-sponsored TODAY trial, which included an evidence-based, comprehensive behavioral therapy component. She was heavily involved in the development of the behavioral curriculum as well as the implementation and fidelity monitoring.

To ensure intervention fidelity and adherence to the delivery of the protocol, a manual of operations will be developed for each session that trained staff will follow when administering the curriculum. These session-specific manuals will explicitly guide staff to correctly deliver the intervention components. All interventionists will participate in a training phase that will involve review of the protocol, intervention materials, and role plays. Regular quality assurance checks will be performed. Staff will undergo regular training refreshers (quarterly), and quality assurance checks will be implemented throughout the project to monitor intervention delivery.

Semaglutide Treatment Arm

Participants assigned to the semaglutide group will initiate treatment with 0.25 mg once-weekly dosing via subcutaneous injection and will follow a dose-escalation regimen with 4-week dose escalation steps to 0.5, 1.0, 1.7 and 2.4 mg. The goal will be to get all participants to the 2.4 mg weekly dose; however, we will not utilize a forced-titration strategy meaning that some participants may be treated at a maximum tolerated dose lower than 2.4 mg. Tolerability will include but not be

limited to GI side effects and hypoglycemia. Participants will remain on semaglutide for the entire 56-week trial intervention period.

Regulatory Status of Semaglutide
Semaglutide is approved by the FDA for use in adults (≥ 18 years old) with obesity. In December 2022 the FDA approved semaglutide for use in children (ages 12-17) with obesity. As this study started prior to FDA approval for use in children, an IND was obtained for the conduct of this study.

4.2 Drug/Device Handling:
Semaglutide will be purchased commercially until it receives FDA approval at which time product will be donated by the manufacturer, Novo Nordisk. Trial product will be managed by the University of Minnesota Investigational Drug Service Pharmacy and will dispensed according to their operating policies. The IDS office specializes in storing and dispensing investigational drugs for clinical trials. Study physicians will write a prescription in order for IDS to dispense the medication. IDS is in a secure facility (behind two locked doors) and maintains refrigerators and freezers with temperature tracking to assure that the drugs utilized in this study will maintain stability. IDS will keep detailed records on the receipt of investigational product (including lot numbers) and detailed records on the dispensing of product to each subject enrolled in the study. IDS is also equipped to destroy any medication that is returned at the end of the study when all drug accountability has been completed. The participant will be taught how to self-administer the medication under the supervision of a parent/guardian. Study staff members will inspect used injection pen devices returned by participants and ask participants to estimate a percentage of missed doses as additional forms of compliance tracking.

The recent FDA approval of Semaglutide (Wegovy) for adults created high demand for the product and has resulted in a widespread shortage of medication at the lower titration doses of 0.25, 0.5, and 1.0 mg. However, the same medication at lower doses used for the treatment of type 2 diabetes (marketed under Ozempic) is not in short supply. We will utilize semaglutide (Ozempic) in the 0.25, 0.5 and 1.0 mg doses until the semaglutide (Wegovy) shortage has eased. Participants will be up-titrated to 1.0 mg using semaglutide (Ozempic) then switch to semaglutide (Wegovy) for doses >1.0 mg. Currently enrolled participants will be provided with an information sheet that details this change and we have developed an instruction sheet for administering Ozempic as the dosage pen is different than the Wegovy dosage pen.

4.3 Biosafety: Not applicable.
4.4 Stem Cells: Not applicable.
4.5 Fetal Tissue: Not applicable.

5.0 Procedures Involved

5.1 Study Design:

This will be a randomized (1:1), head-to-head, 56-week clinical trial examining intensive behavioral counseling (52 contact hours) vs. medical management with semaglutide 2.4 mg weekly plus low-intensity behavioral counseling (12 contact hours) among 120 adolescents with obesity. All investigators will be blinded to treatment condition. In addition, all personnel responsible for performing data collection related to the primary endpoint (BMI) and other secondary physiological assessments on participants will be blinded to treatment condition.

Neurobehavioral Predictors of Response: All participants in both groups will complete neurobehavioral assessment at 5 study visits (included in schedule of events, Table 4).

The schedule of events section (below, Table 4) shows the data that will be collected at each study visit. All participants will receive reimbursement for completing study visit assessments. Study staff will check in with participants to ensure dosing is occurring as outlined in the protocol.

Table 4. Schedule of Events

	Screening	Randomization		1 Year					
			Week 4	Week 8	Week 12	Week 16	Week 26	Week 39	Week 56
Allowable window[&]		± 30d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 15d
Informed consent, assent	X								
Review of eligibility	X								
Physical exam and Tanner staging	X								X
Baseline demographics	X								
Fasting labs: lipids, glucose, insulin, and hemoglobin A1c, and storage of blood for batched biomarker assessment[^@]		X					X		X
Safety labs: comprehensive metabolic panel, complete blood count and hemoglobin A1c[$]	X			X		X			X
Urine pregnancy test		X					X		X
BMI/anthropometrics/blood pressure/heart rate	X	X	X	X	X	X	X	X	X
iDXA (total/regional body fat, BMC)		X					X		X
PHQ-9	X	X					X		X
C-SSRS	X	X					X		X
Assessment of mood changes and thoughts of self-harm; GI symptom assessment		X	X	X	X	X	X	X	X
Neurobehavioral Assessment • BRIEF-SR • NIH Toolbox • CANTAB • BIS/BAS Scale • Kirby Monetary Choice Questionnaire • Food Choice Task		X			X		X	X	X
Eating Behavior, Mood, Quality of Life Questionnaires • PROMIS-Anxiety • IWQOL-Kids • EQ-5D-Y • Visual Analog Scale of Self-Reported Appetite and Sateity • QEWP-! • AEBQ • RED-5 Hedonic Eating • DEBQ • Children's Power of Food Scale • PAQ-A • EDE-Q		X			X		X	X	X
Acceptability questionnaire							X		X
Study drug titration and dispensing[#]		X	X	X	X	X	X	X	X
AE assessment		X	X	X	X	X	X	X	X
Behavioral Program (Intense Arm)			← 52 weekly sessions: 50% in person and 50% virtual →						
Behavioral Program (Medication Arm)			← 12 monthly sessions: 50% in-person and 50% virtual →						

& Allowable window is ± 30 days for the Randomization visit (from Screening), ± 3 days from the Randomization visit for the visits at Weeks 4-56 (with exception of week 56 visit, which is 15 days).

^ Batched biomarker collection for an exploratory assessment of brain inflammation via brain derived exomes

Study drug titration and dispensing will happen only for those participants who are randomized to receive semaglutide. Study drug titration will take place over 16 weeks starting at the Randomization visit; additional AE assessments will be done in this group during the titration period

$ Hemoglobin A1c to be done at Screening.

@ Hemoglobin A1c will not be completed as part of the fasting panel at Randomization

5.3 Study Procedures

Anthropometric Measurements and Quantification of Total Body- and Regional-Fat Depots

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. Total percent body fat, visceral fat, and lean mass will be determined by dual energy x-ray absorptiometry. The scanning table accommodates body sizes of up to 204 kg. Our group has performed much of the work regarding the validation of DXA visceral fat in children and adolescents demonstrating a high correlation with computed tomography and association with cardiometabolic risk factors.[41]

Pubertal Development, Blood Pressure, and Blood Analyses

Tanner stage will be determined by trained personnel. Blood pressure will be obtained on the same arm using the same cuff size and equipment according to standardized procedures[42] and the internal standard operating procedure. Fasting (≥12 hours) blood will be collected for the measurement of lipids, glucose, insulin, and hemoglobin A1c (Fairview Diagnostics Laboratories, Minneapolis, MN). Additional blood for exploratory biomarkers to measure brain inflammation via brain derived exomes will be conducted by the Masonic Institute for the Developing Brain (MIDB).

