Official Title “Pharmacokinetics and Pharmacodynamics of Topiramate for Weight Loss in Youth: PHARMATOP”

Document Date: 05/03/2024

NCT04986631

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***
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☐ **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*	

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☐ **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*	
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PROTOCOL COVER PAGE

Protocol Title	Pharmacokinetics and Pharmacodynamics of Topiramate for Weight Loss in Youth: PHARMATOP
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	Current Academic Status (Student, Fellow, Resident):
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	Telephone Number:
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Scientific Assessment	Nationally-based, federal funding organizations
IND/IDE # (if applicable)	Exempted, IND# 157547
IND/IDE Holder	
Investigational Drug Services # (if applicable)	5867
Version Number/Date:	Version 17.0; 2024May03

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	1/17/2022	1. Specified body composition measures from Tanita scale 2. Change to medication dispensing schedule 3. Change to surveys administered 4. Change to physical exam requirements 5. Added incentive to return electronic prescription bottle	Yes
2	2/14/2022	Medication adherence at Week 2 and Week 4 will be done verbally during the telephone call	
4	2/28/2022	1. Changes to exclusion criteria 2. Revises the recruitment plan for the study 3. Medication compliance will be assessed by pill count at in-person study visits as an additional measure of adherence	Yes
5	3/24/2022	Revises the statistical section of the protocol	No
6	4/21/2022	Adds the use of a recruitment flyer to be used by clinicians recruiting for this study.	No
7	6/16/2022	• Revises the study exclusion criteria with regard to ADHD medications. • Allows a physical exam, as long as it was performed by a CPOM faculty member, performed in the pediatric weight management clinic or performed by a pediatric endocrinologist within 30 days of the Screening/Baseline visit, to be used for this project	

		• Clarifies that an individual with a high PHQ-9 or positive C-SSRS who have a mental health provider or whose primary care provider manages mental health, alerted of the change • allows an individual who is properly trained to conduct the Tanner staging.	
8	07/08/2022	Makes updates per the IRB's continuing renewal review: Adds in pregnancy testing to be performed at all in-person visits	Yes
9	10/07/2022	Revises the study exclusion criteria and adds a survey for females of childbearing potential to the final study visit. Includes a plan for participants who develop suicidal ideation while enrolled in the study.	Yes
10	10/18/2022	Revises section 18.2 of the protocol to conform to the changes made in protocol version 9 (managing participants who manage suicidal ideation).	No
11	03/31/2023	Revises the study exclusion criteria	No
12	04/13/2023	Notes that we may encounter a child who is comfortable with speaking English, but whose parent is more comfortable speaking Spanish. A Spanish language parental consent is being submitted for use in those instances.	Yes
13	05/04/2013	Revises section 9.2 to add in how we plan to communicate with Spanish speaking parents.	No
14	05/23/2023	Makes a clarification to the exclusion criteria regarding glaucoma	No

15	08/21/2023	Revises section 5.2 of the protocol to remove the at home urine pregnancy testing. Clarifies section 13.2 of the protocol to note that urine pregnancy tests will be done at screening/baseline, Week 6, Week 10 and Week 14 visits.	No
16	11/22/23	Adds a PHQ-9 and C-SSRS to the visit at Week 6. Names Dr. Bomberg as the medical monitor for the study and Dr. Brooke Sweeney as the external medical monitor. Adds that the study team may contact the participant's existing mental health provider in the event a participant presents with acute suicidal ideation/behavior at a study visit. Adds a suicide risk assessment at weeks 8 and 14, revises the protocol to note that topiramate cessation without tapering may be recommended in the event of an emergent medical situation.	Yes
17	01/23/2024	Makes some clarification to the study exclusion criteria	No
18	05/03/2024	Revises sections 8.3, 13.2 and the schedule of events to note that urine pregnancy testing will be conducted but that serum pregnancy tests are also acceptable.	Yes

Table of Contents

ABBREVIATIONS/DEFINITIONS

%BF	Percent Body Fat
%BMIp95	Percent of the 95th Body Mass Index Percentile
%EBMIL	Percent Excess Body Mass Index Loss
%TBWL	Percent Total Body Weight Loss
AE	Adverse Event
AEBQ	Adult Eating Behavior Questionnaire
AHC-IE	Academic Health Center – Information Exchange
AUC	Area Under the Curve
BEVQ-15	Beverage Intake Questionnaire 15
BF	Body Fat
BIA	Bioelectrical Impedance
BMI	Body Mass Index
BPIC	Best Practices Integrated Informatics Core
CA	Carbonic Anhydrase
CHIS	California Health Interview Survey
COWA	Controlled Oral Word Association
CPOM	Center for Pediatric Obesity Medicine
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTSI	Clinical and Translational Science Institute
DCRU	Delaware Clinic Research Unit
DF	Degrees of Freedom
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSMB	Data Safety Monitoring Board
DYFAS	Dimensional Yale Food Addiction Scale 2.0 for Children
EBMIL	Excess Body Mass Index Loss
EDE-Q	Eating Disorder Examination Questionnaire
I	Electronic Health Record
FCQ-T-r	Food Craving Questionnaire – Trait -Reduced
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
FPI	Fasting Plasma Insulin
GABA	Gamma Aminobutyric Acid
GLP1-RA	Glucagon-Like Peptide-1 Receptor Agonist
HDL	High Density Lipoprotein
GWAS	Genome-Wide Association Study
HOMA-IR	Homeostatic Model Assessment – Insulin Resistance
HST	Health Science Technology
ID	Identification
iDXA	Dual X-ray Absorptiometry
Kg	Kilograms
LDAP	Lightweight Directory Access Protocol
LDL	Low Density Lipoprotein

LSM	Lifestyle Modification
MHP	Mental Health Provider
MN-POC	Minnesota Pediatric Obesity Consortium
MRN	Medical Record Number
MSV	MilliSievert
NIH	National Institutes of Health
NLME	Non-Linear Mixed Effects
NONMEM	Non-Linear Mixed Effects Modeling
OFV	Objective Function Value
PAQ-A	Physical Activity Questionnaire for Adolescents
PD	Pharmacodynamics
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire – 9
PK	Pharmacokinetics
POPPK	Population Pharmacokinetics
PWMC	Pediatric Weight Management Clinic
RED-5	Reward Based Eating Drive Scale Xt5
SAE	Serious Adverse Event
SCM	Stepwise Covariate Model
SD	Standard Deviation
T2DM	Type 2 diabetes mellitus
TB	Toolbox
TBWL	Total Body Weight Loss
TOPMed	Trans-omics for Precision Medicine
TWL	Total Weight Loss
UMGC	University of Minnesota Genomics Center

1.0 Objectives

Introduction:

Pediatric severe obesity is the fastest growing obesity category in the United States, and anti-obesity pharmacotherapies are promising adjuncts to lifestyle modification (LSM) for the treatment of this disease. While anti-obesity pharmacotherapies have overall been associated with weight loss, there is substantial variability in their individual-level effectiveness. While some patients lose a significant amount of weight with anti-obesity pharmacotherapies, others lose little or even gain weight.

Due to this well-recognized variability in individual-level response, the National Institutes of Health (NIH) has recognized the importance of using precision medicine approaches in order to optimize treatments for pediatric severe obesity. Pharmacometrics, which uses mathematical models to study medication dose-exposure (e.g., blood drug concentrations)-response relationships, is an emerging science that can help determine optimal dosing regimens based upon patient-specific characteristics. Pharmacometrics quantitates the interplay between pharmacokinetics (PK; drug dose-exposure associations) and pharmacodynamics (PD; drug exposure-response associations). Population PK (popPK), a type of PK, can be used to quantitate variability in drug exposure among individuals in order to help inform recommendations on therapeutic individualization (i.e., through tailored dosing). In this study, we will use popPK/PD modeling to characterize associations between anti-obesity pharmacotherapy dose, exposure, and changes in weight and weight-related outcomes in youth with severe obesity.

We will be focusing on topiramate because this medication is commonly prescribed for weight loss in youth with severe obesity and has been associated with highly variable individual-level effectiveness. The weight loss achieved with topiramate occurs through several purported mechanisms including reductions in appetite, food cravings, and binge eating, and adverse alterations in taste for carbonated beverages. It is hypothesized that some of the individual-level effectiveness of this medication on weight loss response is secondary to patient-specific differences in these factors. In a 3.5-month pragmatic-based prospective cohort study (n=65), we will develop a popPK model using sparse sampling by drawing a series of topiramate concentration measures over time in order to begin determining patient-specific factors that contribute to topiramate exposure variability. We will also identify associations between topiramate exposure, changes in eating behaviors, and weight loss outcomes through PD models using regression techniques. We hypothesize that patient-specific characteristics (i.e., age, body mass index (BMI), and sex) will explain some variability in topiramate exposure in youth, and that higher topiramate exposure will be associated with greater improvements in weight loss response and eating behaviors among youth prescribed this medicine for the treatment of pediatric severe obesity.

