Title: Adjunctive Anti-Obesity Pharmacotherapy in Adolescents and Young Adults after Bariatric Surgery: A Randomized Controlled Pilot Study

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Protocol #: 18-2793
Project Title: Adjunctive Anti-Obesity Pharmacotherapy in Adolescents and Young Adults after Bariatric Surgery: A Randomized Controlled Pilot Study
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I. Hypotheses and Specific Aims:

Primary Aim 1: Assess the feasibility (including protocol implementation and acceptability) of a randomized, placebo-controlled, double-blinded, adjunctive 12-week phentermine + topiramate intervention beginning 6-12 months after bariatric surgery, among adolescents and young adults (age 12-24 years) who don't achieve expected weight loss or who remain severely obese (n=14 total).
Hypothesis 1: Protocol implementation, including recruitment and retention, will be feasible based on achievement of adequate enrollment and participant completion of at least 80% of study visits. The experimental group will report better acceptability compared to the control group based on satisfaction with the desired effects of the active drugs.

Secondary Aim 2: Test the initial efficacy of standard of care plus 12 weeks of active drugs or placebo on percent weight loss beginning 6 to 12 months postoperatively.
Hypothesis 2: The experimental group will experience a greater percent weight loss than the control group at the end of the 12 week intervention period.

Secondary Aim 3: Evaluate the initial effects of standard of care plus 12 weeks of active drugs or placebo on cardiometabolic, eating behavior, and quality of life outcomes beginning 6 to 12 months postoperatively.
Hypothesis 3: The experimental group will demonstrate greater improvements than the control group in blood pressure (BP), lipids, alanine aminotransferase (ALT), hemoglobin A1c (HbA1c), and fat mass reduction; and, will report less hunger, increased satiety, more cognitive restraint, decreased daily caloric intake, increased resting metabolic rate, and better quality of life at the end of the 12 week intervention period.

II. Background and Significance:

Severe obesity affects 4.5 million children and adolescents in the US and is rising across all age groups.[1,2] Adolescent severe obesity is associated with significantly increased risks of cardiometabolic disease, decreased quality of life, and premature death.[3–5] The most effective and durable treatment for severe obesity is bariatric surgery.[6] However, large prospective trials among US adolescents demonstrate that even after bariatric surgery, more than 50% will remain *severely* obese at 3 or more years postoperatively,[7,8] despite multidisciplinary lifestyle-based postoperative standard of care. To date, there have been very few pre- or postoperative factors identified among adolescents that predict long-term success after bariatric surgery.[9,10] And, neither preoperative nor postoperative lifestyle-based interventions in adults have had a clinically meaningful impact on long-term weight outcomes.[11,12]

Bariatric surgery is increasingly recognized as an effective and safe tool to treat adolescents with severe obesity.[7,8,13] Current indications for bariatric surgery in adolescents are either 1) A BMI ≥35kg/m^2 or ≥120% of the 95th percentile + an obesity-related comorbidity *or* 2) BMI ≥40kg/m^2 or ≥140% of the

95th percentile alone, *and* a demonstrated ability to adhere to pre- and postoperative recommendations.[13] Maximal weight loss after bariatric surgery in adolescents is typically seen at 1 year (with the most rapid loss within the first 6 months) followed by modest weight regain. In US adolescent cohorts, weight loss at 6 months after surgery closely approximates weight loss achieved at 3 years.[7] Notably, in two large observational trials of US adolescents with severe obesity undergoing bariatric surgery, 55-63% remained severely obese at long-term follow-up.[7,8]

This represents a combination of individuals who did not achieve optimal post-surgical weight loss, who experienced significant weight regain, and/or whose preoperative BMI was so high that even after expected weight loss they remained severely obese. This suggests that bariatric surgery alone will not be the absolute treatment solution for a significant subset of adolescents. These individuals will continue to have unacceptably high personal health risks throughout adulthood, and will pose an ongoing economic and public health burden to society.[14] Interventions that result in even a 1% decrease in obesity prevalence could save an estimated $4 billion/year in medical costs alone.[15]

Numerous studies in adults have demonstrated that the amount of weight loss after bariatric surgery predicts long-term odds of remission for obesity comorbidities. Specifically, total postsurgical weight loss is a predictor of type 2 diabetes remission.[16–18] Further, in the longest published outcomes from the Longitudinal Assessment of Bariatric Surgery Study (LABS-2) cohort 7 years after RYGB, individuals in the most favorable weight trajectory (greatest % weight loss) had significantly higher remission rates of type 2 diabetes, low HDL cholesterol, and hypertension (adjusted relative risk of remission: 2.44, 2.07, and 2.1, respectively) than those with the least favorable trajectory.[19] Finally, degree of postoperative weight loss is associated with improvements in health-related quality of life up to 10 years after surgery.[20] In contrast to adults, in whom specific postoperative behaviors (e.g. weekly self-weighing, not eating when feeling full, and not eating continuously) explain a significant amount of variability in weight loss at three years postoperatively,[21] adolescent behaviors associated with post-operative weight loss have not been identified.[10] In addition, perioperative lifestyle-based interventions in adults have shown limited efficacy on postoperative outcomes. **Anti-obesity medications represent an understudied tool that may augment or maintain weight loss, further increase the odds of comorbidity remission, and reduce risks of recurrent and incident comorbidities in the post-bariatric setting**.

Phentermine as a monotherapy is FDA-approved for short-term treatment of obesity in adolescents ≥17 years. Topiramate has long been used in pediatrics for epilepsy and migraine prevention, and has been studied as an anti-obesity medication in adolescents.[22] Among the 5 medications FDA-approved for long-term treatment of obesity in adults, the combination of phentermine and extended release (ER) topiramate results in the most weight loss at 1 year in placebo-controlled clinical trials (~20lbs, 15mg/96mg dose; ~15lbs, 7.5mg/46mg dose).[23] In two large RCTs of phentermine/topiramate in adults, the odds ratio (OR) for achieving ≥10% weight loss was 11.34, and the OR for discontinuation of drug due to adverse events was 2.32 vs. placebo.[24] This drug combination has never been prospectively studied for obesity treatment in adolescents, despite its frequent empiric clinical use with good patient tolerance. Phentermine acts as a central nervous system stimulant through norepinephrine reuptake inhibition, resulting in appetite suppression and increased resting energy expenditure.[25] Topiramate's exact mechanistic effect on appetite is unclear, but is likely linked to central GABA and dopamine modulation.[25] The only RCT of topiramate for weight loss among adolescents was a pilot study in a non-surgical setting that evaluated 24 weeks at 75mg/day and found no significant difference in mean percent change in BMI, but this may have been affected by the study's 4-week run in of meal replacement.[22] A retrospective review of 15mg/day phentermine + SOC vs. SOC alone among adolescents with obesity/severe obesity demonstrated a greater percent decrease in BMI at 6 months in the phentermine + SOC group vs. matched controls, with no between-group differences in blood pressure.[26] *After* bariatric surgery, several retrospective studies in adults have shown significant beneficial effects of anti-obesity medications (including phentermine, topiramate, and the combination) in halting weight regain and achieving additional weight loss after plateau.[27–30]

Additionally, the first ever framework for the use of anti-obesity medications in adolescents

highlights the post-surgical period as one setting for which pharmacotherapy should be considered, but without a supporting evidence base.[31] Thus, studies of anti-obesity pharmacotherapy in adolescents are needed.