Eating Behavior, Mood, Quality of Life and Acceptability Assessment

Following an overnight fast of 12 hours, we will obtain ratings on 15-cm visual analog scales anchored with “not at all” to “extremely” for appetite. This method has been validated[43] and was utilized in a study of adolescents with severe obesity.[44] Self-reported appetite and satiety will also be measured using the Adult Eating Behavior Questionnaire (AEBQ); note: in our experience, the self-report version (AEBQ) is more appropriate for adolescents vs. the child version (CEBQ). Additional eating behaviors will be address in supplemental questionnaires: Dutch Eating Behavior Questionnaire (DEBQ, restrained, emotional, external eating) and Reward Based Eating Drive Scale X5 (Red-5, hedonic eating). Binge eating behaviors/features will be measured with the Questionnaire of Eating and Weight Patterns – Adolescent (QEWP-A); Loss of Control – Eating Disorder Questionnaire and the Eating Disorder Examination Questionnaire – 6.2.[45] Additional domains are

addressed in the AEBQ including emotional overeating and enjoyment of food and will be captured in supplemental questionnaires: Dutch Eating Behavior Questionnaire, Questionnaire of Eating and Weight Patterns – Adolescent, and Children's Power of Food Scale. Physical activity will also be assessed via the Physical Activity Questionnaire for Adolescents (PAQ-A).

Quality of life will be assessed via the IWQOL-kids (weight-related quality of life), the EQ-5D-Y (quality of life). Anxiety, depression and suicidal ideation will be measured with the PROMIS-Anxiety, PHQ-9 and C-SSRS. Additional assessments include the Behavior Rating Inventory on Executive Function-Self Report (BRIEF-SR) and the NIH Toolbox (cognition battery. Acceptability will be assessed in both groups using Likert scales addressing degree of satisfaction with the treatment intervention (behavioral sessions, and additionally the medication regimen for those assigned to this group), perception of the program, and evaluation of the scope of topics and usefulness of the behavioral counseling sessions.

Neurobehavioral Assessment

Neurobehavioral functioning will be assessed using gold standard objective and self-report measures of inhibition, cognitive flexibility, working memory and reward responsivity. We selected specific measures based on their 1) validation in the adolescent population,[46-52] 2) test-retest reliability, and 3) ability to be administered in a clinical setting (to maximize the potential for translation and clinical implementation). Study staff will administer and/or monitor completion of all assessments, per each assessment's administration guidelines. In total, completing the measures will take participants an estimated 2-2 ½ hours. Importantly, many of these assessments can be completed during "down time" of the overall study visits. Inhibition, cognitive flexibility, working memory and reward responsivity will be assessed with the NIH Toolbox.[46] Cambridge Neuropsychological Test Automated Battery (CANTAB) Stop Signal Task and Gambling Task[49], Behavioral Inhibition Activation System (BIS/BAS) scale[53], Behavior Rating Inventory of Executive Functions-Self Report (BRIEF-SR)[51], Kirby Monetary Choice Questionnaire[52] and the Food choice Task[54]. These items will be reviewed and analyzed as part of Dr. Gross's NIH-funded study.

Additional Health Outcomes, Projected Long-Term Impact, and Cost-Effectiveness

We plan to develop a decision analytic model (or simulation model) that will provide a platform to assess numerous health outcomes and to project the long-term impact of study findings. Outcomes will include: quality of life, participant preferences (acceptability), and participant and family adherence to the treatment plan, which should strongly correlate with the prior two measurements. Using data from the study as the primary source, we will develop a computer-based simulation model that depicts or "recreates" the trial. Projections of estimated benefits, costs, and cost-effectiveness in various settings as well as the potential population impact of the program implementation will be analyzed. The development and validation

of our model will provide a comprehensive platform to assess economic feasibility by varying levels of specific economic and resource constraints.

Safety-Related Assessments

A comprehensive metabolic panel and complete blood count will be performed at selected study visits. Urine pregnancy tests in females of childbearing potential (including females experiencing first menstruation during the study) will be conducted before participants undergo an iDXA scan (Randomization, Week 26, and Week 56). We will require all females who endorse sexual activity with males in the medication group to confirm use of at least two forms of effective contraception defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence. We will instruct all females who miss a menstrual period or when pregnancy is otherwise suspected to perform a pregnancy test. Semaglutide will be stopped in the event of pregnancy. In all participants we will monitor for potential changes in gastrointestinal side effects, the effects of concomitant oral medications (owing to the potential for decreased absorption resulting from possibly delayed gastric emptying), mood changes including depression and suicidal ideation, self harm and injury. We will educate participants assigned to the medication group (and their parents/guardians) on recognition and treatment of hypoglycemia. Assessments of signs/symptoms of hypoglycemia will be performed prior to each dose escalation. Sexual maturation (Tanner stage) and stature will be tracked throughout the study. Additional details of safety-related assessments and oversight can be found elsewhere in the protocol.

Depression and Suicide Monitoring

The PHQ-9 and C-SSRS will measure depression and suicidality and the results will be reviewed by a staff member while the participant is still present at the visit. Participants (and their parents), if the participant is a minor will be referred to a Mental Health Professional (MHP) or to their primary care provider if the subject has a PHQ-9 score of > 15, any suicidal behavior, or any suicidal ideation of type 4 or 5 on the C-SSRS. They will also be provided with the contact information for the nationwide Suicide and Crisis Lifeline (telephone 988 or 988lifeline.org). If the participant endorses current (in that moment), active suicidal ideation with plan and intent, they will also be referred to the emergency department. Participants (and their parent) will be asked if they feel safe enough to leave the research clinic and with the established plan.

A referral to a MHP or primary care provider should also be made if in the opinion of the Investigator it is necessary for the safety of the participant. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the participant, at the discretion of the MHP or primary care provider, can be continued in the trial on randomized therapy.

5.4 Study Duration:

Subjects will be enrolled in the study for 56 weeks (one year). We anticipate that it will take three to four years to meet the trial recruitment goal.

5.5 Use of radiation*:*
This study will consist of four DXA scans, which utilize ionizing radiation. None of the tests done for this study are considered part of standard medical care. The DXA scans each consist of exposure to 0.01 mSv. The average amount of radiation that the average person would receive from the DXA used in this study is less than 1% (3 mrem) of that received from natural sources of radiation by a Minnesota resident in one year (300 mrem).

5.6 Use of Center for Magnetic Resonance Research*:* Not applicable.

6.0 Data and Specimen Banking

Blood samples for lipids (total-, HDL-, and LDL-cholesterol and triglycerides), glucose, insulin, and hemoglobin A1c will be sent to the Fairview Diagnostics Laboratory (which is CLIA licensed) after collection of the sample. Additional blood samples for other non-genetic biomarkers will be sent for an exploratory analysis of brain inflammation to look at brain-derived exomes in plasma by the Masonic Institute of the Developing Brain (MIDB).

7.0 Sharing of Results with Participants

7.1 Participants will receive test results only if deemed clinically-significant or if the participant and/or parent/guardian specifically request this information.

7.2 Sharing of genetic testing:

Disclosure of results: Biomarker analyses that are conducted will not be returned to participants.

8.0 Study Population

8.1 Inclusion Criteria:

- Obesity (BMI ≥ 95th percentile or BMI ≥30 kg/m^2)
- Age 12 to <18 years old

8.2 Exclusion Criteria:

• Tanner stage 1

- Diabetes (type 1 or 2)

• Current or recent (< six months prior to enrollment) use of anti-obesity medication(s) defined as orlistat, phentermine, topiramate, combination phentermine/topiramate, liraglutide (or other GLP-1RA), and/or combination naltrexone/bupropion (monotherapy use of naltrexone or bupropion is not an exclusion)

• Previous bariatric surgery

• Any history of treatment with growth hormone

• Medically-documented history of bulimia nervosa

• Any history of schizophrenia, psychosis, mania, chemical dependency

• Unstable depression requiring hospitalization within the previous 6 months

• Any history of suicide attempt

• History of suicidal ideation or self-harm within the previous 30 days as determined at screening by:

- PHQ-9 score ≥15
- Suicidal ideation of type 4 or 5 on the C-SSRS

• Current pregnancy or plans to become pregnant

• ALT or AST ≥5 times the upper limit of normal

• Creatinine >1.2 mg/dL

• Uncontrolled hypertension as determined by the local medical monitor

• Clinically significant heart disease as determined by the local medical monitor

• Diagnosed and medically-documented monogenic obesity

• Medically-documented history of cholelithiasis

• Untreated thyroid disorder

• Medically-documented history of pancreatitis

• Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2

• Personal history of malignant neoplasms within the past five years

• Hypersensitivity to any component of semaglutide

9.0 Screening

At this visit the subject's parent/legal guardian and the participant will be taken through the consent process and sign the parental consent form and the assent forms after they have had the opportunity to learn about the study and ask any questions that they may have. The participant will undergo the following:

- Review of study eligibility by reviewing medical and medication history
- Physical examination and Tanner staging
- Blood collection (approximately 1 teaspoon) for a comprehensive metabolic panel, complete blood count and hemoglobin A1c
- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Blood pressure will be measured
- Heart rate will be measured
- A PHQ-9 and C-SSRS will be completed by the participant

Randomization Visit:

- Blood collection (approximately 1 tablespoon) will be drawn for fasting labs, and storage for biomarkers
- Urine will be collected for a urine pregnancy test for females of childbearing potential
- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Blood pressure will be measured
- Heart rate will be measured
- A PHQ-9 and C-SSRS will be completed by the participant
- Assessment of mood changes and thoughts of self-harm
- A GI symptom assessment will be undertaken
- Participants will be asked to fill out eating behavior, mood, and QOL questionnaires
- Participant will complete neurobehavioral assessments
- Participants will have a DXA to measure their body fat
- Participants will be randomized, and study drug will be dispensed to participants who are randomized to the medication arm and instructed about the dose titration schedule. Titrations will take place over 16 weeks, with the full dose of study medication to be started at Week 17. Education will be offered on recognition and treatment of hypoglycemia.
- Participants will start their behavioral program, which differs by treatment arm

Week 4:

- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Blood pressure will be measured
- Heart rate will be measured

- Assessment of mood changes and thoughts of self-harm
- A GI symptom assessment will be undertaken
- Assessment of effects of concomitant oral medications
- Adverse events will be reviewed
- Compliance assessment will be performed for medication group; assessment for signs/symptoms of hypoglycemia; and the medication dose will be titrated to the next level
- Participants will continue their behavioral program per their randomization schedule

Week 8:

- Blood collection (approximately 1 teaspoon) for a comprehensive metabolic panel, complete blood count
- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Blood pressure will be measured
- Heart rate will be measured
- Assessment of mood changes and thoughts of self-harm
- A GI symptom assessment will be undertaken
- Assessment of effects of concomitant oral medications
- Adverse events will be reviewed.
- Compliance assessment will be performed for medication group; assessment for signs/symptoms of hypoglycemia; and the medication dose will be titrated to the next level
- Participants will continue their behavioral program per their randomization schedule

Week 12:

- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Blood pressure will be measured
- Heart rate will be measured
- Assessment of mood changes and thoughts of self-harm
- A GI symptom assessment will be undertaken
- Assessment of effects of concomitant oral medications
- Adverse events will be reviewed
- Compliance assessment will be performed for medication group; assessment for signs/symptoms of hypoglycemia; and the medication dose will be titrated to the next level
- Participants will be asked to fill out eating behavior, mood, and QOL questionnaires.
- Participant will complete neurobehavioral assessments.

- Participants will continue their behavioral program per their randomization schedule

Week 16:

- Blood collection (approximately 1 teaspoon) for a comprehensive metabolic panel, complete blood count
- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Adverse events will be reviewed
- Assessment of mood changes and thoughts of self-harm
- A GI symptom assessment will be undertaken
- Assessment of effects of concomitant oral medications
- Compliance assessment will be performed for medication group; assessment for signs/symptoms of hypoglycemia; and the medication dose will be titrated to the maximum dose of 2.4 mg/.075 mL
- Participants will continue their behavioral program per their randomization schedule

Week 26:

- Blood collection (approximately 1 1/3 tablespoon) will be drawn for fasting labs, and storage for biomarkers
- Urine will be collected for a urine pregnancy test for females of childbearing potential
- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Blood pressure will be measured
- Heart rate will be measured
- A PHQ-9 and C-SSRS will be completed by the participant
- Assessment of mood changes and thoughts of self-harm
- Participants will be asked to fill out eating behavior, mood and QOL questionnaires.
- Participant will complete neurobehavioral assessments
- Participants will be asked to fill out acceptability questionnaire
- A GI symptom assessment will be undertaken
- Assessment of effects of concomitant oral medications
- Participants will be asked to fill out questionnaires
- Participants will undergo a DXA to measure body fat
- Participants who are randomized to the medication arm will return their medication and have new study drug dispensed
- Adverse events will be reviewed
- Compliance assessment will be performed for medication group

- Participants will continue their behavioral program per their randomization schedule

Week 39:

- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Blood pressure will be measured
- Heart rate will be measured
- Participants who are randomized to the medication arm will return their medication and have new study drug dispensed
- Adverse events will be reviewed
- Assessment of mood changes and thoughts of self-harm
- Participants will be asked to fill out eating behavior, mood, and QOL questionnaires.
- Participant will complete neurobehavioral assessments
- A GI symptom assessment will be undertaken
- Assessment of effects of concomitant oral medications
- Compliance assessment will be performed for medication group
- Participants will continue their behavioral program per their randomization schedule

Week 56:

- Participants will undergo a physical examination and Tanner staging (not necessary to be repeated if Tanner stage 5 at randomization)
- Blood collection (approximately 1 1/3 tablespoon) will be drawn for a comprehensive metabolic panel, complete blood count, fasting labs, and storage for biomarkers
- Urine will be collected for a urine pregnancy test for females of childbearing potential
- Height, weight, waist and hip measurements will be taken and a BMI will be calculated
- Blood pressure will be measured
- Heart rate will be measured
- A PHQ-9 and C-SSRS will be completed by the participant
- Assessment of mood changes and thoughts of self-harm
- A GI symptom assessment will be undertaken
- Assessment of effects of concomitant oral medications
- Participant will be asked to fill out eating behavior, mood, and QOL questionnaires
- Participant will be asked to complete neurobehavioral assessments
- Participants will be asked to fill out acceptability questionnaire
- Participants will undergo a DXA to measure body fat

- Participants who are randomized to the medication arm will return their medication
- Adverse events will be reviewed
- Compliance assessment will be performed for medication group

10.0 Vulnerable Populations

Participants who are enrolled in this study will be under the age of 18 and will be asked to sign an assent form. At least one parent/guardian will be asked to sign a parental consent form. Parental consent will be obtained before the assent is obtained. Children who turn 18 during the course of the study will be asked to sign a consent form and a HIPAA form once they reach the age of majority.

10.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
Children	Targeted Population
Pregnant women/fetuses/neonates	Excluded from Participation
Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded from Participation
Non-English speakers	Included/Allowed to Participate
Those unable to read (illiterate)	Excluded from Participation
Employees of the researcher	Excluded from Participation
Students of the researcher	Excluded from Participation

Undervalued or disenfranchised social group	Included/Allowed to Participate
Active members of the military (service members), DoD personnel (including civilian employees)	Excluded from Participation
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded from Participation
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included/Allowed to Participate
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Included/Allowed to Participate
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Included/Allowed to Participate
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded from Participation

10.2 Additional Safeguards: Not applicable.

11.0 Local Number of Participants

11.1 Local Number of Participants to be Consented: 250

12.0 **Local Recruitment Methods:** Within the various health systems in our consortium (MN-POC), over 10,000 adolescents with obesity are accessible for recruitment to our clinical trial. Our Center has a track record of successfully enrolling and retaining participants in pediatric obesity clinical trials.[55-57]

12.1 Recruitment Process: Our recruitment process will be two-fold: we will leverage the MN-POC for recruitment. Member institutions include the University of Minnesota, Mayo Clinic, Children's Hospitals and Clinics of Minnesota, and Park Nicollet/HealthPartners, which represent a large portion of the pediatric medical care in Minnesota. We plan on reaching out to physicians in these member institutions and letting them know about the study so that they could refer patients who come into their clinics. We may also work with these and other local health systems to have them send recruitment letters on our behalf to potentially eligible participants. The second method will be to work with our partner, Fairview Research Recruitment Services, to send out recruitment letters and/or emails to individuals who are listed in the electronic medical record system, EPIC, that have not opted out of being contacted about potential research projects. Interested participants will be asked to contact the study team and up to three follow-up phone calls will be made by study staff if the participant leaves a message.

12.2 Identification of Potential Participants:
Both the referrals from MN-POC and the recruitment mailings will request that the interested parties contact the research staff for additional information. If the interested party and the research staff do not connect on the first try, the research staff will attempt to contact the interested parties with up to three follow-up phone calls and/or three emails.

12.3 Recruitment Materials:
A recruitment letter and recruitment flyers will be created for this study and approved by the IRB before use. In addition we will post on social media with a photo and a QR code that will take an individual to a landing page where they can enter information in order to be contacted by the study team to get information about studies that are currently available. We are also working with the medical school to undertake a Google ad campaign.