2.0 Background

2.1 Significance of Research Question/Purpose:

Pediatric severe obesity (defined as age- and sex-adjusted BMI ≥1.2 times the [9]5th percentile and/or BMI ≥35 kg/m^2) is the fasting growing obesity category, affecting ~6% of US youth.[1-3] As most youth with severe obesity fail to achieve clinically significant and durable weight loss with LSM alone,[4] anti-obesity pharmacotherapies are promising adjuncts to LSM in this population.

While anti-obesity medications are overall associated with weight loss, there is substantial variability in their individual-level effectiveness in terms of their impact on weight reduction and improvements in cardiometabolic risk factors and eating behaviors.[5-7] Indeed, some prescribed these medications lose a substantial amount of weight, while others lose little or even gain weight.[6] As severe pediatric obesity is associated with considerable risk for the development of future obesity-related health sequelae including hypertension, type 2 diabetes mellitus (T2DM), and cardiovascular disease, identifying determinants of the variable response seen with anti-obesity pharmacotherapies, which can be achieved through precision medicine approaches, is critical.

The goal of precision medicine is to optimize therapeutic benefit and minimize risk by selecting treatment based on one's personalized characteristics.[8] A 2018 NIH-sponsored workshop on precision medicine approaches for the treatment of severe obesity in adolescents identified, among other issues, the importance of optimizing anti-obesity medication dosing based upon one's metabolism.[9] Pharmacometrics is an emerging science that may help to accomplish this. In brief, pharmacometrics is the study of drug dose-exposure (e.g., blood drug concentration)-response relationships, and is used to quantitate interplays between PK (drug dose-exposure associations) and PD (drug exposure-response associations). PopPK, a type of PK model, is used to quantify variability in drug exposure *among* individuals. Combined PopPK/PD studies can help identify factors that influence the variability in drug exposure and, therefore, can be used to help determine individualized dosing regimens.[10-11] Indeed, popPK/PD studies have helped explain some of the differential response to anti-obesity pharmacotherapies in adults, and have been used to identify individualized dosing regimens to a wide variety of medicines in both pediatrics and adults.[12-13]

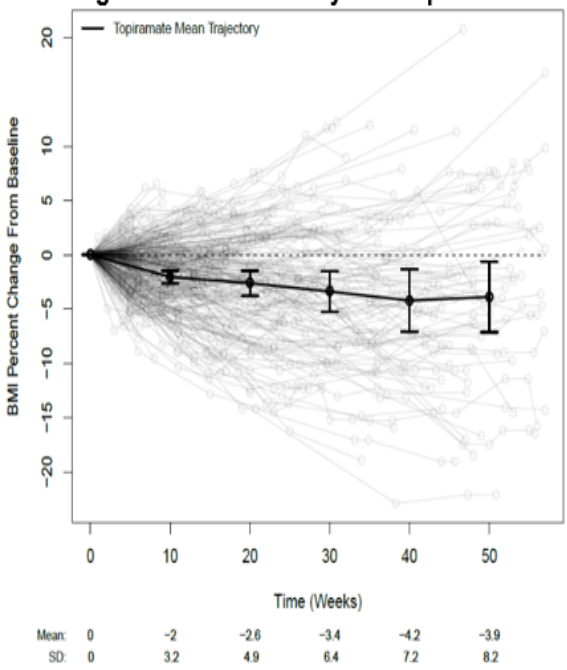
Topiramate, Food and Drug Administration (FDA) approved for the treatment of seizures (in children and adults) and prevention of migraines (in adults), is commonly prescribed for weight loss as an adjunct to LSM in youth with severe obesity.[14] Its central purported mechanisms for weight loss include increasing gamma-aminobutyric acid (GABA) and decreasing glutamate and dopamine secretion, subsequently decreasing appetite, food cravings, and binge eating; and carbonic anhydrase (CA) inhibition which can adversely alter taste for carbonated beverages.[15] Weight loss associated with topiramate is highly variable, as evidenced by studies showing a clinically significant mean 5-7% weight loss after 6-12 months, however, with standard deviations (SDs) consistently greater than mean weight loss.[16-22]

Because of its ubiquitous use in obesity management and known variability in weight loss efficacy, topiramate serves as an ideal model medication to begin our exploration of drug dose-exposure-response relationships to anti-obesity pharmacotherapies in youth with severe obesity. In a 3.5-month pragmatic-based prospective study of youth started on topiramate, we will develop a popPK model by serially measuring topiramate concentrations over time (every 2-4 weeks for a total of 4 measures) in order to determine patient-specific characteristics that contribute to drug exposure variability. Specifically, we will statistically test the importance of age, sex, BMI, and other baseline characteristics as significant determinants of drug exposure. We will also determine associations between topiramate exposure, weight loss outcomes (i.e. BMI reduction, changes in other body weight metrics), and changes in eating behaviors (i.e. appetite, satiety, binge eating tendencies, food cravings, carbonated and/or sugar-sweetened beverage consumption) through PD models that utilize regression techniques.

2.2 Preliminary Data:

In a retrospective cohort study we showed that, among 28 youth with severe obesity prescribed topiramate plus LSM for weight loss in our pediatric weight management clinics (PWMCs), the average BMI reduction was 4.9% after 6 months; however, the SD was 5.8%.[22] This *suggests that, while the combination of topiramate and LSM leads to weight loss on average, the individual-level response is highly variable,* and some individuals may even gain weight on this regimen. While this particular study was small and not powered to explore possible predictors of weight loss response, >475 youth have since been prescribed topiramate in our PWMCs. A review of this data (unpublished) similarly shows a highly variable response to topiramate plus LSM, which can be seen early as 12 weeks and out to 1 year after starting treatment (**Figure 1**).

Figure 1: BMI variability with topiramate



2.3 Existing Literature:

While we have not generated preliminary data directly supporting our study hypotheses, previous studies by others have used popPK/PD modeling to identify drug dose-exposure-response relationships in children and adults without obesity receiving topiramate for epilepsy treatment.[23-25] Specifically, using popPK, Takeuchi et al. found that, for seizure management, topiramate dose adjustments were necessary to reach effective concentrations based upon weight status and concomitant use of other antiepileptic medicines.[23] In a PD study, Vovk et al. found no relation between topiramate concentration and seizure frequency in children and adults with epilepsy.[24] No studies have previously used popPK/PD to determine topiramate dose-exposure-response relationships in terms of this medication's effects on weight loss and weight-related outcomes despite its frequent use for these purposes.

PopPK/PD studies have also been used to determine associations between dose, exposure, and weight loss outcomes to other anti-obesity pharmacotherapies. For example, among adults prescribed liraglutide (a glucagon-like peptide 1 receptor agonist (GLP1-RA) used for T2DM and obesity treatment) plus LSM for weight loss, higher baseline body weight and male sex have been associated with lower liraglutide exposure, and higher liraglutide exposure has been associated with greater weight loss.[12-13] This suggests a possible need for differential liraglutide dosing based on the patient-specific characteristics of baseline body weight and sex in adults with obesity.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Our overall goal is to determine associations between topiramate dose and exposure, and topiramate exposure and weight-related outcomes, in youth with severe obesity prescribed this medication for weight management. Towards this end, **our study has two primary objectives:**

1. *To determine sources of variability in topiramate exposure using popPK modeling:* We hypothesize that patient-specific characteristics including age, sex, and baseline BMI (primary predictors for popPK) will explain some variability in topiramate exposure, assessed by metrics including area under the concentration-time curve (AUC, primary outcome for popPK), among youth with severe obesity.

2. *To determine associations between topiramate exposure and 3-month BMI change using PD modeling:* We hypothesize that higher topiramate exposure (primary predictor for PD) will be associated with greater 3-month BMI reduction, as assessed by percent change in BMI from baseline (primary outcome for PD), in youth with severe obesity.