III. Preliminary Studies

Unpublished latent class growth trajectory modeling data from our group of the Teen-LABS[32] participants 5 years after Roux-en-Y Gastric Bypass (RYGB) or Sleeve Gastrectomy (SG) demonstrate significant heterogeneity in surgical response. Where ≥ 20% BMI loss is considered to be an adequate response, among adolescents who had RYGB, 16% achieved only a 5% BMI loss and another 21% achieved a 16% BMI loss at 5 years. Among those who had SG, 36% achieved only a 7% BMI loss at 5 years postoperatively. Additionally, greater %BMI loss at 6 months postoperatively was associated with a more successful 5-year BMI trajectory. These data further underscore the need for adjunct treatment options for a sizeable subset of adolescents within the first year after bariatric surgery.

The Bariatric Surgery Center at Children's Hospital Colorado[33], led by Drs. Thomas Inge (Surgical Director) and Megan Kelsey (Medical Director), began seeing patients in June 2017. Patients undergo either SG or RYGB. Over the last 25 months, patient volume has accelerated, and currently there are 103 patients in the program (Mean age: 17 [Range: 10-36]; Female: 73%; Race/Ethnicity: 46% Hispanic, 27% Non-Hispanic White, 14% Black, 13% Other). Based on a chart review of current postoperative patients who have had surgery ≥6 months ago, we estimate that 2 patients per month will meet inclusion criteria for this study. Therefore, we anticipate that 14 patients will be eligible for enrollment during the proposed 7-month recruitment timeline (Table 2). This allows for a 29% reduction in eligible individuals from the combination of upfront decline and dropout to successfully meet the target sample size of 10. This does not account for projected increases in overall Bariatric Surgery Clinic patient volume over the proposed timeline.

The patented combination pill phentermine/topiramate XR (trade name Qsymia) is generally not covered by Colorado insurance plans and costs ~$200/month out of pocket, which makes it inaccessible for the vast majority of our patient population. We, like other pediatric weight management programs, prescribe phentermine and *immediate release* topiramate as individual medications (~$30/month). This research proposal was designed to mimic this usual practice of prescribing individual phentermine and immediate release topiramate pills, which will allow for a more realistic assessment of feasibility and increases generalizability.

Prior to study start, within the Bariatric Surgery Center, we had managed 13 patients perioperatively on phentermine, topiramate, or the combination for weight stabilization/loss. The PI and primary mentor continue to manage many additional patients on topiramate and phentermine in the broader Lifestyle Medicine weight management program at Children's Colorado, and we have developed clinical guidelines for the use of these medications at CHCO. In our perioperative experience, these medications are generally very well-tolerated.

Given the current Food and Drug Administration labeling for each of the proposed study drugs, **the PI has successfully obtained an Investigational New Drug Application (IND 142590) for this pilot study**. The IND is active for the use of phentermine and immediate release topiramate in 12-24 year olds after bariatric surgery as defined in this research protocol. We will follow a data and safety monitoring plan (see page 12), which includes an appointed Safety Officer in conjunction with IRB approval and study launch.

IV. Research Methods

A. Outcome Measure(s):

Primary Aim 1:

Feasibility

- Protocol Implementation: recruitment, enrollment, randomization, and dropout rates

- Acceptability: *Adherence* to medication: Self-report by questionnaire, pill counts and urine amphetamine testing | *Tolerability to medication*: Self-report by questionnaire assessing effects, side effects, barriers to adherence, and standardized assessment of possible adverse effects by study staff

Secondary Aim 2:

- Weight, BMI

Secondary Aim 3:

- Manual blood pressure
- Fasting lipid panel: Total cholesterol, HDL, non-HDL, LDL, Triglycerides
- Alanine aminotransferase (ALT) as a surrogate for non-alcoholic fatty liver disease improvement
- Hemoglobin A1c (HbA1c)
- Dietary intake
- Resting metabolic rate
- Body composition and Bone density
- Eating behaviors
- Physical activity
- Quality of Life

B. Description of Population to be Enrolled:

Fourteen patients (7/arm) followed in the Children's Hospital Colorado Bariatric Surgery Center who meet inclusion criteria: 12-24yo; s/p SG or RYGB; *and* at 6-12 months post bariatric surgery[a], have either a) not achieved mean expected weight loss based on national standards and still have at least class 1 obesity or b) remain severely obese (≥120% of 95%ile or BMI ≥35kg/m2 for 12-17yo; BMI ≥35kg/m2 for 18-24yo) will be randomized 1:1 to pharmacotherapy + SOC[b] or placebo + SOC in double-blind fashion. Expected weight loss at 6, 9, and 12 months postoperatively will be defined as a ≥26%, ≥28%, and ≥31% decrease in weight, respectively, from preoperative weight (within 1 week of surgery) as was observed in the Teen-LABS study.[7]

Exclusion criteria: absolute contraindication to phentermine or topiramate (i.e. phentermine: history of coronary artery disease, stroke, arrhythmia, congestive heart failure, uncontrolled hypertension), hypersensitivity to sympathomimetic amines, current or recent (within 14 days) use of monoamine oxidase inhibitors, glaucoma, or hyperthyroidism; topiramate: hypersensitivity to topiramate, history of nephrolithiasis), concomitant use of phenytoin, carbamazepine, or carbonic anhydrase inhibitors (e.g. zonisamide, acetazolamide, or dichlorphenamide), use of anti-obesity medication within 6 months of screening, initiation of a new medication associated with weight loss or gain within 30 days of screening, hypothalamic obesity, unmanaged (e.g. without medications and/or psychotherapy) clinically significant (determined by a mental health professional using diagnostic instruments and/or clinical interview) depression or anxiety, history of any suicidal behavior within 30 days of screening or any suicidal ideation with either some intent to act or with intent and a specific plan within 30 days of screening, history of severe psychiatric disorders (i.e. schizophrenia), severe hepatic impairment (ALT >10x upper limit of normal or known synthetic liver dysfunction), moderate or severe renal impairment (GFR <30mL/min/1.73m^2), inability to meet minimum nutrition requirements, current pregnancy/plans to become pregnant for 16 weeks from study drug start date, and any females without a long acting reversible contraceptive (LARC) who do not commit to using 2 forms of birth control. (Of note, the vast majority of female patients undergoing surgery have a LARC placed intra-operatively, significantly reducing pregnancy risk during the trial). Patients on medications for hypertension, dyslipidemia, depression, and anxiety should be on these at a stable dose for ≥4 weeks prior to study enrollment, and on contraception for ≥7 days prior to study enrollment.

- Maximum number of subjects (patients + parent/guardian/LAR counted separately) needed to consent at all sites: 60
- Maximum number of local subjects (patients + parent/guardian/LAR counted separately) that will be consented, including screen failures and withdrawals: 60
- Number of local subjects (patients + parent/guardian/LAR counted separately) necessary to collect sufficient data to answer the research question: 20

Recruitment and Informed Consent/Assent Plan:

The PI and/or professional research assistant (PRA) will review the charts of bariatric surgery patients prior to their projected Screening Visit (6, 9, or 12 months postoperatively) to assess the percent weight loss trajectory over the preceding postoperative visits to identify those who have not achieved expected weight loss and/or whose baseline BMI was so high that even if they were to achieve expected weight loss, they would continue to have severe obesity. Chart review for evidence of any exclusion criteria will also be performed. For patients who don't have any exclusion criteria by chart review and attend the postoperative clinical visit 3 months prior to their projected Screening Visit, the PI/PRA will present them the Recruitment Flyer either in person, via secure video call, via research MyChart message in the Epic electronic medical record, or by telephone with the Recruitment Flyer emailed. For those who express interest, the study team will at the same time complete the Pre-screening Consent Script requesting permission to contact the family within the week before their Screening Visit with a reminder to fast, if not already done clinically. On the day of the Screening Visit, the PI/PRA will review the measured weight/height to confirm whether or not weight/BMI inclusion criteria are met. If weight/BMI inclusion criteria are met, the PI/PRA will approach the individual and parent/guardian/LAR/proxy during that visit to discuss eligibility, complete the inclusion/exclusion criteria form, obtain consent/assent if the patient/parent qualify and are interested, and collect Enrollment Visit measures.