12.4. Payment:
Participation in this study is time intensive for the subject and their family members. Payment will be made by the Greenphire ClinCard on the following schedule:

- Screening visit: $50
- Randomization visit: $150
- Week 12 visit: $50
- Week 26 visit: $250
- Week 39 visit: $50
- Week 56 visit: $250

Parents/guardians attending the randomization, 26-week, and 56-week visits will be offered a meal voucher or Greenphire ClinCard for a meal ($10 value) since these visits are long in duration. In addition to the reimbursement structure

detailed above, a supplemental completion bonus of $100 can be earned for the week 56 visit. Therefore, participants will be eligible to receive total reimbursement/compensation of $350 for the week 56 study visit. No reimbursement will be offered for the in-person or virtual counseling sessions.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances:

Subjects will be allowed to withdraw from the study at any time. Subjects may be withdrawn from the study at any time based upon investigator judgement.

In the event that a participant has a serious adverse event that is deemed related to the study medication and/or procedures by either the external or internal medical monitor, the participant will be required to immediately discontinue the intervention.

Participants who express interest in stopping study medication but who feel they may still benefit from the lifestyle therapy will be allowed to remain in the study but off of study medication. These participants will be analyzed as part of the intent-to-treat population but will not be included in the per-protocol analysis. Participants who stop study medication but remain in the study to complete lifestyle therapy but express an interest in re-starting study medication will be allowed to do so as many times as they wish if the PI and medical safety officer believe it to be safe for the participant to do so.

13.2 Withdrawal Procedures:

Any subject who is removed from the study by the principal investigator or who requests to be withdrawn from the study will be asked to return for one final visit to assess adverse events and to collect any unused study medication and do a final study medication compliance.

13.3 Termination Procedures:

It will be noted in the subject enrollment log that the subject has been discontinued from the study and the date of the last study related visit. No additional data will be collected after that time. Data that has already been collected can be used in the study analysis.

14.0 Risks to Participants

14.1 Foreseeable Risks:

Risks of blood sampling: There is a minimal risk of bruising, fainting, and infection associated with blood draws.

Risks of exposure to ionizing radiation: The DXA scans involve exposure to a very low dose of ionizing radiation. The average amount of radiation that the average person would receive from the DXA used in this study is less than 1% (3 mrem) of that received from natural sources of radiation by a Minnesota resident in one year (300 mrem).

Expected Adverse Events -Semaglutide: The US FDA-approved Prescribing Information (PI) will be used to assess expectedness.[63] The most common adverse reactions, reported in greater or equal to 5% are nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, upset stomach, dizziness, feeling bloated, burping, decrease in blood sugar (in people with type 2 diabetes), flatulence, gastroenteritis, gastroesophageal reflux, and gastritis. Semaglutide like other GLP-1 receptor agonists causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown if semaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans. Therefore, the use of semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type (MEN2). Semaglutide may also cause acute kidney injury, hypersensitivity, diabetic retinopathy complications in patients with type 2 diabetes, increased heart rate, and suicidal behavior and ideation. Injection site reactions may occur.

Risks of questionnaires and neurobehavioral assessments: Potential risks related to these tests include emotional distress related to thinking about sensitive topics and possible "test fatigue." Participants always have the option not to respond to questions.

14.2 Reproduction Risks: All female subjects who are sexually active with males must agree to use two forms of birth control during their time in the study. Females of childbearing potential will have urine pregnancy tests at each visit requiring a DXA scan. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable, but least effective, methods of birth control include male condoms (with or without spermicide) and female condoms. Any two of the methods listed above is acceptable.

14.3 *Risks to Others*: Not applicable.

14.4 *Definition of Adverse Events (AE):* An adverse event is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product. An adverse event can be any unfavorable and unintended sign, including

an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

14.5 *Definition of a Serious Adverse Event (SAE):* A serious adverse event is an AE that fulfills at least one of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgement, they may jeopardize the patient or subject or require medical or surgical intervention to prevent one of the outcomes listed in the definition.
- Suspicion of transmission of infectious agents must always be considered an SAE.

14.6 *Definition of an Adverse Reaction*: An Adverse Reaction is an adverse event for which the causal relationship between the product and that Adverse Event is suspected.

14.7 *Definition of a Serious Adverse Reaction*: An Adverse event which fulfills both the criteria for a Serious Adverse Event and the criteria for an Adverse Reaction.

14.8 *Definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR)*: An SAE which is unexpected and regarded as possibly or probably related to the trial/study product by the investigator.

14.9 *Classification of an Adverse Event:*

Severity of Event. The severity of all AEs will be assessed by the study clinician using the following grading system:

- Grade 1: Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life
- Grade 4: Life-threatening: urgent intervention indicated
- Grade 5: Death related to adverse event

Relationship to Study Intervention: All AEs must have their relationship to 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. In a clinical trial, the study product must always be suspect.

- Unrelated: clearly not related to the investigational agent(s)
- Unlikely: doubtfully related to the investigational agent(s)
- Possible: may be related to the investigational agent(s)
- Probable: likely related to the investigational agent(s)
- Definite: clearly related to the investigational agent(s)

Expectedness: The local medical monitor will be responsible for determining whether an 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 based on the PI.[63] When an AE involves mental health issues, both the medical monitor and Dr. Amy Gross (who is overseeing the NIH-funded neurobehavioral portion of this project) will discuss the relationship and expectedness and will ensure that events are reported.

14.10 Time Period and Frequency for Event Assessment and Follow-Up: All AEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

The PI will notify the IRB, the external medical monitor, NovoNordisk, the NIH, and the FDA of any SAE that meet the definition of SAR or SUSAR. Notifications will be provided within five days of knowledge of the event. All pregnancies will be reported to NovoNordisk and will include the study name, unique subject number, subject initials, subject sex, subject age, trial drug, reported causality and outcome.

The DSMB will be provided with AE and SAE information prior to their review of the study, at least every six months.

15.0 Potential Benefits to Participants

We believe the potential benefits to the participants outweigh the risks in this study. We expect that most, if not all, participants will experience some degree of weight loss. Participants randomized to receive medication may benefit further. The side effect profile of semaglutide has been demonstrated to be acceptable in adults and the proposed tests are not more than minimal risk.

16.0 Statistical Considerations

16.1 Data Analysis Plan:

There are 3 analysis populations planned. Intention-to-treat (ITT) will include any participant randomized according to their treatment assignment. Per-protocol (PP) will include those without major protocol violations as determined by the principal investigator and documented on protocol deviation case report forms. The safety population will include all who receive treatment, according to treatment received.

16.2 Power Analysis:

Mean percent change in BMI from baseline to 56 weeks will serve as the primary endpoint for which the sample size determination has been based. We will also perform categorical analyses comparing the proportions in each group achieving ≥5%, ≥10%, 15%, and 20% BMI reduction to address treatment response heterogeneity. Using data reported from clinical trials referenced in the evidence review commissioned by the USPSTF to inform the pediatric obesity screening recommendations and taking into consideration the refractory nature of adolescent obesity, we have liberally projected up to 5% BMI reduction on average in the group assigned to the intensive behavioral intervention. Based on data from one of the large phase III clinical trials of semaglutide in adults presented earlier, we have conservatively projected approximately 10% BMI reduction on average in the group randomized to low-intensity behavioral intervention plus semaglutide. This estimate includes the placebo-subtracted efficacy of semaglutide plus the effect of the behavioral intervention. Therefore, we conservatively anticipate a difference of at least 5% between the groups in the change in BMI from baseline to 56 weeks.

We estimate having a dropout rate of no more than 20% (our previous clinical trial experience with this population has been 10-15%). Using BMI variability estimates from our previous trials in this population over 12 months 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 the table below the power associated with a very conservative, yet clinically-meaningful control-subtracted treatment effect: BMI reduction of 5% based on an overall sample size of 120 (60 in each treatment arm) and a range of degrees of attrition (including rows reflecting scenarios of higher than expected levels).

Revised sample size of 120 (60 in each of two arms)

Power; rho=0.6	
Reduction from baseline	**5%**
Two-sided Unadjusted	**97.1%**
Two-sided with 10% attrition	**95.6%**
Two-sided with 15% attrition	**94.5%**
Two-sided with 20% attrition	**93.2%**

Regarding attrition, our group has demonstrated a strong track-record of retention success in our clinical trials of adolescent participants with severe obesity. In an ongoing NIDDK-funded (R01) pharmacotherapy clinical trial among adolescents with severe obesity, our retention rate following randomization is 88% (53 out of 60 have either completed the full 12-months of study participation or remain active in the trial with most having completed their 6-month visit). Therefore, based on our track-record in this specific patient population, we anticipate having a dropout (lost to follow up) rate no higher than 20% for the primary endpoint at 56 weeks following randomization.