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

Our study has several secondary objectives:

1. *To determine associations between topiramate exposure and other weight loss outcomes*, including total weight loss (TWL; kg), percent total body weight loss (%TBWL), percent excess BMI loss (%EBMIL), and reduction in percent of the 95th BMI percentile (%BMIp95). We hypothesize that higher topiramate exposure, assessed by metrics including AUC, will be associated with greater 3-month total weight loss, increased %TBWL and %EBMIL, and greater reductions in %BMIp95 in youth with severe obesity.

2. *To determine how topiramate exposure affects eating behaviors in youth severe obesity*. We hypothesize that higher topiramate exposure will be associated with reduced hunger, binge eating, food cravings, and consumption of sugar-sweetened and/or carbonated beverages; and increased satiety, all measured via validated questionnaires and compared to baseline measures, in youth with severe obesity.

3. *To determine associations between topiramate exposure and changes in cardiometabolic risk factor labs*. We hypothesize that higher topiramate exposure will be associated with greater 3-month improvements in insulin sensitivity (measured by homeostatic model assessment – insulin resistance (HOMA-IR) and hemoglobin A1c) and lipid levels (including increased HDL and lower LDL and triglycerides) in youth with severe obesity.

4. *To determine associations between body fat percentage and topiramate exposure, and to determine if body fat percentage is a better predictor of topiramate exposure compared to BMI*. We hypothesize that increased percent body fat (%BF) as assessed by dual x-ray absorptiometry (iDXA) and bioelectrical impedance (BIA) will be associated with decreased topiramate exposure, and that %BF will correlate more strongly with topiramate exposure compared to BMI in youth severe obesity.

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

4.1 Description:

Overview:

We will perform a 3.5-month prospective cohort study consisting of adolescents (12 to <18 years old) with severe obesity prescribed topiramate, and designed to be analyzed by nonlinear mixed-effects (NLME) approaches. We will quantitate relationships between PK parameters and patient-specific factors using popPK modeling in order to better predict topiramate exposure. Specifically, we will evaluate the importance of baseline factors including age, sex, and BMI as

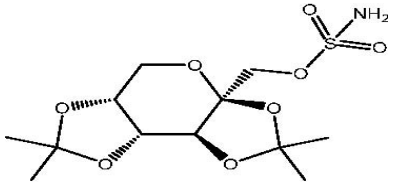
significant determinants of topiramate exposure. Our quantification of topiramate exposure will then allow us to establish topiramate exposure-weight loss outcome relationships using PD modeling. This can eventually help us determine optimal topiramate dosing strategies in youth with severe obesity prescribed this medication for weight management.

We will recruit study participants primarily from our PWMCs among adolescents with severe obesity who are deemed by prescribing physicians as appropriate candidates to receive topiramate for the indication of weight management. Additional study participants may be recruited among those who contact CPOM (after receiving recruitment letters for CPOM studies), are interested in participating in a study that specifically involves the initiation of an active anti-obesity pharmacotherapy at study onset (versus possibility of receiving a placebo), and who qualify (meet inclusion/exclusion criteria). Study participants will be consented and assented prior to enrollment, and study visits will take place in the Delaware Clinical Research Unit (DCRU). This is an open-label study and, therefore, all participants will be prescribed topiramate. During the first two weeks, all participants will be titrated up to topiramate 75 mg daily (the most commonly used dose in our PWMC) or their maximum-tolerated dose. They will then remain on this dose for the next 3 months until study completion. During the study, participants will receive LSM and undergo a series of anthropometric and laboratory assessments (including topiramate levels and labs evaluating for insulin resistance and lipids), and questionnaires that assess eating behaviors.

Topiramate and Dosing:

Topiramate is 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate. The molecular formula is C12H21NO8S and its molecular weight is 339.4. Topiramate is a white to off-white crystalline powder with a bitter taste. It is freely soluble in methanol and acetone, sparingly soluble in pH 9 to pH 12 aqueous solutions, and slightly soluble in pH 1 to pH 8 aqueous solutions. Its structural formula is:

Figure 2: Molecular Structure of Topiramate



The precise mechanism of action of topiramate on chronic weight management is not known. However, central purported mechanisms for weight loss include increasing GABA and decreasing glutamate and dopamine secretion, subsequently decreasing appetite, food cravings, and binge eating; and CA inhibition, which can adversely alter the taste of carbonated beverage.[15]

Based on data from weight loss studies in youth and adults; safety data from several pediatric studies; and instructions on FDA-approved labels, topiramate will be initiated at 25 mg daily and escalated to 50 mg after one week and 75 mg after two weeks.[21,26-30] 75 mg daily is the most often prescribed dose in our PWMCs, and was safe and well tolerated in CPOM's previous trial examining topiramate for BMI reduction in this population.[30] We will also follow generative verbal fluency during this study with the Controlled Oral Word Association (COWA) test, sensitive for phonetic fluency and used in multiple topiramate studies.[31-33] Patients not tolerating dose escalation will be reduced to the 50 or 25 mg dose (depending upon tolerability) for the

remainder of the trial, per protocol from our previous trial (only occurred in one of 30 of participants).[30]

4.2 Drug/Device Handling:

This study is open-label and, therefore, no placebo will be utilized. The topiramate used in this study will be managed by the University of Minnesota Investigational Drug Service (IDS) Pharmacy and will be dispensed according to their operating policies. The IDS specializes in storing and dispensing medications 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 studies maintain stability. IDS will keep detailed records on the receipt of topiramate (including lot numbers) and detailed records on the dispensing of product to each participant 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.

4.3 Biosafety: N/A

4.4 Stem Cells: N/A

4.5 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design:

This will be a 3.5-month open-label, pragmatic-based study to determine associations between topiramate dose, exposure, weight loss outcomes (i.e., BMI reduction, improvements in cardiometabolic risk factor labs), and eating behaviors (i.e., hunger, satiety, binge eating, food craving, consumption of sugar-sweetened and/or carbonated beverages) in youth with severe obesity prescribed this medication for weight management. The study cohort will be recruited primarily among youth receiving care through our PWMCs. Additional study participants may be recruited among those who contact CPOM (after receiving recruitment letters for CPOM studies), are interested in participating in a study that specifically involves the initiation of an active anti-obesity pharmacotherapy at study onset (versus possibility of receiving a placebo), and who qualify (meet inclusion/exclusion criteria). We will recruit youth ages 12 to <18 years old. The schedule of events (**Table 1**) shows the data that will be collected at each study visit. Following topiramate initiation, adherence will be assessed every other week by review of electronic prescription bottles, and side effects will be assessed throughout the study at in-person study visits or via phone calls.

Table 1: Schedule of Events

	Screening/Baseline	Week 6	Week 8	Week 10	Week 14
Visit Number	1	2	3	4	5
Review Inclusion/Exclusion Criteria[1]	x				
Consent/Assent	x				
Demographics[2]	x				
Physical Exam[3]	x				x
Tanner Staging[3]	x				
BMI/Anthropometrics[4]	x	x		x	x
Blood Pressure/Heart Rate	x	x		x	x
Pregnancy Testing and questionnaire[14]	x	x		x	x[14]
Safety Labs[5]	x	x			
Cardiometabolic Risk Labs (fasting)[6]	x				x
Genotyping[7]	x				
Topiramate concentration		x	x	x	x
iDXA (body composition)[8]	x				
Bioelectrical Impendence Anaysis[9]	x	x		x	x
Eating Behavior and Physical Activity Questionnaires[10] • Hunger/Satiety Visual Analog Scales • AEBQ • FCQ-T-r • dYFAS • RED-5 • PAQ-A	x	x			x
Sugar Consumption[11] • BEVQ-15	x	x			x
Eating Disorder Examination Questionnaire (EDE-Q)	x	x			x
Depression and Suicide Screening[12] • PHQ-9 • C-SSRS	x	x	x	x	x
Neurocognitive Testing[13] • COWA • NIH-TB List Sorting Working Memory Test • NIH-TB Pattern Comparison Test	x	x		x	x
Lifestyle Counseling	x	x			
Registered Dietician Visit	x	x			
Drug Dispensing	x		x		
Adherence	← Assessed at in person visits via electronic prescription bottles and pill count and at weeks 2 and 4 via phone call →				
Side Effects, Inter-current Illnesses, Concomitant Medications Review	← Assessed weeks 6, 8, 10, and 14 at study visit; weeks 2, and 4 via phone call →				