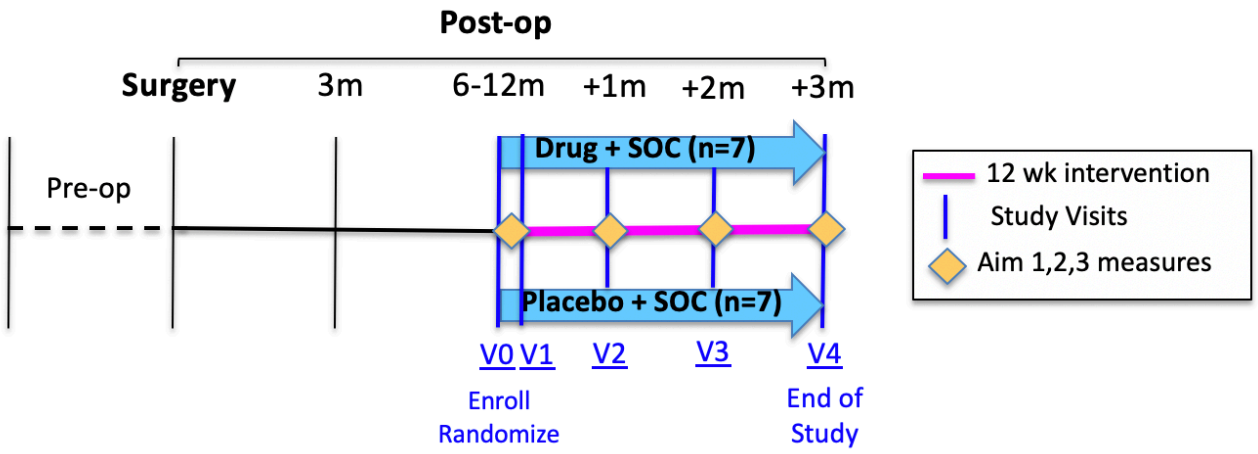
When a participant chooses to take the consent home first to read it and/or to reduce in-person time on campus, the study team may use an eConsent process. In either situation, the eConsent process could be completed in advance of the Screening/Enrollment Visit, with enrollment contingent on results of the screening bloodwork and urine pregnancy test for females. A link to the eConsent will be emailed to the participant in advance of the informed consent discussion using REDCap's survey distribution tool. The eConsent form is designed to allow the participant to navigate forward and backward through the entire form and to access the form at a later time if desired. As this research is FDA-regulated study, an impartial witness will also participate in the informed consent discussion. This witness will either be a family member of the participant's choosing, or a clinician, researcher, or PRA who is not part of the study team. The discussion will begin with identification of who is participating. During the informed consent discussion, the potential participant's questions will be answered and at the end, the participant will verbally confirm they agree to be in the study. Because there can only be one signature ("certifier") for each REDCap eConsent form, there are separate REDCap eConsent forms for the parent/guardian/LAR/proxy, adolescent/young adult, witness, and researcher. The eConsent gives subjects the option to download a copy of the signed form. If a participant refuses or is unable to eConsent but is still interested in participating, a physical consent will be collected by the study team at the next in-person visit to the bariatric surgery center.

Similarly, an eAssent process may be used when a participant (12 years old without intellectual disability OR those 12-24 years old with intellectual disability who have decisional capacity determined using the COMIRB-preferred method) chooses to take the assent home first to read it and/or to reduce in-person time on campus. In either situation, the eAssent process could be completed in advance of the Screening/Enrollment Visit, with enrollment contingent on results of the screening bloodwork and urine pregnancy test for females. A link to the eAssent will be emailed to

the participant in advance of the informed assent discussion using REDCap's survey distribution tool. The eAssent form is designed to allow the participant to navigate forward and backward through the entire form and to access the form at a later time if desired. During the informed assent discussion, the potential participant's questions will be answered and at the end, the participant will verbally confirm they agree to be in the study. Because there can only be one signature ("certifier") for each REDCap eAssent form, there are separate REDCap eAonsent forms for the adolescent/young adult and the researcher presenting the form. The eAssent gives subjects the option to download a copy of the signed form. If a participant refuses or is unable to eAssent but is still interested in participating, a physical assent will be collected by the study team at the next in-person visit to the bariatric surgery center.

C. Study Design and Research Methods

Figure 1. Study Design



The pharmacotherapy group will receive oral phentermine and immediate release topiramate in combination, up-titrated to goal doses of 16mg and 100mg, respectively over 4 weeks*, then maintained at this dose for 8 additional weeks. Topiramate is gradually down-titrated during weeks 13 and 14 to prevent possible discontinuation symptoms.

Dosing Schedule[†,§]

Uptitration:

- Week 1: 4mg phentermine + 25mg immediate release topiramate
- Week 2: 8mg phentermine + 50mg immediate release topiramate
- Week 3: 12mg phentermine + 75mg immediate release topiramate

Goal Dose:

- Weeks 4-12: 16mg phentermine + 100mg immediate release topiramate

Discontinuation (at study Visit 4):

- Week 13: Discontinue Phentermine + Decrease topiramate to 50mg
- Week 14: Decrease topiramate to 25mg for 7 days, then discontinue

(*) Participants who do not tolerate goal doses will be maintained at the highest tolerated dose.
(§) Per existing literature[34] and discussion with pharmacy, participants with moderate hepatic impairment (ALT >3x ULN but <10x ULN on two consecutive measures outside of acute illness, and no evidence of hepatic synthetic dysfunction), will follow the same dosing schedule, with doses reduced as needed based on side effects (See Procedure for Study Drug Dose Reduction/Discontinuation).

(†) All topiramate and phentermine doses will be taken once daily in the morning. Per detailed discussion with pharmacy, once daily dosing of 100mg per day immediate release topiramate is expected to be effective and safe in adolescents, and thus does not require BID dosing.

We chose to intervene at 6-12 months postoperatively because the first year after surgery represents the most rapid phase of weight loss, and interventions that can prolong this most rapid phase may result in improved long-term weight loss outcomes. We are not intervening earlier because there is a gradual dietary progression followed through the first 3 months after surgery and we want participants to be following this stable "lifelong nutrition plan" for at least 3 months before introducing medications that can further alter hunger and satiety.

Standard of care will be delivered throughout the study via the Children's Colorado Bariatric Surgery Clinic's multidisciplinary team, which targets nutrition, physical activity, and self-monitoring. This includes routine in-person clinic visits at 6, 9, and 12 months postoperatively.

Concomitant Medications

Background concomitant medications may be adjusted during the treatment period. Any modifications will be recorded at each study visit within the Concomitant Medication Form. Anti-hypertensives may be adjusted during the treatment period by the study team. In our experience, some patients who have significant weight loss on phentermine/topiramate, may have a decrease in blood pressure, necessitating a reduction in anti-hypertensive medication dose. Psychiatric medications may be altered by the participant's primary psychiatric prescriber.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

1) Study medications

Overall, we contend that for adolescents and young adults who have undergone the most effective and durable treatment available (bariatric surgery) for severe obesity, and *remain* at high risk for future obesity-related morbidity and premature mortality, the potential benefits of a 12-week trial of phentermine + topiramate outweigh the potential risks.