Tertiary Endpoint(s): Neurobehavioral Predictors of Response

Because the tertiary aims started after commencement of the overall study, we conservatively selected a sample size of N=116 for power calculations. For tertiary aim 1, our power analysis used a regression model with the latent factors as primary predictors and 2 potential confounders. Under these assumptions, we will have 80% power to detect an effect size of at least $\boldsymbol{\eta}^2$=0.081 if we used the latent factors for two domains (e.g., only inhibition and reward responsivity), or an effect size of at least $\boldsymbol{\eta}^2$=0.100 if we used the latent factors for all four domains (see Future 1). Prior research showed similar or larger effect sizes ($\boldsymbol{\eta}^2=0.091$ to $\boldsymbol{\eta}^2=0.194$) in the association between BMI reduction and neurobehavioral measures[58]. For tertiary aim 2, we anticipate, based on data from the literature[59,60] that approximately half of the study participants in each treatment arm will achieve a BMI reduction of at least 5% at 6 months. We calculated the minimum detectable odds ratio for a latent factor for only one domain, assuming that a participant who is ”average” in this domain (i.e., when the latent factor is mean-centered across study participants) has an equal chance of maintaining or not maintaining BMI reduction. Under these assumptions, we will have 80% power to detect an odds ratio of at least OR=2.11. Decreasing the probability of someone with “average” neurobehavioral functioning to maintain a BMI reduction to 0.25 increases the minimum detectable odds ratio to OR=2.36. Strong associations (OR=4.191) between reward-related decision making and BMI reduction maintenance have been previously reported.[61] For tertiary aim 3, we expand the models in the power analysis from tertiary aim 1 to include a treatment group indicator and an interaction term between the treatment group and the latent factor. Under this expanded model, we will have 80% power to detect an effect size for the joint

effect of the latent factor, group indicator, and interaction term of at least η^2=0.108 if we used the latent factors for two domains, or an effect size of at least η^2=0.132 if we used the latent factors for all four domains. These minimum detectable effect sizes are larger relative to tertiary aim 1 due to the use of more predictors in the model, but they are still modest in practice and are similar or smaller in magnitude compared to previously reported effect sizes.[58]

16.3 Statistical Analysis:

Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations, median and range 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. All safety outcomes will be evaluated and monitored throughout the trial.

Primary Endpoint

Compare the effectiveness of intensive behavioral counseling vs. medical management plus low-intensity behavioral counseling on mean percent change in BMI from baseline to 56 weeks of follow-up in adolescents with obesity. We hypothesize that semaglutide 2.4 mg weekly plus low-intensity behavioral counseling will elicit superior reductions in BMI (primary efficacy endpoint) compared to intensive behavioral counseling at 56 weeks (primary outcome assessment timepoint).

The primary analysis will be conducted using the ITT population to compare the mean BMI percent change from randomization to 56 weeks of follow-up between the treatment groups, adjusted for BMI at randomization 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 PP population will also be conducted along with consideration of adjustment for residual imbalances between treatment groups after randomization (e.g., in sex). Graphical evaluation will also accompany numerical results, including waterfall plots for visual representation of heterogeneity in BMI percent change.

Secondary Endpoints

We will also evaluate other relevant BMI endpoints including change in absolute BMI, BMI percent of the 95th percentile, and BMI percent of the median. In addition, we will address the important issue of clinical relevance by describing the proportion of participants with ≥5%, ≥10%, ≥15%, and ≥20% BMI reduction (from randomization) at 56 weeks with 95% CIs based on inverting the score test. These values will also be compared using the difference in proportions between treatment groups accompanied by 95% CIs and P-values based on the Chi-squared test. We have also identified subgroups for evaluation of heterogeneity of treatment effect. These include sex as a biological variable, age as proxy for

cognitive development (12-14 years; 15-17 years), race (Caucasian vs. minority), and baseline BMI (<40; 40 and higher). Each of these will be evaluated by incorporating the corresponding indicator and interaction with treatment assignment in a linear regression model and presented as point estimates within each subgroup. Robust variance estimation will be used for CIs and P-values. In an exploratory fashion, we will also evaluate outcomes by socioeconomic status as measured by maternal education, family income, public vs. private insurance status, and zip code (geocoding). These will be evaluated with an interaction term in a regression framework and presented as point estimates within each subgroup along with CIs and P-values using robust variance estimation.

Compare the effectiveness of intensive behavioral counseling vs. medical management plus low-intensity behavioral counseling on body fat, cardiometabolic risk factors, and quality of life in adolescents with obesity. We hypothesize that semaglutide 2.4 mg weekly plus low-intensity behavioral counseling will elicit superior reductions in body fat and greater improvements in cardiometabolic risk factors and quality of life compared to intensive behavioral counseling at 56 weeks (primary outcome assessment timepoint).

We will evaluate differences in total body- and visceral-fat (absolute mass and percent), cardiometabolic risk factors (blood pressure, lipids, glucose), CRP, oxLDL, and IWQOL over the full length of follow-up for each time point they are measured. The evaluation will be in a similar fashion as the primary outcome wherein analyses will be adjusted for values at randomization. Longitudinal analyses will also be conducted, incorporating the multiple time points out to 56 weeks during which these measurements will be obtained. These analyses will allow us to compare the durability of comprehensive, intensive behavioral counseling vs. medical management plus low-intensity behavioral counseling on mean BMI percent change from baseline and mean change from baseline of body fat, cardiometabolic risk factors, and quality of life. Supportive analyses using the PP population for each secondary endpoint will also be conducted.

Compare the number of adverse events and safety outcomes for intensive behavioral counseling vs. medical management plus low-intensity behavioral counseling in adolescents with obesity. We hypothesize that the number of gastrointestinal-related adverse events will be higher in those randomized to semaglutide but that changes in other safety outcomes will be approximately equal between groups (pubertal development, depression, and suicidal ideation).

The safety analysis will include all participants who receive treatment, according to treatment received. Analyses of adverse events will be primarily descriptive reporting the number and percentage of adverse events along with categorizations of seriousness, severity, frequency (within a participant), and perceived

relatedness to the intervention. Regarding the safety outcomes, it should be noted that many of the measures are continuous and do not have established cut-points indicating a specific safety signal. Therefore, we will evaluate the change from randomization to 56 weeks of follow-up for gastrointestinal-related adverse events, as well as pubertal development, depression, and suicidal ideation between groups, adjusted for each value at randomization. Confidence intervals (CIs) and P-values will be based on robust variance estimation.

Evaluate the implementation feasibility of the two strategies by assessing acceptability, adherence, rate of attrition, and cost-effectiveness. We hypothesize that semaglutide plus low-intensity behavioral counseling will have a higher rate of acceptability and adherence, lower rate of attrition, and will be more cost-effective as compared to intensive behavioral counseling.

Metrics of acceptability, adherence, and rate of attrition will each be evaluated in a similar fashion as other secondary endpoints wherein CIs and P-values will use robust variance estimation. Simulation model and cost-effectiveness - the trial will serve as the primary source of data for model inputs to inform the construction of the initial version of the model as it will mirror or recreate the two study cohorts within the two strategy arms in the trial. The trial results, particularly the BMI changes over time, will provide calibration targets, which will be used to validate the model. The results of Aims 1 and 2 will provide additional patient information that will inform differences in project intervention impact by specific setting. Additional model parameters or inputs necessary to develop a population-level model will be derived by and estimated from the literature, such that the model's generalizability can be expanded to include new clinical and geographical settings. In addition, baseline prevalence rates and characteristics of youth with obesity in different regions of the country will be obtained from the CDC's National Health and Nutrition Examination Survey (NHANES), a nationally representative sample. When more granular clinical data regarding patient-level information are not available within NHANES, literature searches will provide additional information and plausible ranges or estimates for the model. Cost estimates for the model will be derived using individual patient data from the trial, applying microcosting techniques, and utilizing published literature estimates including the use of adult Medicare reimbursement schedules when pediatric estimates are not available. Costs will be adjusted for inflation using the consumer price index for the year of the analysis. Quality of life (QoL) utility scores for obesity related states will be derived from published estimates in the literature, using adult values when necessary. Expert opinion will be reserved for circumstances when no published estimates are available.