[1] Will be reviewed by study principal investigator and/or co-investigator
[2] Demographics including age, sex, race/ethnicity
[3] Physical exam does not need to be repeated if one was done by CPOM faculty, in the pediatric weight management clinic, or by a pediatric endocrinologist within 30 days prior to Screening/Baseline visit. Tanner determined by Marshall-Tanner criteria examining breast and pubic hair development (girls) or genitalia and pubic hair (boys); to be performed by a trained professional.
[4] Height, weight, BMI, waist circumference, hip circumference
[5] Creatinine (to assess renal function) and bicarbonate (to assess for presence of metabolic acidosis)
[6] Lipids (total, LDL-, HDL-cholesterol, triglycerides), glucose, insulin, hemoglobin A1c.
[7] DNA collection via salivary collection kits
[8] iDXA to include total and regional body fat measures
[9] Performed using Tanita scale
[10] Including hunger/satiety Visual Analog Scales, Adult Eating Behavior Questionnaire (AEBQ), Food Craving Questionnaire-Trait-Reduced (FCQ-T-r), Dimensional Yale Food Addiction Scale 2.0 for Children (dYFAS), Reward Based Eating Drive Scale X5 (RED-5), and Physical Activity Questionnaire for Adolescents (PAQ-A)
[11] Assessed via the Beverage Intake Questionnaire 15 (BEVQ-15)
[12] PHQ-9 to be conducted at Baseline/Screening, Week 6 and Week 10. Columbia-Suicide Severity Rating Scale (C-SSRS) to be conducted at all visits
[13] Controlled Oral Word Association (COWA) test, NIH-TB List Sorting Working Memory Test and NIH-TB Pattern Comparison Test
[14] Urine pregnancy preferred, but serum may be utilized. Females who undergo pregnancy testing will be asked to complete a questionnaire about their experience at the Week 14 visit

5.2 Study Procedures:

Anthropometric Measurements and Body Fat Composition:

Figure 3: Tanita® Scale

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 and 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 then be calculated by standard convention: weight in kilograms divided by 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 (iDXA, GE Healthcare). The scanning table accommodates body sizes of up to 204 kg. Our group has done some of the early work regarding validation of iDXA visceral fat in children and adolescents.[34] As an additional measure of body composition, we will also utilize a DC-430U Tanita® scale (Tanita Corporation of America Inc, Arlington Heights, IL), which is an FDA-cleared bioelectrical impedance analysis device that calculates fat, muscle, water, and bone mass (**Figure 3**). This measurement will be obtained in light clothing, and without shoes and socks. Specific measures obtained via the Tanita scale will include weight, fat percent (with desirable range), fat mass (with desirable range), fat free mass, and body mass index.

Pubertal Development, Blood Pressure, and Blood Analyses:

Pubertal stage (Tanner stage) will be determined at the baseline/screening visit by trained pediatricians using Marshall-Tanner criteria examining breast and pubic hair development for girls and genitalia and pubic hair development for boys.[35-36] This will not be performed if this exam was previously performed by a pediatric weight management clinic provider and/or pediatric endocrinologist within the last 30 days prior to the baseline/screening visit, with results available in the EHR.

Blood pressure measurements will be obtained manually on the same arm using the same cuff size and equipment. Standardized procedures will be employed as described previously.[37] Individual cuff size will be determined by measuring the arm circumference midway between the acromial process and the bony olecranon. Sitting blood pressure and heart rate will be measured after the participant has been resting quietly for 10 minutes. Measurements will be made three consecutive times (3-minute intervals). The final two of three measurements will be averaged.

Cardiometabolic risk factor labs will be drawn fasting (≥12 hours) and will include measurements of plasma glucose (FPG), plasma insulin (FPI), hemoglobin A1C, and lipids (total-, LDL-, HDL-cholesterol, and triglycerides). These will all be assayed in Fairview Diagnostics Laboratories (Minneapolis, MN – a Center for Disease Control and Prevention certified laboratory). The fasting insulin and glucose measures will be used to determine a HOMA-IR, a commonly used surrogate

marker of insulin resistance in children and adults,[38] which will be calculated per standard convention:

$$\text{FPG (nmol/l)} \times \text{FPI (microU/l)}/22.5$$

Topiramate levels will be drawn at 6, 8, 10, and 14 weeks, corresponding to 4, 6, 8, and 12 weeks after the participant has reached 75 mg daily (or the maximum tolerated dose). All topiramate samples will be spun at 10,000 x g for 10 minutes, 5 to <120 minutes after blood draw, and frozen (-80°C) until analysis per standard protocol.[39] We will measure topiramate concentrations by a previously validated liquid chromatography-mass spectrometry (LCMS) assay in the lab of Dr. Angela Birnbaum (Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota).[39]

DNA Collection and Genotyping:

DNA salivary collection kits (Oragene, Ontario, Canada) will be used to collect DNA. All samples returned will be stored at room temperature until processing. DNA extraction, quantification, and genotyping will be performed by the University of Minnesota Genomics Center (UMGC) following standard procedures. Genotyping will be performed using the Infinium™ Global Screening Array-24 v2.0 BeadChip (Illumina, San Diego). Inclusion criteria for SNPs will be a minor allele frequency >1%, call rate >98%, and Hardy-Weinberg equilibrium (p>1E-5). We will then impute all samples to the Trans-Omics for Precision Medicine (TOPMed) reference panel using the Michigan Imputation server.

Eating Behaviors/Features and Physical Activity Questionnaires:

Eating behaviors/features and physical activity questionnaires are summarized in **Table 2**. We will obtain self-report ratings (average over the preceding week) for appetite and satiety on 15-cm visual analog scales anchored with "not at all" to "extremely." This method has been validated for use in appetite research[40] and was utilized by Sysko et al. in a study of adolescents with severe obesity.[41] An additional self-reported appetite and satiety measure will be the Adult Eating Behavior Questionnaire (AEBQ; note: in our experience, the self-report version (AEBQ) is more appropriate for adolescents compared to the child version (CEBQ)).[42]

Food craving will be measured with the Food Craving Questionnaire-Trait-Reduced (FCQ-T-r) and food addiction with the Dimensional Yale Food Addiction Scale 2.0 for Children (dYFAS).[43-44] Binge eating behaviors/features will be measured with the Reward Based Eating Drive Scale X5 (RED-5), in addition to the Eating Disorder Examination Questionnaire (EDE-Q).[45-46] Dietary intake of sugar-sweetened and/or carbonated beverages will be measured via questions from the Beverage Intake Questionnaire 15 (BEVQ15).[47] Finally, physical activity will be measured with the Physical Activity Questionnaire for Adolescents (PAQ-A).[48]

Table 2: Eating Behavior/Features, Physical Activity, Neurocognitive Testing, and Safety Questionnaires

Type of Questionnaire	Name of Questionnaire	What Questionnaire Measures	Number of Questions	Visit Performed
Eating Behaviors/Features	Visual Analog Scales	Hunger, satiety	2	1, 2, 5
	Adult Eating Behavior Questionnaire (AEBQ)	Hunger, satiety, emotional eating, hedonic eating	35	1, 2, 5
	Food Craving Questionnaire-Trait – Reduced (FCQ-T-r)	Food craving	15	1, 2, 5
	Dimensional Yale Food Addiction Scale 2.0 for Children (dYFAS)	Food addiction	13	1, 2, 5
	Reward Eating Drive Scale X5 (RED-5)	Binge eating features	5	1, 2, 5
	Beverage Questionnaire (BEVQ15)	Sugar beverage intake	15	1, 2, 5
Physical Activity	Physical Activity Questionnaire for Adolescents (PAQ-A)	Physical activity	9	1, 2, 5
Neurocognitive Testing	Controlled Oral Word Association	Verbal fluency	3	1, 2, 4, 5
	NIH-TB List Sorting Working Memory Test	Working memory	N/A (up to 7 minutes to complete)	1, 2, 4, 5
	NIH-TB Pattern-Comparison Processing Test	Processing Speed	N/A (up to 1.5 minutes to complete)	1, 2, 4, 5
Safety Questionnaires	Eating Disorder Examination Questionnaire (EDE-Q)	Eating disorders	28	1, 2, 5
	Patient Health Questionnaire-9 (PHQ-9)	Depression	9	1,2, 4
	Columbia-Suicide Severity Rating Scale (C-SSRS)	Risk for Suicidality	Up to 10	1, 2, 3, 4, 5

Safety-Related Assessments:

Please see **Table 1**. A creatinine and bicarbonate to assess for renal disease and metabolic acidosis will be performed at baseline and one month after topiramate has reached the maximum dose in this study (75 mg or maximum-tolerated dose). We will require all female participants to confirm use of two forms of contraception if sexually active.