Phentermine and immediate release topiramate are already being empirically used off label in pediatric weight management programs as an adjunctive tool for weight loss when lifestyle-based interventions +/- bariatric surgery have not resulted in acceptable weight loss or cardiometabolic risk reduction. We are proposing a systematic way to begin to study this empiric use among adolescents and young adults following bariatric surgery. In all existing trials registered on clinicaltrials.gov using phentermine, topiramate, or the combination of the two for the treatment of obesity in children and adolescents, individuals with prior bariatric surgery have been specifically excluded.

The FDA recommends that obesity pharmacotherapy interventions last at least 1 year in duration. However, for a pilot study with a primary aim of feasibility and acceptability in a novel setting, 12 weeks may be considered reasonable.

Phentermine (Justification/Rationale)

1) Phentermine alone is FDA approved as an adjunct to behaviorally based interventions for the short-term treatment of obesity in patients 17 or older with a BMI ≥30kg/m2 or ≥27kg/m2 plus an obesity-related comorbidity. The present study proposes to use the lowest dose formulation commercially available (8mg scored tablet available as trade name Lomaira[35]) for maximal flexibility in uptitration and dose adjustment based on possible side effects.

2) Ryder et al.'s 2017 retrospective review of phentermine's effectiveness and side effect profile in a cohort of 25 obese adolescents who had not undergone bariatric surgery at the University of Minnesota's Pediatric Weight Management Clinic is the only contemporary published study of phentermine in obese adolescents.[26] The authors compared adolescents who received phentermine (15mg/day) + SOC to adolescents who received SOC alone, matched on age and BMI. The phentermine + SOC group vs. SOC alone achieved a greater percent BMI reduction at 1, 3, and 6 months, with no difference in systolic or diastolic blood pressure between the groups. Heart rate was statistically significantly higher in the phentermine group at 3 months, but not at 1 or 6 months after phentermine initiation.
3) Within pediatrics, there is a much larger body of literature examining the use of FDA-approved stimulant medications for first-line treatment of attention deficit hyperactivity disorder (ADHD).[36,37] Adderall is approved for use in children as young as 3 years of age and methylphenidate is approved in children 6 and older. Guidelines do not recommend any differential treatment for children/adolescents with overweight or obesity. We argue that the use of phentermine for weight loss poses no greater expected risk in the target population than that of an overweight/obese child or adolescent receiving stimulants for ADHD. And, that the same precautions applied to children and adolescents for whom an ADHD stimulant is considered (i.e. patient selection and monitoring) can be equally applied to those who receive phentermine for weight loss.
4) The proposed period of drug exposure for this initial pilot study is limited, and consistent with the Pediatric Endocrine Society's guidelines for an initial trial of weight loss medication.[38]
5) While the target age range for the proposed study is somewhat broad (12-24 years old), the mean age of our bariatric surgery clinic population is 16 years. Phentermine *is* FDA-approved for short-term use (12-weeks or fewer) in individuals 17 years or above.
6) Obesity-associated cardiovascular risk can be reduced with even modest weight loss.[39] This risk reduction is balanced with the possible increased cardiovascular risk associated with use of phentermine.
7) Phentermine is contraindicated in pregnancy. All female bariatric surgery candidates routinely undergo contraceptive counseling preoperatively with a gynecologist. The vast majority of females have a long acting reversible contraceptive (LARC) placed prior to or at the time of surgery. Those who do not must be on two forms of birth control. Additionally, a urine pregnancy test will be obtained at enrollment and each study visit.
8) The Children's Colorado Bariatric Surgery Center is medically supervised by Drs. Matt Haemer (Nutrition), Megan Kelsey (Endocrinology), Shikha Sundaram (Gastroenterology/Liver), and Sonali Patel (Cardiology). The behavioral health specialist within the Bariatric Surgery Center is pediatric clinical psychologist Dr. Richard Boles. In the event of an adverse cardiovascular side effect associated with phentermine use as part of this study, we have the ability to obtain prompt clinical evaluation by a Lifestyle Medicine cardiologist. Similarly, in the event of an adverse side effect related to mood, we have the ability to arrange a prompt mental health evaluation with a Lifestyle Medicine clinical psychologist. The PI and primary mentor/bariatric clinic medical director Megan Kelsey will manage any other physical medical side effects that may arise.

***Phentermine Risk Mitigation Strategy (also see Table 2)*:**

Steps to mitigate potential risks related to phentermine in this study include exclusion of individuals with any absolute contraindication to phentermine (as defined by the FDA label), drug interaction check prior to initiation, review of baseline kidney function, ALT, urine pregnancy tests at enrollment and every study visit, baseline echocardiogram per standard of care in individuals with hypertension or severe obstructive sleep apnea + known poor adherence to positive pressure therapy who have not had one in the previous 6 months, documented commitment from female participants who don't have a LARC, to use two forms of

birth control, phone calls at 1, 2, and 3 weeks after study pill initiation and weekly during any additional titration during the protocol to assess for adverse effects, and evaluation of heart rate, blood pressure, comprehensive review of systems and a physical exam performed by a study physician at enrollment and every study visit.

Topiramate

1) The present study proposes to use generic immediate release topiramate tablets.
2) Topiramate alone is not FDA-approved to treat obesity at any age.
3) In pediatrics, there is extensive experience using topiramate in children as young as 2 years old for seizure disorders with dosing frequently between 200-400mg/day, compared to the 100mg per day maximal dose proposed in this study. Topiramate is also FDA-approved for migraine prophylaxis in adolescents 12 years and older at a recommended dose of 100mg/day.
4) Topiramate is a known teratogen. All female bariatric surgery candidates routinely undergo contraceptive counseling preoperatively with a gynecologist. The vast majority of females have a long acting reversible contraceptive (LARC) placed prior to or at the time of surgery.
5) Potential adverse effects of topiramate include paresthesias, fatigue, dysgeusia, psychomotor slowing, nephrolithiasis, anhidrosis/hypohidrosis, trouble with memory/concentration/word finding, and change in mood.[40] In the event of an adverse side effect related to mood, we have the ability to arrange a prompt mental health evaluation with clinical psychologist Dr. Boles. The PI and primary mentor/bariatric clinic medical director Megan Kelsey will manage any physical medical side effects that may arise.

***Topiramate Risk Mitigation Strategy (also see Table 2)*:**

Although the weight loss effect of topiramate is dose-dependent up to ~200mg/day,[41] adverse cognitive side effects are more commonly seen at doses over 100mg/day, and also when topiramate is not gradually uptitrated.[42,43] Thus, the maximum dose chosen for this study is 100mg/day using a gradual up-titration of 25mg per week. Additional steps to mitigate potential risks related to topiramate include exclusion of individuals with any absolute contraindication to topiramate (as defined by the FDA label), drug interaction check prior to initiation, review of baseline bicarbonate, kidney function, ALT, documented commitment from female participants who don't have a LARC to use two forms of birth control, urine pregnancy test at enrollment and every study visit, phone call at 1, 2, and 3 weeks after study pill initiation and weekly during any additional titration during the protocol to assess for adverse effects, and comprehensive review of systems and a physical exam performed by a physician at enrollment and every study visit.

Phentermine + Topiramate

1) Extended release topiramate in combination with phentermine (trade name Qsymia) is FDA approved for chronic weight management in adults 18 years and older with a BMI ≥30kg/m2 or ≥27kg/m2 plus an obesity-related comorbidity.
2) Phentermine and Topiramate were paired to theoretically reduce/neutralize the side effects seen with either medication alone, and additively or synergistically impact weight loss.
3) The longest published (2 year) weight outcomes and safety data from phentermine + controlled release (CR) topiramate in adults demonstrate a -10.5%, -9.3%, and -1.8% change in weight from baseline in the phentermine 15mg/topiramate CR 92mg, phentermine 7.5mg/topiramate CR 46mg, and placebo groups respectively.[44] Subjects in both phentermine/topiramate CR groups demonstrated greater cardiometabolic benefits than the placebo group including greater reductions in triglycerides, greater increases in HDL cholesterol, greater improvements in insulin sensitivity, and the need for fewer

antihypertensive, lipid lowering, and diabetic medications. The 15mg/96mg group demonstrated the lowest risk of progression to type 2 diabetes (76% risk reduction vs. 54% for the 7.5mg/46mg group). Anxiety-related adverse events were lowest in the placebo group and highest in the 15mg/96mg group, but depression-related adverse events were similar between placebo and 15mg/96mg groups. There were no serious cardiac, metabolic, or mental health-related adverse events and no deaths in this extension study.