Tertiary Endpoint(s): Neurobehavioral Predictors of Response

Data will be collected that map to each of following domains: inhibition, cognitive flexibility, working memory and reward responsivity. For each domain, we will use factor analysis to create a single latent factor that summarizes the information within that domain, thereby creating a score for that domain for each participant. The latent factors will be created at each of the baseline and the 6-months visits to characterize neurobehavioral functioning at those time points. Furthermore, a factor analysis on change scores will create latent factors that characterize the changes in neurobehavioral functioning. These latent factors will be used as predictors in the models described below. Using these latent factors as predictors leads to a substantial reduction in dimensionality and multiplicity. The latent factor summarizing each domain borrows strength across all measures within that domain. Altogether, we expect that using these latent factors will improve statistical power in identifying predictors of BMI reduction and maintenance.[62]
For tertiary aim 1, identifying baseline neurobehavioral predictors of weight loss response in adolescents with obesity undergoing intervention, linear models will be used to quantify the association between percent BMI reduction at 6 months (the primary outcome) and the latent factors associated with baseline neurobehavioral functioning (the primary predictors).

For tertiary aim 2 (i.e., for initial responders, identify neurobehavioral predictors of weight loss maintenance at 12 months), analyses will be restricted to the participants who experience $\geq$ 5% BMI reduction at 6 months (the responders). BMI reduction at 12 months will be quantified for each responder to determine whether they maintained their BMI reduction. Logistic regression will be used with BMI reduction maintenance (durability of the initial $\geq$5% BMI reduction) at the 12 months visit as the primary outcome. We will consider each of the latent factors at baseline and the latent factors on the change scores as primary predictors; the former quantifies the relationship between the neurobehavioral functioning with future BMI reduction maintenance, and the latter quantifies the relationship between the *change* in neurobehavioral functioning with future BMI reduction maintenance. Second, we will model BMI reduction maintenance at 12 months using generalized linear mixed models (GLMMs). Using the data across all visits quantifies how neurobehavioral functioning and change in neurobehavioral functioning contribute to within- and between-person variability in BMI reduction maintenance.

For tertiary aim 3, evaluating differences in predictors of response between intensive LMT and GLP-1RA therapy, we expand on the models in Aim 1 by including two terms to each model: i) a group indicator for the treatment arm, which will quantify the differences in the primary outcome between treatment arms, and ii) an interaction term between the group indicator and the primary predictor, which will quantify the differences between treatment arms in the

association between the primary predictor with the primary outcome. For exploratory analyses to evaluate the differences between predictors of long-term maintenance to intensive LMT and GLP-1RA therapy, we will follow a similar strategy by expanding the models in Aim 2.

The longitudinal design of the study allows us to conduct supplementary analyses to thoroughly explore and identify neurobehavioral predictors of long-term BMI reduction response. In particular, we will use the longitudinal trajectory of BMI at 3, 6, 9, and 12 months as the primary outcome in a linear mixed model (LMM). We will use as predictors the latent factors at baseline and the latent factors on the change scores, and we will also adjust for time and for BMI at baseline. In tertiary aim 2 we focused our analyses only on responders, but here we will look at **all** adolescents so that we can obtain a more complete picture on how BMI, the neurobehavioral predictors, and the relationship between the two change over time. Furthermore, if we add a group indicator for the treatment arm, its interaction with time, and its interaction with the neurobehavioral predictors, we can assess how the temporal trajectories of BMI differ across treatment. Altogether, these supplementary analyses will complement and expand the scope of the primary aims with an eye toward maximizing the overall impact.

The models for each tertiary described above used the latent factors, each of which serves as a summary of the measures in one of the domains of interest (inhibition, cognitive flexibility, working memory and reward responsivity). Consequently, the models lose specificity in which measure is predictive of BMI reduction or BMI reduction maintenance. To address this, exploratory analyses will refit each model described above, but instead of using the latent factor as a predictor we instead use the neurobehavioral measures. This allows us to explore the predictive capability of *each* measure. Due to the large number of statistical tests in these exploratory analyses, we will focus on the resulting model fit and predictive capability of each measure, which can guide our future research on the relationship between these measures and BMI reduction and maintenance.

The tertiary models described above will adjust for potential confounders, namely, age, sex as a biological variable, general intellectual functioning, race/ethnicity, and socioeconomic status. Residual analyses will be conducted to check for model fit and the model assumptions. Model selection criteria that balance model fit with complexity, [e.g., the Akaike Information Criterion (AIC)], will be used for model selection.

16.4 Data Integrity:

Validation of the simulation model described in specific aim #3 will be through the process of calibration. The primary calibration target will be the aggregate BMI for the cohort. The BMIs of the individual hypothetical patients in the simulation

model will be pooled to determine if model outputs or results match or reproduce trial results. If they do not, model inputs will be revised until there is adequate reproduction of trial BMI results.

Sensitivity Analyses - one-way sensitivity analyses will be conducted to investigate and explore the effects of changes in model parameters on outcomes across a wide range of values, including intervention effect sizes, adherence/participation rates. Additionally, probabilistic sensitivity analysis will be performed. Distributions for specific parameters will be assigned and more than 1,000,000 iterations performed to gain further insight into the optimal strategy under uncertain conditions within our defined willingness to pay (WTP) threshold. In circumstances where there are limited data to inform model projections, best efforts will be used to find and integrate available data in a systematic, transparent way.

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 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). In particular, for the primary analysis we will use multiple imputation techniques for participants on whom we do not have a final measurement. The imputation model will be stratified by treatment group and include baseline values at randomization, and change from baseline at all interim visits. Additional variables for inclusion in the model include age, race, sex, and tanner stage. Imputation will be used to estimate treatment group differences, 95% confidence intervals, and *P* values; observed data will be used to estimate within treatment group changes. If the analyses with and without multiple imputed values differ substantially, then exploratory analyses will be performed to evaluated factors that may have contributed to the differences. Secondary endpoints will be handled similarly.

17.0 Health Information and Privacy Compliance

17.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

17.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☒ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☒ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other.

17.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

We will work with Fairview Research Administration to pull a pool of individuals who have agreed, in their electronic medical record, to learn about potential research studies. The data will be placed in the data shelter so that recruitment letters and/or emails can be generated and sent to potential participants. Individuals who have indicated that they do not want to be contacted about research will not be approached.

17.4 Approximate number of records required for review: >10,000

17.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

17.6 Explain how the research team has legitimate access to patients/potential participants:

This has been explained in other sections of the protocol.

17.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☒ In the data shelter of the Information Exchange (IE)

☒ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☐ In REDCap (recap.ahc.umn.edu)

☒ Store ☐ Analyze ☐ Share (with DSMB)

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In OnCore (oncore.umn.edu)

☒ Store ☒ Analyze ☐ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☒ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☒ Store ☐ Analyze ☐ Share

☐ Other. Describe:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as an tablet or smartphone not previously listed

17.8 Consultants. Vendors. Third Parties. None.

17.9 Links to identifiable data:
Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Blood samples that are 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.

17.10 Sharing of Data with Research Team Members.
Study team members will have access to Box, and OnCore.

17.11 Storage and Disposal of Paper Documents:
All data will be stored in locked offices and will not be released without consent of participants. As this study has multiple entities with oversight, records will not be destroyed until the latter of the following:

- NIH: 3 years after the study ends;
- FDA: 2 years after withdrawal of the IND for this application;
- HIPAA: 6 years after the date it went into effect.

18.0 Confidentiality

Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released without consent of participant. Data that is collected will be entered into OnCore which is only accessible by the study team. Blood samples that are sent to laboratories will be identified only by study identification number and never by name. Data to be used in scientific presentations or publications will not contain participant identifiers.

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

19.1 Data Integrity Monitoring.
The study will undergo regular monitoring (at least annually) 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 regulatory monitoring of all research-related activities and is offered free of charge through the University of Minnesota Clinical and Translational Science Institute (CTSI). Monitoring of fidelity to the protocol (e.g. protocol deviations) will be performed at each monitoring visit. Monitoring staff will present a summary report to the PI after each monitoring session. If necessary, corrective action plans will be devised and implemented by the PI to address deficiencies.