We will monitor for depression, suicidal behavior and ideation, acute secondary angle closure glaucoma, renal stones, cognitive impairment, decreased bicarbonate indicating metabolic acidosis, and elevated creatinine. Changes in neurocognitive function (verbal fluency) and working memory will be evaluated using the Controlled Oral Word Association (COWA) test and the NIH-TB List Sorting Working Memory Test, and NIH TB Pattern Comparison Processing Test, respectively, at each in-person study visit, aside from the week 8 blood draw-only visit.[49-50] Of note, the COWA is sensitive for phonetic fluency and has been used in multiple studies involving topiramate.[51-53]

Participants will be assessed for depression with the Patient Health Questionnaire-9 (PHQ-9) at the Screening/Baseline, Week 6 and Week 10 visits. Participants will be assessed for suicide with

the Columbia-Suicide Severity Rating Scale (C-SSRS) at all visits.[54-55] A participant will be referred to a mental health provider (MHP) or primary care provider if the participant has a PHQ-9 score of ≥15, any suicidal behavior, or any suicidal ideation of type 4 or 5 on the C-SSRS and a member of the study team may contact a participant's existing mental health provider if a participant presents with acute suicidal ideation/behavior at a study visit. The decision as to whether the participant will be allowed to continue in the trial will be made by the local medical monitor (Dr. Eric Bomberg) in consultation with the MHP or primary care provider after the referral clinical visit. Participants who already have an existing mental health provider and/or are followed by their primary care provider for mental health will have their mental health provider and/or primary care provider alerted if the participant has a PHQ-9 score of ≥15 or any suicidal behavior or suicidal ideation of type 4 or 5 on the C-SSRS.

Eating disorders will be evaluated using the eating disorder examination-questionnaire (EDE-Q).[46] Any participant endorsing vomiting, laxative use, and/or diuretic use for weight control (via the EDE-Q by standard scoring procedures), will be interviewed by a pediatric behavioral psychologist using the Eating Disorders Module of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). If disordered eating is present upon clinical interview, the participant will be removed from the study and referred to an eating behavior specialist for clinical follow-up. If no eating disorder is present, the participant may continue in the study.

5.3 Study Duration:

14 weeks, including 2 weeks of topiramate titration up to 75 mg daily (or maximum tolerated dose; as described in **Section 4.1**) followed by 12 weeks on topiramate.

5.4 Use of radiation:

The iDXA consists of exposure to 0.01 mSv. In comparison, a resident of the State of Minnesota receives approximately 3 mSv from natural background radiation as a result of living in Minnesota. There are no other sources of radiation in this study.

5.5 Use of Center for Magnetic Resonance Research*:* N/A

6.0 Data and Specimen Banking

6.1 Storage and Access:

Blood Samples:

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.

DNA Specimens:

The DNA specimens (saliva kits) will be stored in the Pediatric Research BioBank until processing, located in the 717 Delaware Building. These specimens will then be transferred to the University of Minnesota Genomics Center for DNA extraction, quantification, and genotyping. After completion of these steps, specimens will then be transferred back to the Pediatric Research BioBank, where they will be banked for future use. We will bank these samples indefinitely. DNA

specimens will only be handled by the study personnel including the study investigator, co-investigators, and coordinator(s).

Electronic Health Record (EHR) Data Storage and Access:

Identifiable information from the EHR will only be accessed through the AHC-IE, which is a secured data shelter, and only via UMN-issued encrypted password-protected computers. Only study investigators will have access to the data, and sharing of the data will only be via the ACE-IE secured data shelter, UMN Box, and REDCap. We will work with UMN Best Practices Integrated Informatics Core (BPIC) for EHR data gathering, storage, and preparation for analysis.

6.2 Data:

Results from the Fairview Diagnostics Laboratories will be posted to the patient's chart and will also be logged into REDCap. The data will be kept with a unique identification (ID) link. The principal investigator will retain the link to the patients' names, which will be stored in the ACE-IE and only accessed via UMN-issued encrypted password-protected computers. Data, including results from Fairview Diagnostics Laboratories, will be entered into a REDCap database on the secure web interface with data checks used during data entry to ensure data quality. REDCap is a widely-used, powerful, reliable, and well-supported system. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional Lightweight Directory Access Protocol (LDAP) server. The database and web server are both housed on secure servers operated by UMN Health Sciences Technology (HST). The servers are in a physically secure location on the UMN campus and are backed up nightly, with the backups stored in accordance with the HST retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. The HST servers provide a stable, secure, well-maintained, and high capacity data storage environment. Access to the study's data in REDCap will be restricted to members of the study team by username and password.

6.3 Release/Sharing:

Access to the study data REDCap will be restricted to the members of the study team by username and password.

7.0 Sharing of Results with Participants

7.1 Sharing results:

Given the pragmatic nature of this study, participants will receive laboratory test results, which will be shared by a study team member. However, for the genetic analysis (DNA collection and genotyping), only aggregate results will be shared with participants as described below.

7.2 Sharing of genetic testing:

7.2.1 Disclosure of results:

Only aggregate results of the genetic analyses (DNA collection and genotyping) will be shared with participants. We are not planning to disclose individual results of genetic testing to participants.

7.2.2 If returning results to participants:

- *Aggregate or individual results*: Aggregate.
- *Laboratory results*: N/A
- *Plan for return of results to participants*: Results will be returned via a study website after publication of the study results.
- *Types of results to be returned to participants*: Participants will not be provided with complete datasets. We will return lay summaries of the publications to the participants.

7.2.3 Future analysis of genotypes: N/A

8.0 Study Population

8.1 Inclusion Criteria:

- Body Mass Index (BMI) ≥1.2 times the 95th percentile (age and sex-adjusted) and/or BMI ≥ 35 kg/m^2
- Ages 12 to <18 years old
- If recruited from PWMC: Deemed appropriate candidates to receive topiramate (without contraindications) for weight loss by an obesity medicine specialist at the University of Minnesota

8.2 Exclusion Criteria:

- History of metabolic/bariatric surgery
- Obesity associated with a diagnosed genetic disorder (i.e. monogenic obesity, Prader-Willi, Bardet-Biedl syndrome)
- Clinically diagnosed hyperthyroidism or uncontrolled hypothyroidism as determined by local medical monitor (Dr. Eric Bomberg) (who is a board certified endocrinologist)
- History of acute angle closure glaucoma. Individuals with other types of glaucoma will need approval from the participant's ophthalmologist to be enrolled.
- History of nephrolithiasis
- History of a seizure disorder (aside from febrile seizures)
- Major psychiatric disorder as determined by local medical monitor
- History of bulimia nervosa or anorexia nervosa
- History of suicide attempt within one year of the screening visit
- History of active suicidal ideation or self-harm within 30 days of the screening visit
- Current or recent (< 6 months prior to enrollment) use of topiramate or phentermine/topiramate
- Current or recent (< 6 months prior to enrollment) use of other anti-obesity medication(s) defined as metformin, orlistat, phentermine, liraglutide/semaglutide (or other GLP1-RAs), naltrexone, and/or combination naltrexone/bupropion (monotherapy use of bupropion is not an exclusion), **unless** participant has been on stable doses for ≥ 6 months. Of note, if a dose of phentermine was increased from 15 mg daily to 18.75 mg daily during this period, it is not considered a dose increase.

- Current or recent (< 6 months prior to enrollment) use of medication(s) associated with weight gain (e.g. oral steroids, anti-psychotics), **unless** participant has been on stable doses of such medication(s) for ≥ 6 months
- Current or recent (< 6 months prior to enrollment) use of long-acting stimulant medications, **unless** participant has been on stable doses of such medication for ≥ 6 months. In terms of short-acting ADHD stimulant medications, the PI will determine eligibility based on weight and dose (no studies have shown this contributes to weight outcomes).
- Baseline bicarbonate < 18 mmol/L
- Baseline creatinine > 1.2 mg/dL
- Females: pregnant, planning to become pregnant, or, if sexually active, unwilling to use 2+ acceptable contraceptive methods during the study period

8.3 Screening:

Patients seen in the University of Minnesota PWMCs who are deemed appropriate candidates to receive topiramate (without contraindications) for weight loss by an obesity medicine specialist will be referred for this study.