4) There is no data to suggest that there are unique or increased risks associated with the combination of these two medications, compared to the individual risks of each medication alone.

Table 2. Possible adverse reactions of medications and mitigation plan

Phentermine	**Plan to Mitigate Risk** (Details of the data and safety monitoring plan (DSMP) can be found in the next section of the protocol)
Common[35]	
Restlessness, Irritability, Anxiety	DSMP; Mood assessment preoperatively, at enrollment, and at every study visit; Prompt mental health evaluation/management available on site
Dizziness	DSMP
Insomnia	Will be taken in the morning to prevent disruption of sleep
Dry mouth, dysgeusia, diarrhea, constipation	DSMP
Increased heart rate and/or blood pressure	We are starting with the lowest possible dose available and increasing to a maximum dose comparable to the highest Qsymia dose (15mg) evaluated, and less than 50% of the highest available dose (37.5mg); DSMP (including blood pressure, heart rate, review of systems, and physical exams at every study visit). Individuals who meet inclusion criteria and have well-controlled hypertension, must have a cardiac echocardiogram reviewed by Cardiology within the prior 6 months before the initiation of phentermine, consistent with the Children's Colorado Lifestyle Medicine clinical protocol.
Rare, but Serious	
Primary pulmonary hypertension, Regurgitant cardiac valvular disease	DSMP (including blood pressure, heart rate, review of systems, and physical exams at every study visit). Individuals who meet inclusion criteria and have well-controlled hypertension, must have a cardiac echocardiogram reviewed by Cardiology within the prior 6 months before the initiation of phentermine, consistent with the Children's Colorado Lifestyle Medicine clinical protocol.
Tolerance, Diversion potential (without clear evidence of withdrawal)[45]	Short duration of intervention may reduce risk of tolerance.
Serotonin Syndrome	Drug interaction check; DSMP

Hypoglycemia (in the presence of glucose lowering drugs)	Patients with diabetes are being excluded from this study, so the chance that a participant is on a glucose-lowering agent is very low. Drug interaction check; DSMP; Availability of pediatric endocrinologist to adjust medications as needed to maintain normoglycemia
Psychosis	DSMP; Mood assessment preoperatively, at enrollment, and at every study visit. Prompt mental health evaluation/management available on site
Pregnancy Risk Factor Category: X (Contraindicated in pregnancy)	Pregnancy tests at every study visit Requirement for females to either have a LARC (majority) or documented commitment to use 2 forms of birth control
Topiramate	**Plan to Mitigate Risk** (Details of the data and safety monitoring plan (DSMP) can be found in the next section of the protocol)
Common (≥5% more frequent than placebo or low-dose Topamax as monotherapy) in controlled, epilepsy clinical trials[40]	
Paresthesia	DSMP
Anorexia, Weight Loss	Desired effect
Fatigue, Somnolence	Pairing with a stimulant
Dizziness	DSMP
Psychomotor slowing, Difficulty with memory, concentration, attention, other cognitive problems, Confusion	Gradual (4-week) uptitration to 100mg max dose[42,43]; DSMP
Mood problems	DSMP; Mood assessment preoperatively, at enrollment, and at every study visit. Prompt mental health evaluation/management available on site
Fever, Infection	DSMP
Flushing	DSMP
Common (≥5% more frequent than placebo) in controlled, migraine clinical trials[40]	
Paresthesia	DSMP
Taste perversion	DSMP
Common (≥5% more frequent than placebo) in the only RCT for weight loss in severely obese adolescents[22]	
Paresthesia	DSMP
Amenorrhea	Monitoring plan (not unexpected for our females with LARCs)
Concussion	DSMP
Dizziness	DSMP
Dysgeusia	DSMP
Tendon Injury	DSMP
Fever due to pharyngitis	DSMP
Nausea, Vomiting, Diarrhea	DSMP
Rare, but Serious[40]	

Acute myopia, Secondary angle closure glaucoma	DSMP
Oligohidrosis, Hyperthermia	DSMP (including temperature at every study visit)
Metabolic acidosis	Bicarbonate at enrollment, visit 2, and visit 4
Suicidal ideation/attempt	DSMP with assessment at every study visit
Fetal toxicity (Pregnancy Risk Factor Category D- positive evidence of risk)	Pregnancy tests at enrollment and every study visit Requirement for females to either have a LARC (majority) or documented commitment to use 2 forms of birth control
Withdrawal symptoms	Gradual discontinuation at the end of the study
Hyperammonemia and encephalopathy	Drug interaction check; DSMP
Kidney stones	BMP at enrollment, visit 2, and visit 4; Drug interaction check; DSMP
Topiramate-Ethanol interaction (potential to cause increased CNS depression)	Counseling about alcohol avoidance, and specific language about this risk in the consent/assent

Methods for systematically assessing changes in mood, suicidality, and cognition.

Mood:

Changes in mood will be systematically screened for using the Center for Epidemiologic Studies Depression Scale (CES-D). This is a 20-item self-report questionnaire that covers areas including depressed mood, feelings of guilt/worthlessness, helplessness, psychomotor retardation, loss of appetite and sleep disturbance over the previous week.[46] This instrument has yielded adequate internal reliability that is robust to age, clinical vs. nonclinical setting, and risk of bias.[47] The original version of the measure is appropriate for individuals 12 years of age and older. The CES-D is routinely administered to individuals receiving care at the Children's Colorado Bariatric Surgery Center at every follow-up pre-operative and post-operative clinic appointment.

The proposed study will additionally administer the CES-D at all study visits not aligned with a clinical visit and will be scored by the PI or professional research assistant. A CES-D score <20 indicates no to mild depressive symptoms. And a CES-D score ≥20 indicates elevated depressive symptoms. This is based on a metaregression that supported higher cut points having better diagnostic accuracy.[47]

Any study participant who a) newly scores ≥20 at any time during the study or b) has a baseline score of ≥20 and who demonstrates any absolute increase in this score, compared to previous measures, will be discussed within 72 hours with the Bariatric Surgery Center's pediatric clinical psychologist to consider a more comprehensive follow-up clinical interview. The clinical interview will guide additional management recommendations, which may include psychoeducation on depression, a referral to therapy, a referral to psychiatry, and/or a reduction of study medication.

Weekly phone calls after study drug start also include a question about depressed mood over the previous week and if present, ask participants to rank this as mild, moderate, or severe. If depressed mood is present and moderate or severe, the PI will discuss follow-up steps with the participant and caregiver within 24 hours of identification after consulting with study psychologist Dr. Boles; If mild and new, the PI will discuss with study psychologist Dr. Boles within 1 week of identification.

Suicidality:

Suicidal ideation and behavior will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS)[48,49] at enrollment and each study visit. Any participant who reports suicidal behavior or suicidal ideation with some intent to act (Type 4) or with intent and a specific plan (Type 5) during the study will be discussed with the PI during *that visit*. The PI will determine whether the participant should be escorted to the Children's Hospital Colorado Emergency Department for an emergent mental health evaluation or will be discussed within 72 hours with the Bariatric Surgery Center's pediatric clinical psychologist for additional assessment/treatment recommendations.