19.2 Data and Safety Monitoring.

An internal medical monitor will review all adverse events and serious adverse events regularly throughout the trial. In addition, an independent (not involved in the trial) external medical monitor will review all serious adverse events regularly throughout the trial. A data and safety monitoring board (DSMB) will be established, which will include at least one adult obesity medicine specialist or endocrinologist, one pediatric obesity medicine specialist or endocrinologist, and one biostatistician. DSMB members will not be affiliated with the study. The DSMB will meet regularly (frequency to be determined by DSMB members but no less than every six months) 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 PI, co-investigators, and external medical monitor advising on the continuation of the study and any suggestions for trial improvement. This report will also be sent to the assigned NIH Program Director and the IRB. An important charge of the DSMB will be to closely monitor progress and timelines related to recruitment goals, fidelity to the protocol (e.g. regularly review the number and types of protocol deviations), as well as monitor the quality and integrity of the data. The DSMB will communicate any concerns relevant to these issues of trial conduct to the PI and note specific recommendations for improvement in the meeting report.

In the event that a participant has a serious adverse event that is deemed related to the study medication and/or procedures by either the internal or external medical monitor, the participant will be required to immediately discontinue the intervention. The overall study may be stopped at any time at the request of the PI, internal or external medical monitor and/or the DSMB. The main adverse effects that we expect to observe with semaglutide are GI-related. Participants may be removed from the study if suicidal ideation is present at any time during the trial or if any clinically significant changes (at the discretion of the internal or external medical monitor) in mood and/or depression are observed. If the ratio of participants assigned to medication vs. behavioral counseling alone developing a serious adverse event (for the medication group, deemed related to study

medication) requiring withdrawal exceeds 4:1 (after ≥50% enrollment and a minimum of 5 total events, regardless of group assignment), the trial will be stopped. Patients will be instructed that they may withdraw from the study at any time and for any reason.

19.3 Suicidal Behavior and Suicidal Ideation

Participants (and their parents, if the participant is a minor) will be referred to a mental health professional (MHP) or to their primary care provider if the subject has a PHQ-9 score of > 15, any suicidal behavior, or any suicidal ideation of type 4 or 5 on the C-SSRS. They will also be provided with the contact information for the nationwide Suicide and Crisis Lifeline (telephone 988 or 988lifeline.org). If the participant endorses current (in that moment), active suicidal ideation with plan and intent, they will also be referred to the emergency department. Participants (and their parent) will be asked if they feel safe enough to leave the research clinic. If a participant (and their parent) do not feel safe we can help guide them to the emergency department.

20.0 Provisions to Protect the Privacy Interests of Participants

20.1 Protecting Privacy:

Please see HIPCO ancillary review

20.2 Access to Participants*:*

Please refer to the recruitment section.

21.0 Compensation for Research-Related Injury

21.1 Compensation for Research-Related Injury:

Treatment for injuries that result from participating in the research activity will be available. Those treatments include first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to the subject or to their insurance company. Subjects will be encouraged to contact the study team if they think that they have suffered a research related injury.

21.2 Contract Language:

Not applicable.

22.0 Consent Process

22.1 Consent Process (when consent will be obtained):

Parental/guardian consent and participant assent will be obtained by a study investigator or a designated study coordinator after explaining the study in detail, asking the participant and the parents/guardians to explain the purpose, risk and benefits, and other details of the study, and giving the participant and parents/guardians an opportunity to as questions. A copy of the signed forms will be given to the participants and the parents/guardians.

We will make every attempt to conduct parental re-consent and participant re-assent in a face-to-face manner. However if this process is not an option for the family, we would send the family the revised parental consent and assent forms and then set up a time to call them on the phone or Zoom with them to explain the revisions to the parental consent and assent and let them ask any questions that they might have. If the parent and child are amenable to the changes, we will ask that they sign and return the forms to us for counter signature and we will then send them complete executed copies and document in the participant notes the reconsent process.

22.2 Waiver or Alteration of Consent Process (when consent will not be obtained):

There is no plan to request a waiver or alteration of the consent process.

22.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

There is no plan to request a waiver of written/signed documentation.

22.4 Non-English Speaking Participants:

We plan to enroll Spanish speaking participants. Assent and consent documents will be translated to Spanish and a Spanish speaking study coordinator will perform the consenting process for these individuals.

22.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

This study will enroll subject who are under the age of 18 and they will be asked to sign and IRB-approved assent form. Their parents/guardians will be asked to sign a parental consent form.

Individuals who sign an assent form but turn 18 during the course of the study will be asked to sign a consent form and HIPAA to indicate that they are still willing to participate in the study once they reach the age of majority. A copy of the consent form will be given to the participant.

22.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

Not applicable.

22.7 Adults Unable to Consent:

Not applicable.

23.0 Setting

23.1 Research Sites:

- Center for Pediatric Obesity Medicine (CPOM).

- Delaware Clinical Research Unit (DCRU).
- M Health Clinics and Surgery Center.

23.2 International Research: Not applicable.

24.0 Multi-Site Research

Not applicable.

25.0 Coordinating Center Research

Not applicable.

26.0 References

1. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. JAMA 2018;319:1723-5.
2. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics 2007;120 Suppl 4:S164-S92.
3. Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017;102:709-57.
4. Grossman DC, Bibbins-Domingo K, Curry SJ, et al. Screening for Obesity in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. JAMA 2017;317:2417-26.
5. O'Connor EA, Evans CV, Burda BU, Walsh ES, Eder M, Lozano P. Screening for Obesity and Intervention for Weight Management in Children and Adolescents: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2017;317:2427-44.
6. Danielsson P, Kowalski J, Ekblom O, Marcus C. Response of severely obese children and adolescents to behavioral treatment. Arch Pediatr Adolesc Med 2012;166:1103-8.
7. Johnston CA, Tyler C, Palcic JL, Stansberry SA, Gallagher MR, Foreyt JP. Smaller weight changes in standardized body mass index in response to treatment as weight classification increases. J Pediatr 2011;158:624-7.
8. Kalarchian MA, Levine MD, Arslanian SA, et al. Family-based treatment of severe pediatric obesity: randomized, controlled trial. Pediatrics 2009;124:1060-8.
9. Knop C, Singer V, Uysal Y, Schaefer A, Wolters B, Reinehr T. Extremely obese children respond better than extremely obese adolescents to lifestyle interventions. *Pediatr Obes* 2015 Feb;10(1):7-14.
10. Kumar S, King EC, Christison AL, et al. Health Outcomes of Youth in Clinical Pediatric Weight Management Programs in POWER. J Pediatr 2019;208:57-65 e4.
11. Savoye M, Shaw M, Dziura J, et al. Effects of a weight management program on body composition and metabolic parameters in overweight children: a randomized controlled trial. JAMA 2007;297:2697-704.
12. Savoye M, Nowicka P, Shaw M, et al. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics 2011;127:402-10.

13. Shaffer LA, Brothers KB, Burkhead TA, Yeager R, Myers JA, Sweeney B. Factors Associated with Attendance after Referral to a Pediatric Weight Management Program. J Pediatr 2016;172:35-9.
14. Skelton JA, Goff DC, Jr., Ip E, Beech BM. Attrition in a Multidisciplinary Pediatric Weight Management Clinic. Child Obes 2011;7:185-93.
15. Skelton JA, Beech BM. Attrition in paediatric weight management: a review of the literature and new directions. Obes Rev 2011;12:e273-e81.
16. Smith KL, Kerr DA, Howie EK, Straker LM. Do Overweight Adolescents Adhere to Dietary Intervention Messages? Twelve-Month Detailed Dietary Outcomes from Curtin University's Activity, Food and Attitudes Program. Nutrients 2015;7:4363-82.
17. MacLean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. Am J Physiol Regul Integr Comp Physiol 2011;301:R581-R600.
18. Kelly AS, Fox CK, Rudser KD, Gross AC, Ryder JR. Pediatric obesity pharmacotherapy: current state of the field, review of the literature and clinical trial considerations. Int J Obes (Lond) 2016;40:1043-50.
19. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med 2007;357:2329-37.
20. Bjerregaard LG, Jensen BW, Angquist L, Osler M, Sorensen TIA, Baker JL. Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes. N Engl J Med 2018;378:1302-12.
21. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011;365:1876-85.
22. Twig G, Yaniv G, Levine H, et al. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. N Engl J Med 2016;374:2430-40.
23. Twig G, Tirosh A, Leiba A, et al. BMI at Age 17 Years and Diabetes Mortality in Midlife: A Nationwide Cohort of 2.3 Million Adolescents. Diabetes Care 2016;39:1996-2003.
24. Buscot MJ, Thomson RJ, Juonala M, et al. BMI Trajectories Associated With Resolution of Elevated Youth BMI and Incident Adult Obesity. Pediatrics 2018;141.
25. Kelly AS, Metzig AM, Rudser KD, et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. Obesity (Silver Spring) 2012;20:364-70.
26. Kelly AS, Rudser KD, Nathan BM, et al. The effect of glucagon-like Peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. JAMA Pediatr 2013;167:355-60.
27. Kelly AS, Auerbach P, Barrientos-Perez M, et al. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. NEJM 2020; 382:21128.
28. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gall LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF. STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. .2021 Mar 18; 384(11):989..
29. Kirk S, Armstrong S, King E, et al. Establishment of the Pediatric Obesity Weight Evaluation Registry: A National Research Collaborative for Identifying the Optimal Assessment and Treatment of Pediatric Obesity. Child Obes 2017;13:9-17.