Screening/Baseline Visit (Visit 1):

Participants will be asked to present at this visit after having fasted for ≥12 hours. At this visit, the participant's parent/legal guardian will be taken through the consent process and will sign the parental consent form, and the participant will be asked to sign the assent form, after all have had the opportunity to learn about the study and ask any questions they may have. The participant will then undergo the following:

- Review of inclusion/exclusion criteria
- Demographics including age, sex, self-reported race/ethnicity, home address, total family combined income, parents' level of education and employment status
- Physical exam and tanner stage. The physical examination will not need to be repeated if performed by a CPOM faculty member, pediatric weight management provider, and/or pediatric endocrinologist within the last 30 days before Screening/Baseline visit. A trained professional can perform the Tanner staging.
- BMI/Anthropometrics: height, weight, waist and hip circumference, and BMI
- Blood pressure and heart rate
- Pregnancy test for females
- Contraceptive counseling
- Review of medications
- Blood draw for safety labs (creatinine and bicarbonate) and cardiometabolic risk labs (lipids, glucose, insulin, and A1c)
- Genotyping (via saliva collection)
- iDXA (body composition)
- Bioelectrical impedance analysis (via Tanita Scale)
- Eating behavior and physical activity questionnaires (hunger/satiety visual analog scales, AEBQ, FCQ-T-r, dYFAS, RED-5, BEVQ-15, PAQ-A)
- Safety questionnaire for eating disorders (EDE-Q)

- Depression and suicide screening (PHQ-9 and C-SSRS). Participants whose tests show that they have active suicidal ideation will be referred to their own mental health provider, have a mental health referral generated or be referred to the emergency department
- Neurocognitive testing (COWA test, NIH-TB List Sorting Working Memory Test, NIH-TB Pattern Comparison Processing Speed Test)
- Lifestyle and registered dietician counseling

Week 2 (± 7 days from enrollment):

- Side effects, inter-current illnesses, medication review and adherence (via phone call)

Week 4 (± 7 days from enrollment):

- Side effects, inter-current illnesses, medication review and adherence (via phone call)

Week 6 (± 7 days from enrollment; Visit 2):

- BMI/Anthropometrics
- Blood pressure and heart rate
- Blood draw for safety labs (creatinine and bicarbonate)
- Pregnancy test for females
- Topiramate concentration
- Bioelectrical impedance analysis (via Tanita Scale)
- Eating behavior and physical activity questionnaires (hunger/satiety visual analog scales, AEBQ, FCQ-T-r, dYFAS, RED-5, BEVQ-15, PAQ-A)
- Safety questionnaire for eating disorders (EDE-Q)
- Depression and suicide screening (PHQ-9 and C-SSRS)
- Neurocognitive testing (COWA test, NIH-TB List Sorting Working Memory Test and NIH-TB Pattern Comparison Processing Speed Test)
- Lifestyle and registered dietician counseling
- Side effects, inter-current illnesses, medication review
- Adherence (via electronic prescription bottle review and counting pills)

Week 8 (± 7 days from enrollment; Visit 3; lab draw only):

- Topiramate concentration
- Side effects, inter-current illnesses, medication review (via phone call or in-person)
- Adherence (via electronic prescription bottle review and counting pills)
- Suicide screening (C-SSRS)
- Drug dispensing

Week 10 (± 7 days from enrollment; Visit 4):

- BMI/Anthropometrics
- Blood pressure and heart rate

- Pregnancy test for females
- Topiramate concentration
- Bioelectrical impedance analysis (via Tanita Scale)
- Depression and suicide screening (PHQ-9 and C-SSRS)
- Neurocognitive testing (COWA test, NIH-TB List Sorting Working Memory Test, NIH-TB Pattern Comparison Processing Speed Test)
- Side effects, inter-current illnesses, medication review
- Adherence (via electronic prescription bottle review and counting pills)

Week 14 (± 7 days from enrollment; Visit 5):

- Physical exam, performed by a trained pediatrician
- BMI/Anthropometrics
- Blood pressure and heart rate
- Blood draw for cardiometabolic risk labs (lipids, glucose, insulin, and A1c)
- Pregnancy test for females and questionnaire about the testing
- Topiramate concentration
- Bioelectrical impedance analysis (via Tanita Scale)
- Safety questionnaire for eating disorders (EDE-Q)
- Eating behavior and physical activity questionnaires (hunger/satiety visual analog scales, AEBQ, FCQ-T-r, dYFAS, RED-5, BEVQ-15, PAQ-A)
- Neurocognitive testing (COWA test, NIH-TB List Sorting Working Memory Test, NIH-TB Pattern Comparison Processing Test)
- Side effects, inter-current illnesses, medication review
- Suicide screening (C-SSRS)
- Adherence (via electronic prescription bottle review and counting pills)

9.0 Vulnerable Populations

9.1 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	Excluded from Participation

not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	
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).	Excluded from Participation
Any other circumstance/dynamic that could increase vulnerability to	Excluded from Participation

coercion or exploitation that might influence consent to research or decision to continue in research.	

9.2 Additional Safeguards:

At least one parent signature is required for permission for a minor to enroll in the study. Children ages 8 to <18 years old will be asked to document their agreement by signing an assent form. The research will not involve wards of the state or any other agency, institution, or entity. All consent and assent will be documented.

It is possible that the parent of a child may not be comfortable with reading and speaking English and would prefer that the consent be available in Spanish. For that reason, we have had the parental consent translated into Spanish. As most of the children we encounter are comfortable with speaking and reading English, we will not be translating the assent form at this time. We have two native Spanish speakers on our team who can help with answering questions that might arise with the parent at visits.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:

All participants will be consented locally. The approximate number of participants we plan to enroll is 65. The lowest number that will allow for data analysis is 40, and the maximum that might agree to participate is 80.

11.0 Local Recruitment Methods

11.1 Recruitment Process:

One of the primary strengths of this study is its pragmatic nature. Our 3.5-month duration (2 weeks to increase topiramate to maximum dose, followed by 3 months on this dose) for this study was chosen because the FDA, as well as most obesity management guidelines,[1-3] recommend that pharmacotherapies used for obesity treatment either be altered or discontinued after 3 months if response is insufficient. For example, the FDA recommends that for adults on the combination of phentermine 7.5 mg/topiramate 46 mg daily, if weight loss is <5% at 3 months, then the dose should be titrated up to the maximum-strength dose of phentermine 15 mg/topiramate 92 mg daily. Most patients prescribed an anti-obesity medication are, therefore, generally on the medication for at least 3 months on the same dose assuming they do not develop adverse effects to the treatment. In this sense, this study largely entails the addition of measures including anthropometrics (e.g. height, weight, BMI), blood draws, and questionnaires onto routine clinical care being performed in our and other weight management clinics. We believe that this will substantially facilitate recruitment for our study.

At the Center for Pediatric Obesity Medicine (CPOM), we have strong recruitment infrastructure. For this study, participants will primarily be recruited directly from our PWMCs by providers and support staff within the clinics. Additional participants may be recruited among those who contact CPOM (after receiving recruitment letters for CPOM studies), are interested in

participating in a study that specifically involves the initiation of an active anti-obesity pharmacotherapy at study onset (versus possibility of receiving a placebo), and who qualify (meet inclusion/exclusion criteria). Inclusion in the study will be determined by the enrollment criteria. There is a vast number of potentially eligible participants. Our PWMCs generally have ≥3,000 patient visits per year, a number that is continuing to rise with the recent expansion of our clinical capacity and volume (four new obesity medicine specialists hired in the last few years; seven total obesity medicine providers). Further, ≥500 youth to date have been prescribed topiramate through our clinics and, with our recent clinical expansion, this number is expected to continue to substantially grow. Given our clinical volume and our established recruitment infrastructure, we do not anticipate problems with recruiting the cohort during the study duration.

If recruitment is below target for any reason, we can utilize partner institutions within the Minnesota Pediatric Obesity Consortium (MN-POC) for assistance with recruitment. Member institutions of MN-POC include the University of Minnesota, Mayo Clinic, Children's Hospitals and Clinics of Minnesota, and Park Nicollet/Health Partners, collectively representing a large portion of the pediatric medical care provided in the state of Minnesota. All MN-POC institutions are within reasonable driving distance of the University of Minnesota, and most refer patients to our PWMCs for obesity management already.