For both mood and suicidality, if a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the patient, at the discretion of the mental health provider, should be continued in the trial on randomized therapy.

Cognition:

At 1, 2, and 3 weeks after study medication initiation, weekly during any additional titration during the protocol, and at each study visit, participants will be asked to complete a self-report checklist of possible adverse effects that have reported associations with the active study drugs, which include changes in memory, attention/concentration, word-finding/language, and overall academic/job performance, along with the perceived severity of each (mild, moderate, or severe).

Severe cognitive difficulty, which is a drug dose reduction/discontinuation criteria, will be defined as self-report of a "severe" change in memory, attention/concentration, or word finding/language that the participant believes is significantly impacting academic or job performance and that is not otherwise explained by non-study medication related factors.

Of note, in the one randomized controlled trial of topiramate for weight loss among severely obese adolescents[50] (24-week intervention of 75mg/day topiramate vs. placebo), Fox et al. found no significant differences between topiramate and placebo groups on subscales of the Cambridge Neuropsychological Test Automated Battery (CANTAB) or Behavioral Rating Inventory of Executive Function-Self Report (BRIEF-SR), and on the Connors Continuous Performance Test II (CPT II), the only significant finding was faster reaction time in the topiramate group compared to the placebo group.

2) **Data and Safety Monitoring Plan (DSMP)**:

Definitions: The PI will use the FDA's/Center for Drug Evaluation and Research's "Guidance for Industry Investigators Safety Reporting Requirements for INDs and BA/BE Studies" document to define the terms: adverse event (AE), suspected adverse reaction, adverse reaction, unexpected, serious, and life-threatening.

1. **Describe who will monitor for unanticipated problems of subjects**: The PI and the professional research assistant (who reports directly to the PI) will primarily monitor for unanticipated events (e.g. breach of confidentiality) and unexpected adverse events. Additionally, a Safety Officer will be appointed to this study to objectively oversee unanticipated problems. We define an unexpected AE (21 CFR 312.32(a)) as an adverse event or suspected adverse reaction that is not listed in the FDA-approved label or is not listed at the specificity or severity that has been observed. Unexpected also refers to AEs or suspected adverse reactions that are mentioned as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with phentermine or

immediate release topiramate. All unanticipated problems will be reported to COMIRB within 5 days of the occurrence.

2. **Will the PI be responsible for ongoing review of local adverse events and serious adverse events? (physical or psychological harm to subjects)**: Yes. The PI will be responsible for ongoing review of local AEs and serious adverse events (SAE).

   We define an AE **(21 CFR 312.32(a))** as any untoward medical occurrence associated with the use of the study drugs, whether or not considered drug related. This may be any unfavorable or unintended sign (e.g. abnormal lab), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.

   We define an SAE **(21 CFR 312.32(a))** as an adverse event or suspected adverse reaction that results in any of the following: death, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other events could be considered serious if they may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed outcomes (e.g. allergic bronchospasm requiring intensive treatment).

   Specifically, an AE form will be completed for any complaints/AEs that are participant-reported or elicited during the study. And an SAE report will be generated if criteria are met. AEs will be identified with the following procedures:

   -Comprehensive review of systems at every study visit (to capture possible AEs not reported previously)
   -Physical exam at every study visit (e.g. new murmurs, rubs, or gallops, new increased work of breathing, new pulmonary edema, new peripheral edema);
   -Vitals at every study visit (e.g. new fever, tachycardia, new elevated blood pressure/hypertension)
   -Phone call 1, 2, and 3 weeks after study drug initiation and in-person with a questionnaire at visits 2, 3, and 4 to review known possible side effects of phentermine and topiramate
   -Lab monitoring: basic metabolic panel (to assess for new metabolic acidosis: bicarb < 18 mmol/L); urine pregnancy tests for all females at every visit.
   -Monitoring of mood, suicidality, and cognition per above with validated assessments at enrollment and every study visit (e.g. new or worsened depression, new suicidal ideation/behavior)
   -Between study visits, participants with questions about symptoms will also be encouraged to call the PI directly (voicemail messages are forwarded to the PI's password-protected email)

3. **To what external entities will local adverse events be reported?:** In addition to COMIRB, the PI will report local adverse events to the FDA, according to their safety reporting requirements: https://www.fda.gov/downloads/Drugs/Guidances/UCM227351.pdf). Specifically, the PI will report to the Division of Metabolism and Endocrinology within the FDA's Center for Drug Evaluation and Research, which reviewed the IND application for this study. The PI will report to this Division: 1) Any unexpected fatal or life-threatening suspected adverse reactions no later than 7 calendar days after initial receipt of the information, and 2) Any a) serious, unexpected suspected adverse reactions, b) findings from other clinical/animal/in-vitro studies

that suggest significant human risk, and c) a clinically important increase in the rate of serious suspected adverse reactions no later than 15 calendar days after determining that this information qualifies for reporting.

4. **Will periodic global review of safety/adverse events (serious adverse events and adverse events) occur?**: Yes, reviews will be performed by the PI, and a three-member data and safety monitoring board (DSMB), including a primary Safety Officer.

Reviewer	Expertise	Review Frequency	Written Reports	Report Frequency
PI	Board Certified in Internal Medicine and Pediatrics; Assistant Professor in Pediatrics, Section of Nutrition with specialized training in pediatric anti-obesity pharmacotherapy; Primary author of Children's Hospital Colorado's Lifestyle Medicine clinical protocols for anti-obesity pharmacotherapy.	Monthly	Yes	Within 5 days of any SAE and monthly for all other AEs
Medical/Safety Officer	Endocrinology faculty member with expertise in pediatric clinical trials	Every 3 months	Yes	Every 6 months
Data and Safety Monitoring Board (DSMB)	Safety Officer (above) + 2 additional faculty with clinical and clinical trial expertise in using anti-obesity pharmacotherapy across the age range studied	Every 6 months	Yes	Every 6 months

A three-member Data and Safety Monitoring board, including a primary Safety Officer, who are independent of the study personnel, have been appointed to this study. Like the study staff, they will be blinded to participants' randomized treatment assignments.

The Safety Officer will:
1) Approve criteria for modifying or discontinuing study drugs for individual participants
2) Review data generated by the study, including study safety events (SAEs) every 3 months for the duration of the study.

The three-member Data and Safety Monitoring Board will:
1) Evaluate the progress of the trial, including periodic assessments of recruitment, screen failures, enrollment, and retention
2) Report on the safety and progress of the study every 6 months
3) Consider the impact of new or relevant information such as scientific or therapeutic developments (provided by the PI) that may have an impact on the safety or scientific integrity of the study.
4) Determine whether the overall integrity and conduct of the study remain acceptable

5) Based on these responsibilities/functions, the DSMB will act in an advisory capacity and recommend one of the following actions to the PI (Dr. Moore) every 6 months:

A) Continue the study according to the protocol and any related amendments.
B) Modify the study protocol. Modifications may include, but are not limited to, changes in inclusion/exclusion criteria, frequency/mechanism of safety monitoring, alterations in study procedures, and changes in duration of observation and follow-up.
C) Discontinue the study (with provisions for organized discontinuation in accordance with safe medical practice).

5. **Will any formal interim analysis be performed?:** Interim assessments of feasibility, acceptability, and safety per above will be performed, but there will be no formal interim analysis for this 12-month study.