30. Wilfley DE, Staiano AE, Altman M, et al. Improving access and systems of care for evidence-based childhood obesity treatment: Conference key findings and next steps. Obesity (Silver Spring) 2017;25:16-29.
31. Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a Disease: The Obesity Society 2018 Position Statement. Obesity (Silver Spring) 2019;27:7-9.
32. Sherwood NE, Jeffery RW, Welsh EM, Vanwormer J, Hotop AM. The drop it at last study: six-month results of a phone-based weight loss trial. Am J Health Promot 2010;24:378-83.
33. Sherwood NE, Crain AL, Martinson BC, et al. Keep it off: a phone-based intervention for long-term weight-loss maintenance. Contemp Clin Trials 2011;32:551-60.
34. Sherwood NE, Jeffery RW, Pronk NP, et al. Mail and phone interventions for weight loss in a managed-care setting: weigh-to-be 2-year outcomes. Int J Obes (Lond) 2006;30:1565-73.
35. French SA, Sherwood NE, Veblen-Mortenson S, et al. Multicomponent Obesity Prevention Intervention in Low-Income Preschoolers: Primary and Subgroup Analyses of the NET-Works Randomized Clinical Trial, 2012-2017. Am J Public Health 2018;108:1695-706.
36. Sherwood NE, Levy RL, Langer SL, et al. Healthy Homes/Healthy Kids: a randomized trial of a pediatric primary care-based obesity prevention intervention for at-risk 5-10 year olds. Contemp Clin Trials 2013;36:228-43.
37. Boutelle KN, Cafri G, Crow SJ. Parent-only treatment for childhood obesity: a randomized controlled trial. Obesity (Silver Spring) 2011;19:574-80.
38. Boutelle KN, Norman GJ, Rock CL, Rhee KE, Crow SJ. Guided self-help for the treatment of pediatric obesity. Pediatrics 2013;131:e1435-42.
39. Boutelle KN, Braden A, Douglas JM, et al. Design of the FRESH study: A randomized controlled trial of a parent-only and parent-child family-based treatment for childhood obesity. Contemp Clin Trials 2015;45:364-70.
40. Saelens BE, Sallis JF, Wilfley DE, Patrick K, Cella JA, Buchta R. Behavioral weight control for overweight adolescents initiated in primary care. Obes Res 2002;10:22-32.
41. Wilfley DE, Stein RI, Saelens BE, et al. Efficacy of maintenance treatment approaches for childhood overweight: a randomized controlled trial. JAMA 2007;298:1661-73.
42. Bosch TA, Dengel DR, Kelly AS, Sinaiko AR, Moran A, Steinberger J. Visceral adipose tissue measured by DXA correlates with measurement by CT and is associated with cardiometabolic risk factors in children. *Pediatr Obes* 2015 June;10(3):172-9.
43. Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. Int J Obes Relat Metab Disord 2000;24:38-48.
44. Sysko R, Devlin MJ, Schebendach J, et al. Hormonal responses and test meal intake among obese teenagers before and after laparoscopic adjustable gastric banding. Am J Clin Nutr 2013;98:1151-61.
45. Binford RB, le GD, Jellar CC. Eating Disorders Examination versus Eating Disorders Examination-Questionnaire in adolescents with full and partial-syndrome bulimia nervosa and anorexia nervosa. Int J Eat Disord 2005;37:44-9.

46. Weintraub SS, Dikmen KS, Heaton SR, Tulsky DD, Zelazo JP, Bauer EP, et al. Cognition assessment using the NIH Toolbox. Neurology. 2013;80(11_Supplement_3 Suppl 3):S54-S64. doi: 10.1212/WNL.0b013e3182872ded.
47. Zelazo PD, Anderson JE, Richler J, Wallner-Allen K, Beaumont JL, Weintraub S. II. NIH TOOLBOX COGNITION BATTERY (CB): MEASURING EXECUTIVE FUNCTION AND ATTENTION. Monographs of the Society for Research in Child Development. 2013;78(4):16-33. doi: 10.1111/mono.12032.
48. Luciana M. Practitioner Review: Computerized assessment of neuropsychological function in children: clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB). Journal of child psychology and psychiatry. 2003;44(5):649-63. doi: 10.1111/1469-7610.00152.
49. CANTAB® [Cognitive assessment software]. Cambridge Cognition; 2019. p. All rights reserved. .
50. Cooper A, Gomez R, Aucote H. The Behavioural Inhibition System and Behavioural Approach System (BIS/BAS) Scales: Measurement and structural invariance across adults and adolescents. Personality and individual differences. 2007;43(2):295-305. doi: 10.1016/j.paid.2006.11.023.
51. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior Rating Inventory of Executive Function, Second Edition (BRIEF 2). Lutz, FL: PAR Inc; 2015.
52. Konecky B, Lawyer SR. Steeper Delay Discounting Among Substance-Abusing and Substance-Dependent Adolescents Versus Controls. Journal of child & adolescent substance abuse. 2015;24(4):207-11. doi: 10.1080/1067828X.2013.778801.
53. Carver CS, White TL. Behavioral Inhibition, Behavioral Activation, and Affective Responses to Impending Reward and Punishment: The BIS/BAS Scales. Journal of personality and social psychology. 1994;67(2):319-33. doi: 10.1037/0022-3514.67.2.319.
54. Steinglass J, Foerde K, Kostro K, Shohamy D, Walsh BT. Restrictive food intake as a choice—A paradigm for study. International Journal of Eating Disorders. 2015;48(1):59-66. doi: 10.1002/eat.22345.
55. Fox CK, Kaizer AM, Rudser KD, et al. Meal replacements followed by topiramate for the treatment of adolescent severe obesity: A pilot randomized controlled trial. Obesity (Silver Spring) 2016;24:2553-61.
56. Kelly AS, Metzig AM, Rudser KD, et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. Obesity (Silver Spring) 2012;20:364-70.
57. Kelly AS, Rudser KD, Nathan BM, et al. The effect of glucagon-like Peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. JAMA Pediatr 2013;167:355-60.
58. Nederkoorn C, Jansen E, Mulkens S, Jansen A. Impulsivity predicts treatment outcome in obese children. Behaviour research and therapy. 2007;45(5):1071-5. doi: 10.1016/j.brat.2006.05.009.
59. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, et al. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. The New England journal of medicine. 2020;382(22). doi: 10.1056/NEJMoa1916038.
60. O'Connor EA, Evans CV, Burda BU, Walsh ES, Eder M, Lozano P. Screening for Obesity and Intervention for Weight Management in Children and Adolescents: Evidence Report and

Systematic Review for the US Preventive Services Task Force. JAMA : the journal of the American Medical Association. 2017;317(23):2427-44. doi: 10.1001/jama.2017.0332.

61. Brockmeyer T, Simon JJ, Becker A, Friederich H-C. Reward-related decision making and long-term weight loss maintenance. Physiology & behavior. 2017;181:69-74. doi: 10.1016/j.physbeh.2017.09.008.
62. Hayes JF, Eichen DM, Barch DM, Wilfley DE. Executive function in childhood obesity: Promising intervention strategies to optimize treatment outcomes. Appetite. 2018;124:10-23. doi: 10.1016/j.appet.2017.05.040.
63. WegovyTM semaglutide injection 2.4 mg. Package insert. Novo Nordisk A/S, 2021.