11.2 Identification of Potential Participants:

From the PWMC, youth with severe obesity will be identified by PWMC providers as appropriate candidates to receive topiramate. The study PI (Dr. Bomberg) is a PWMC provider and is, therefore, in regular communication with other PWMC providers. Additional participants may be recruited among those who contact CPOM (after receiving recruitment letters for CPOM studies), are interested in participating in a study that specifically involves the initiation of an active anti-obesity pharmacotherapy at study onset (versus possibility of receiving a placebo), and who qualify (meet inclusion/exclusion criteria). After identification, potential participants will be given an IRB-approved recruitment letter about the project. Interested participants will be asked to contact the study team, and up to five follow-up phone calls will be made by study staff if the potential participant leaves a message. Further, with verbal parental permission, PWMC providers will also contact the study team about potential participants identified. The only information provided to the study team prior to official enrollment will include name and contact information.

11.3 Recruitment Materials:

Recruitment letters will be created for this study and approved by the IRB before use. Appropriately certified staff within the PWMC may approach potential participants and speak to them about the study and provide them with a flyer with a QR code that connects them to the research coordinator and indicates a preferred method of communication (email, phone or text).

11.4 Payment:

While this study is largely pragmatic in nature in the sense that it largely entails the addition of measures including anthropometrics, blood draws, and questionnaires onto routine clinical care being performed in PWMCs, we still recognize the additional commitment needed from the

participant and family members. Therefore, the children who participate in this study will receive payment for the visits they complete. Payments will be made by the Greenphire ClinCard.

- Screening/baseline visit: $50
- Week 6 visit: $35
- Week 8 visit (blood draw only): $25
- Week 10 visit: $40
- Week 14 visit: $50
- Return of electronic prescription bottle (Visit 14): $25
- Total: $225

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

Participants will be allowed to withdraw from the study at any time. Those who wish to withdraw may notify the research team in writing or by telephone. Participants may also be withdrawn from the study at any time based upon investigator judgement. Finally, 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 (Dr. Brooke Sweeney and Dr. Eric Bomberg, respectively), the participant will be required to immediately discontinue the intervention.

12.2 Withdrawal Procedures:

As it is generally recommended that patients choosing to discontinue topiramate be weaned off of this medication, we will recommend for any participant choosing to withdraw from the study, or being withdrawn as described above, the following weaning schedule (consistent with clinical practice in the PWMC):

- Take 50 mg daily for one week, followed by:
- Take 25 mg daily for one week, and then discontinue.

In the event of an emergent medical situation, it may be recommended to cease topiramate without tapering the dose. For those participants that choose to withdraw, we will not plan to collect any additional data beyond that point, as the primary data of import in this study is topiramate concentration levels.

12.3 Termination Procedures:

It will be noted in the participant enrollment log that the participant has discontinued 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.

Given the pragmatic nature of this study, including the fact that most participants recruited will be from our PWMCs and will continue to be followed through our PWMCs (if they so desire) after their participation in this study has terminated, many participants completing this study may continue to take topiramate after study completion. In that case, per usual clinical practice the medication will be prescribed by the participant's PWMC provider. For those not yet followed in the PWMC who are interested in continuing topiramate and/or being followed in our clinics, appointments in the PWMC will be established for continuation of topiramate and ongoing clinical management. All additional follow up in the PWMC will continue as per usual clinical

practice. If a participant elects to discontinue topiramate after study completion, we will use the same withdrawal procedure as described in **Section 12.2**, and additional topiramate will be provided by the IDS for this purpose**.**

13.0 Risks to Participants

13.1 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 iDXA scans involve exposure to a very low dose of ionizing radiation. The average amount of radiation that the average person would receive from the iDXA used in this study is less than 1% (0.01 mSv) of that received from natural sources of radiation by a Minnesota resident in one year (3 mSv).

Neuropsychological assessments (questionnaires): Potential risks related to the questionnaires include emotional distress related to thinking about and recording eating behavior symptoms, as well as possible "test fatigue."

Risk from salivary collection (spitting into a tube or having saliva collected with a swab): There are no known health risks to participants related to the collection of saliva.

Personal Information: There is a risk that personal information could accidentally be released to someone other than study staff. We keep all personal information in computer databases protected by passwords or in locked file cabinets. Only study staff will have access to these documents and files. All individuals with the ability to access protected health data have completed HIPAA and Collaborative Institutional Training Initiative (CITI) training.

DNA/Genotyping: We are requesting consent to store and process DNA. We will be performing genotyping through the use of a genome-wide association (GWAS) chip. Results from a GWAS chip rarely imply much about an individual's risk of disease. Rather, GWAS can identify regions of linkage disequilibrium containing potentially causal events. We will also be requesting consent for sequencing DNA. When this is done, it is similar to a fingerprint and is thus unique. All precautions will be taken to protect participant privacy and confidentiality. All genetic information will be stored in a secure database that is only labelled with an identification number. Only the investigators and the study team members will have access to this data as needed to carry out their study-related duties. DNA extraction, quantification, genotyping, and sequencing studies will be performed by the UMGC, which also has strict privacy rules in place to protect participant identity. Nevertheless, it is possible that someone in the future could identify a participant based on this unique genetic information. The DNA analysis will occur after all participant visits have occurred for the study. Any leftover saliva samples will be returned to the study team. The saliva sample collected can only be initially processed for approximately five years. Any saliva that remains after the sample is analyzed will be put back into storage indefinitely and may be used for future research projects. .

Expected Adverse Events – Topiramate: A majority of patients tolerate topiramate well and have no adverse events. Adverse events, if they do occur, are generally mild to moderate in intensity. The following have been identified as the most common potential adverse events related to topiramate: paresthesia (tingling in the hands, feet, and/or face), dysgeusia (altered or metallic

taste), fatigue, dizziness, somnolence, nervousness, psychomotor slowing, difficulty with memory and/or concentration/attention, cognitive problems, confusion, mood problems, fever, infection, and flushing. In our experience, the most common side effect is transient irritability and rarely do patients discontinue topiramate due to side effects. Of note, we will be following generative verbal fluency during the study with the COWA test and working memory via the NIH-TB List Sorting Working Memory Test and Pattern Comparison Processing Speed Test. According to the package insert, the following additional adverse reactions to topiramate have been identified:

- Acute myopia and secondary angle closure glaucoma
- Oligohidrosis and hyperthermia
- Metabolic acidosis
- Suicidal behavior and ideation. Participants who have active suicidal ideation will be referred to their own mental health provider, have a mental health referral generated or be referred to the emergency department.
- Fetal toxicity
- Kidney stones
- Seizure precipitation with sudden withdrawal
- Hyperammonemia and encephalopathy
- Hypothermia

13.2 Reproduction Risks:

Topiramate can cause fetal harm in pregnant women. Available data indicate an increased risk in oral clefts (cleft lip with or without cleft palate) with first trimester exposure to topiramate. When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring. Therefore, all female participants who are sexually active must agree to use two forms of birth control during their time in the study. Females of childbearing potential will have pregnancy tests at baseline/screening (during which visit they also complete the iDXA scan) and at the Week 6, Week 10 and Week 14 visits. Urine pregnancy tests will be used as often as possible, but a serum pregnancy test may also be conducted. If a patient becomes pregnant while taking topiramate, treatment will be discontinued immediately and the patient will be apprised of the potential hazard to a fetus again at that time.

13.3 Risks to Others: N/A

13.4 Definition of Adverse Events (AE):

An adverse event is any untoward medical occurrence in a clinical study participant 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.

13.5 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

13.6 Classification of an Adverse Event:

Severity of Event: The severity of all AEs will be assessed by the internal safety monitor 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 study, the study product must always be suspected.

- *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 internal safety 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.

13.7 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 topiramate (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 in the 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. As described in **Section**

5.1, at each study encounter study staff will inquire about the occurrence of AEs/SAEs since the last encounter. Events will be followed for outcome information until resolution or stabilization.

The PI will notify the IRB and external medical monitor (Dr. Brooke Sweeney) of any SAE that meets the definition of being an unanticipated problem that involves risk to subjects or others (UPIRTSO) within five days of knowledge of the event. The DSMB will be provided with AE and SAE information prior to their review of the study, at least every six months.

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

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 and improvements in eating behaviors during the study. Since data from studies in youth receiving topiramate have shown an overall reduction in BMI with topiramate plus LSM, it is reasonable to expect similar results in this proposed study focused on characterizing associations between topiramate dose, exposure, and weight loss outcomes in youth with severe obesity.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

PopPK analysis will be conducted using NONMEN® following best practice guidelines set forth by Byon et al.[56] We will assume that the structural model of topiramate follows a one-compartment model with 1st-order absorption and elimination per previous topiramate studies.[23-25] Topiramate concentrations (collected 4, 6, 8, and 12 weeks after 75 mg or maximum-tolerated topiramate dose reached) will be modeled using non-linear mixed effects (NLME). Topiramate exposure (assessed by area under the curve (AUC)), as well as additional variables including apparent clearance, volume of distribution, and inter-individual variability will be estimated with popPK, described in **Section 15.3**. The effects association of topiramate exposure (AUC) on weight loss outcomes (BMI reduction, changes in eating behaviors and cardiometabolic risk labs) will be performed using linear regression with robust estimation for confidence intervals and p-values. We will also explore potential non-linear relationships with cubic splines.