6. **Are there defined participant discontinuation criteria?**: There are no *participant* discontinuation criteria. However, there are defined *drug* discontinuation criteria as follows:

a) Development of an anaphylactic allergic reaction, pulmonary hypertension, evidence of new valvular heart disease, uncontrolled systemic hypertension, new arrhythmia (including persistent tachycardia), severe anxiety unresponsive to dose decrease, psychiatric disorder that cannot be adequately treated with psycho- and/or pharmacotherapy at the discretion of the study's clinical psychologist, serotonin syndrome, or pregnancy during the pharmacotherapy intervention will lead to discontinuation of phentermine.
b) Development of an anaphylactic allergic reaction, nephrolithiasis, severe, persistent cognitive difficulties, psychiatric disorder that cannot be adequately treated with psycho- and/or pharmacotherapy at the discretion of the study's clinical psychologist, new acute myopia or secondary angle closure glaucoma, severe metabolic acidosis, hyperammonemia with encephalopathy, or pregnancy during the pharmacotherapy intervention will lead to discontinuation of topiramate.
c) If one medication is stopped secondary to the criteria above, the participant, if in agreement, will be continued on the other medication as monotherapy.
d) With consent, participants for whom one or both medications are stopped will continue to be followed according to the proposed study timeline.

7. **How will the PI/research team determine if an adverse event (AE) is related to either of the study drugs?**

Relatedness will be defined according to the National Institutes of Health National Institute on Aging Data Safety and Monitoring Plan Toolkit template (https://www.nia.nih.gov/research/dgcg/clinical-research-study-investigators-toolbox/data-and-safety-monitoring) as follows:

- **Definitely Related**: The AE is clearly related to the study drug i.e. an event that follows a reasonable temporal sequence from administration, follows a known or expected response pattern to the drug (intervention), that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- **Possibly Related**: An AE that follows a reasonable temporal sequence from administration of the study drug (intervention), follows a known or expected response pattern to the intervention, but that could readily have been produced by a number of other factors.
- **Not Related**: The AE is clearly not related to the drug i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the

onset of the event and the study intervention and/or causal relationship is considered biologically implausible.

8. **Are there <u>overall protocol/study</u> stopping rules?**: Any life-threatening adverse drug experience (other than an anaphylactic reaction), or death of any patient, determined to be associated with either study drug.

2) Data collection tools

- <u>Primary Aim 1</u>: *Questionnaires*. We believe these represent a minimal risk to participants. The only potential study-related burden for these tools is the time required to complete them, which we have factored into our determination for incentives. These are essential to adequately address Aim 1.
- <u>Secondary Aim 2</u>: *Weight*. Measuring weight is a standardized part of every primary care and most specialty care medical visits throughout the lifespan. We believe this represents minimal risk to participants. In the perioperative setting for adolescent bariatric surgery, patients have the option to decline being informed of their weight if this increases stress, anxiety, or other emotional discomfort. Change in weight is the central physiologic measure of interest for this study to assess initial efficacy of the medication vs. placebo group.
- <u>Secondary Aim 3</u>: *Venipuncture for bloodwork, manual blood pressure, DEXA, indirect calorimetry, and questionnaires*.

    - We believe the manual blood pressure and questionnaires (routine components of most medical visits) both represent minimal risk.
    - For routine clinical care, all bariatric surgery patients undergo venipuncture for lab monitoring at 6, 9, and 12 months postoperatively. Study-specific labs will be added to these routine blood draws. The additional study-specific blood tests are needed to detect any changes (between intervention and control groups) in lipids, ALT, and/or hemoglobin A1c as a result of the medication. A pediatric CTRC research nurse will be scheduled to obtain labs at study visit 2, and at Enrollment and study visit 4 if not obtained by the clinical lab. The risks of a venipuncture include pain at the puncture site, possible bruising and edema around the puncture site, less commonly dizziness/presycope/syncope, and rarely infection.
    - DEXA scans will be performed at Visits 1 and 4 (of the total body, hip, and spine). The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect participants. The potential risks related to the additive effect of radiation over a lifetime is included in the assent/consent.
    - Indirect calorimetry will be performed at Visits 1 and 4, and uses a canopy method. Potential risks include a feeling of claustrophobia, which are included in the assent/consent.

- *Optional banking of specimens for future research*: This is an optional procedure. For those who assent/consent, blood and urine samples will be collected at Enrollment, Visit 2, and Visit 4. DNA will be isolated from a portion of the whole blood collected at the Enrollment visit only in Dr. Christina Aquilante's lab at the University of Colorado Skaggs School of Pharmacy after all samples are collected. Prior to DNA isolation, the samples will be stored at -80°C. The isolated DNA will be stored at -20°C. All other blood and urine specimen, will be processed, fractionated (as appropriate), aliquoted and stored at -80°C.

3) Research-specific study visits

- Patients in the Bariatric Surgery program at Children's Colorado have several standard postoperative visits in the first year after surgery including at 3, 6, 9, and 12 months. The screening/enrollment visit will take place concurrent with the 6, 9, or 12 month postop visit whenever possible. For those with a screening/enrollment visit at 6 or 9 months, Visit 4 will typically take place concurrent with the 9 or 12 month postop visit, respectively. For those with a screening/enrollment visit at 12 months, Visit 4 will typically not be concurrent with a regularly scheduled postop visit.
- There will be a screening visit at 6, 9, or 12 months postoperatively. Eligible participants will be consented at this visit, and will be asked to come to campus ~1 week later for study visit 1. Enrollment and Visit 1 cannot be combined because it is unrealistic to screen, consent, randomize, obtain study drug, and complete additional measures after an already lengthy clinical appointment.
- The Children's Hospital Colorado Lifestyle Medicine weight management program's clinical protocols for anti-obesity pharmacotherapy require monthly clinic visits for the first three months after initiation for monitoring of effects and side effects. The proposed study protocol follows this standard.

Data Collection Tools (See Table 3. below for Schedule of Measures)

a) Sociodemographic characteristics: age, sex, race/ethnicity, insurance, highest level of primary caregiver's education, household size and income, government-based assistance, and presence/absence of food insecurity will be obtained from the medical record and the Demographics Form.
b) Feasibility of protocol implementation: rates of recruitment, enrollment, randomization, and dropout
c) Study medication adherence & tolerability: assessed by 1) Questionnaire: description/dose/start date of medications, missed doses, and checklists of: effects, adverse effects, and evidence-based barriers to adherence[51,52]; 2) Pill counts; 3) Urine amphetamine screen
d) Self-reported changes to all **non-study** medications: name/dose, interim changes
e) Patient/family satisfaction questionnaire will assess: reasons for participation, experience during study visits, satisfaction with the effect of the study medication/placebo, ease of communication with study staff, and time burden/inconvenience
f) Biological outcome and safety measures: Weight, height, heart rate (HR), BP, basic metabolic panel, lipids, ALT, HbA1c, and pregnancy test
g) Optional Biobanking: Gold top (serum-3.5mL blood), Purple top (EDTA-4mL whole blood), Green top (heparinized plasma-4mL blood), and Urine (volume that remains after the urine pregnancy test for females and a separate urine collection for males) will be collected with participant assent/consent for future research questions.
h) 3-day dietary record: Participants will complete a dietary record on 3 consecutive days (2 weekday, 1 weekend day) based on standardized protocols for dietary assessment.[53]
i) Previous Day Physical Activity Recall (PDPAR): validated and reliable questionnaire that detects changes in physical activity behavior.[54]
j) Impact of Weight On Quality of Life-Kids & Lite (IWQOL-Kids & Lite): Kids: 27-item self (validated up to age 19) + parent-report assesses the impact of weight on: physical comfort, body esteem, social life, and family relations, and has known minimally clinically important difference scores and high test-retest reliability.[55,56] Adult (≥ age 20): 31-item validated tool that assesses overall, physical, self-esteem, sexual, public distress, and work.[57]
k) PedsQL: a validated measure of overall health-related quality of life
l) Center for Epidemiologic Studies Depression Scale (CES-D): a 20-item self-report questionnaire that covers areas including depressed mood, feelings of guilt/worthlessness, helplessness, psychomotor retardation, loss of appetite and sleep disturbance over the previous week. It has good internal reliability that is robust to age, clinical vs. nonclinical setting, and risk of bias.[47]

m) Columbia Suicide Severity Rating Scale (C-SSRS): a validated, clinician-administered assessment of suicidal ideation and behavior among adolescents and adults.[48]
n) Resting Metabolic Rate: using a canopy system
o) DEXA-3 site: total body scan to measure body composition; hip and spine scans to determine bone density, all using standardized protocols
p) Visual Analogue Appetite Ratings (VAS): self-reported assessment of hunger/satiety before and after meals and snacks
q) Three Factor Eating Questionnaire (TFEQ): validated questionnaire that measures cognitive restraint, uncontrolled eating, and emotional eating[58]
r) Eating in the Absence of Hunger (EAH) parent-report: validated measure that describes eating when not hungry[59]