15.2 Power Analysis:

In line with the goals of this pilot study, our sample size was chosen to strike a balance between recruitment, feasibility, potential attrition, and the amount of data deemed necessary to inform the aims and design of a subsequent NIH R01. Results from previous simulations and statistical methods for repeated measures outcomes using sparse sampling in popPK suggest that bias and precision are acceptable as sample sizes approach 50.[57-59] Assuming 25% drop-out, higher than usual for CPOM clinical trials (10-15%), we will recruit 65 participants. The power will depend on the range of values observed for the exposure predictor (AUC). Based on the variability observed from a pilot study of similar dose and age, and allowing for drop-out of as many as 15, we will have 80% power for an association of 4.75kg per 20 mcg*h/ml.[60]

15.3 Statistical Analysis:

Pharmacokinetic Modeling (dose-exposure relationships):
Topiramate concentrations will be modeled using a non-linear mixed effects (NLME) regression

implemented in NONMEM® (ICON Development Solutions, Ellicott City, MD). NLME is robust with respect to sparse data sets such as ours, hence appropriate for this analysis. Compartment models best describing topiramate will be selected based on diagnostic plots and fall in objective function values (OFVs). Covariates known to effect drug disposition (e.g. BMI, sex, race/ethnicity, genomics, as determined by a genetic risk score (GRS) will be included in the model-building algorithms. An automated stepwise covariate model (SCM) procedure will be used to screen covariates.[31] The SCM involves forward selection and backward elimination steps: forward addition followed by backward deletion. Covariates that upon inclusion reduced the OFV by at least 3.84 (statistical significance of $p<0.05$, based on a Chi-squared distribution (degrees of freedom (df) = 1)), will be sequentially added. After stepwise addition of all significant covariates, backward deletion will be performed wherein removal of covariates that increase the OFV by at least 6.84 (statistical significance of $p<0.01$ based on a Chi-squared distribution (df = 1)), will be considered significant. Final model parameter estimates and their 95% confidence intervals will be qualified by re-estimation using a nonparametric bootstrap approach generating 1,000 bootstrap datasets. Parameter estimates are rank ordered and the values at the 2.5% and 97.5% of the rank order are used as the lower and upper bounds of the bootstrap 95% confidence interval. The 50th percentile (median) is used as the bootstrap parameter estimate.[31]

Pharmacodynamic Modeling (exposure-response relationships):

The association of topiramate exposure (AUC) on weight loss outcomes (BMI reduction, changes in eating behaviors and cardiometabolic risk labs) will be performed using linear regression, adjusting for model covariates, with robust estimation for confidence intervals and p-values. We will also explore potential non-linear relationships utilizing cubic splines.

15.4 Data Integrity:

Despite our best efforts, it is possible that some data will be missing, which could limit interpretation of the 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, we will use a last observation carried forward approach for participants on whom we do not have a final measurement. Observations obtained during interim visits will be used for these analyses, and additional sensitivity analyses.

16.0 Health Information and Privacy Compliance

16.1 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: N/A

☐ 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.

16.2 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. Describe: N/A

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

All participants in this study will be recruited directly from our PWMCs among patients who are receiving care by PWMC providers. Therefore, study staff will not have access to records of other individuals, including those who have not agreed to have their information used for research.

16.4 Approximate number of records required for review: >1,000

16.5 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.

Participants will receive telephone calls and emails regarding the study. The details of the telephone calls that this study requires is outlined in the consent forms. Emails that contain protected health information (PHI) will be sent to the participant/parent via a secure, encrypted manner.

16.6 Explain how the research team has legitimate access to patients/potential participants: This has been explained in other sections of the protocol.

16.7 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

☐ 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

16.8 Consultants. Vendors. Third Parties. N/A

16.9 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 laboratories will be identified only by study identification number, never by name. Similarly, DNA samples both in CPOM and those sent to UMGC will be identified only be study identification, never by name. Data to be used in scientific presentations or publications will not contain participant identifiers.

16.10 Sharing of Data with Research Team Members.

Study team members will have access to UMN Box, RedCAP, OnCore, and the ACE-IE.

16.11 Storage and Disposal of Paper Documents:

All paper documents will be stored in locked offices and will not be released without participant consent.

17.0 Confidentiality

17.1 Data Security:

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 laboratories will be identified only by study identification number, never by name. Similarly, DNA samples both in CPOM and those sent to UMGC will be identified only be study identification, never by name. Data to be used in scientific presentations or publications will not contain participant identifiers.

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

18.1 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 FDA. 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.

18.2 Data Safety Monitoring.

An internal medical monitor (Dr. Eric Bomberg) will review all adverse events and serious adverse events regularly throughout the study. In addition, an independent (not involved in the study) external medical monitor (Dr. Brooke Sweeney) will review all serious adverse events regularly throughout the study. 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 pediatric 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 study to review data and evaluate participant safety.

A charter for the DSMB will be developed and approved by its members along with a plan for frequency of data review prior to the commencement of the study. Review materials for the DSMB will be prepared and presented by the study biostatistician, Dr. Kyle Rudser. A report from each meeting will be sent to the PI and co-investigators 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. Important charges 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), and to closely monitor the quality and integrity of the data. The DSMB will communicate any concerns relevant to these issues of study conduct to the PI and note specific recommendations for improvement in meeting reports.

In the event that a participant has a serious adverse event that is deemed related to topiramate (this is an open-label study; all participants will receive topiramate) and/or procedures by either the internal or external medical monitor, the participant will be required to discontinue the intervention following the withdrawal procedures as outlined in **Section 12.2**. The overall study may be stopped at any time at the request of the PI, internal or external medical monitor and/or the DSMB. 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 (see **Section 5.2**). Patients will be instructed that they may withdraw from the study at any time and for any reason.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

We understand that the decision to participate in clinical research is personal. Potential participants do not need to decide during a PWMC visit if they would like to participate in clinical research. During the PWMC visit, potential participants will be offered written information about the study and asked if it is okay for our study team to reach out for further details. Participants will be told that taking part in clinical research is not mandatory, and their participation in this study is entirely optional. See HIPCO ancillary review for further details.

19.2 Access to Participants*:* Please refer to the recruitment section.

20.0 Compensation for Research-Related Injury

20.1 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 participant or to their insurance company. Participants will be encouraged to contact the study team if they think that they have suffered a research related injury.

20.2 Contract Language: N/A

21.0 Consent Process

21.1 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, risks and benefits, and other details of the study, and giving the participant and parents/guardians an opportunity to ask questions. A copy of the signed forms will be given to the participants and the parents/guardians.

21.2 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.

21.3 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.

21.4 Non-English Speaking Participants:

We do not plan on enrolling non-English speaking participants at this time.

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

This study will enroll participants who are under the age of 18, and they will be asked to sign an 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.

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

21.7 Adults Unable to Consent: N/A

22.0 Setting

22.1 Research Sites: University of Minnesota (CPOM, Delaware Clinical Research Unit (DCRU))

22.2 International Research: N/A

23.0 Multi-Site Research: N/A

24.0 Coordinating Center Research: N/A

25.0 Resources Available

25.1 Resources Available:

Funding to perform this study will be obtained from the National Institutes of Health as part of Dr. Bomberg's K23 Career Development Award grant (DK125668: *Precision Medicine Approaches to Obesity Pharmacotherapy in Youth with Severe Obesity*).

For this study, participants will primarily be recruited directly from our PWMCs by providers and support staff within the clinics. Our PWMCs have ≥3,000 patient visits a year, a number that has been increasing with the recent expansion of our clinical capacity and volume (four new obesity medicine specialists hired over the last few years; currently seven total providers). Further, well over 500 youth to date have been prescribed topiramate for weight management in our clinics, a number that is also increasing with our clinical expansion. In addition, CPOM providers an extremely strong recruitment and retention infrastructure, and has retained 85-90% of participants in prior pharmacotherapy trials that were far longer durations than the 3.5 months proposed in this study.[61-63]

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