Route of Data Collection: To reduce in-person time on campus for participants, components of Study Visits 1-4 will be collected remotely (designated by superscript "R" in Table 3 below) either via secure video call or telephone call (with questionnaires emailed) in the participant's/guardian's preferred language within the same week and ideally on the same day as the study visit. These measures will be conducted remotely unless it is not possible or places an undue burden on the participant to do so (e.g. participant does not have a reliable internet connection or has a limited phone data plan that incurs significant charges). Pill count will require a video connection. All other measures require in-person collection/administration to appropriately collect outcome/safety data.

Table 3. Schedule of Measures

"X"= Study specific **"O"**= Standard of Care #= Bariatric Clinic or CHCO CTRC ‡= + Adult CTRC or CHCO Radiology/CTRC R= can be delivered remotely	**SCREENING/ ENROLLMENT# 6-12 mo post-op**	**STUDY VISIT 1#,‡ ~1wk after Enrollment**	**STUDY VISIT 2# 4wks after Visit 1**	**STUDY VISIT 3# 4 wks after Visit 2**	**STUDY VISIT 4#,‡ 4 wks after Visit 3**
Review of Inclusion/Exclusion criteria	X				
Echocardiogram (ONLY for those with Hypertension or Severe OSA with poor PAP adherence IF not obtained in the prior 6 months)	O				
Demographics Form		X^R			
Feasibility of protocol implementation (e.g. enrollment rates, dropout rates)	X	X	X	X	X
Study medication adherence & tolerability- Study Med Form			X^R	X^R	X^R
Study medication adherence- (pill count)- Study Med Form			X^R	X^R	X^R
Study medication adherence (urine amphetamine screen)		X	X	X	X
Review of all non-study medications (self-report)	X	X^R	X^R	X^R	X^R
Patient/family satisfaction survey					X^R
Weight, Height, Temperature, HR, BP; Review of Systems; Physical exam		X	X	X	X
Urine pregnancy test	X	X	X	X	X
Lipid panel, ALT, HbA1c	X				X
Basic metabolic panel	X		X		X
Optional Biobanking	X		X		X
3-day diet record review		X^R			X^R
Previous Day Physical Activity Recall (PDPAR)		X^R			X^R

IWQOL-Kids (≤19yo)/-Lite (≥ 20yo) & Parent Report		X^R			X^R
PedsQL (general health-related quality of life)		X^R			X^R
CES-D (Depression Screen)	O	X	X	X	X
C-SSRS (Suicide Screen)	X	X	X	X	X
Resting metabolic rate		X			X
DEXA-3 site		X			X
***Clinical Intervention/Translation Core*: Eating behavior questionnaires (VAS, TFEQ, EAH)**		X^R	X^R	X^R	X^R

In addition to the above in-person study visits and designated remote data collection, there are eight standard study phone calls in the protocol:

- Phone Call 1: 1-2 days before the Screening/Enrollment Visit 0 (Reminder to fast)
- Phone Call 2: 1 week before Visit 1 (Phone Call Script 1)
- Phone Call 3: 1 week after Visit 1 (Phone Call Script 2)
- Phone Call 4: 2 weeks after Visit 1 (Phone Call Script 2)
- Phone Call 5: 3 weeks after Visit 1 and 1 week before Visit 2 (Phone Call Scripts 1 & 2)
- Phone Call 6: 1 week before Visit 3 (Phone Call Script 1)
- Phone Call 7: 1 week before Visit 4 (Phone Call Script 1)
- Phone Call 8: 1 week after last dose of study drug (Phone Call Script 2)

If a participant requires additional dose titration during the protocol, the PI will conduct additional weekly phone calls until study medication dosage is stable.

E. Potential Scientific Problems:

Benchmarks for success, pitfalls, and alternatives:

Primarily, we expect this protocol to demonstrate feasibility, which will form the foundation for a larger study of pharmacotherapy as an adjunct to bariatric surgery. Secondarily, we expect to demonstrate short-term efficacy of pharmacotherapy in terms of promoting additional weight loss and improving biological markers.

Pitfalls: The perioperative bariatric surgery process is time-intensive, which may impact a family's decision to enroll/complete a study that requires three to four visits outside of routine clinical care. Each of the 4 study visits will be reimbursed at $100/visit, with an additional possible $50 earned at Visit 4 if pre-defined medication adherence targets are met (total $400-$450). Participants traveling specifically for this research study (i.e. not already traveling for a clinical reason) who live >100 miles away from the Anschutz Medical Campus, will be reimbursed up to $300 for lodging, flight, and/or gas mileage expenses per study visit. Additionally, study medications will be provided at no cost. And, those in the placebo group may benefit relative to those not in the study because of the association between increased medical contacts and improved obesity outcomes. Our inclusion criteria combines two patient subgroups- those who do not achieve adequate weight loss and those who remain severely obese regardless of adequate weight loss. Although response to surgery is different, the ongoing risk for obesity-related morbidity is expected to be similar. Preliminary analysis of initial efficacy measures (Aims 2,3) for these two groups will be conducted to allow for detection of differences. Finally, we recognize that this "12 week" intervention includes 4 weeks of up-titration of medication. Thus, the duration on goal therapeutic doses of 16mg phentermine and 100mg immediate release topiramate is only 9 weeks. This decision was driven by the primary feasibility aim, and reduces participant burden. Depending on the outcome of this study, future studies with primary aims of efficacy and safety could prolong the duration of exposure at the goal doses of medication.

Alternatives: Given our success in using these anti-obesity medications clinically and previous experience and success of the study mentors in clinical trials, we feel confident in our ability to recruit and retain participants. However, if study numbers fall short within the timeframe of the funding, we can recruit older adolescents and young adults within the 18-24 year age range through an established relationship with the adult bariatric surgery program and Anschutz Health and Wellness Center at the University of Colorado. Regardless of the outcomes, the skills I will develop from this study will still be highly applicable to future studies. Specifically, as a PI of an investigation that uses RCT methodology, intervention development and testing, analysis, and dissemination, I would be well positioned to investigate other adjunctive perioperative therapies for severe obesity (e.g. intensive nutritional strategies).

F. Data Analysis Plan:

Sample size justification: Based on recommended practice for pilot studies,[60] the minimum sample size (10 total participants, 5 per arm) is driven by the primary aim of the study and represents a balance between participant availability (patient volume and recruitment timeline), and acceptable precision around feasibility estimates (Aim 1), which will be used for subsequent study planning. It is *not* based on a power calculation for group differences seen in any Aim 2 or 3 measures. To estimate precision around dropout and medication tolerability rates, we used a confidence interval approach with normal approximation of the binomial calculation[60–62]: First, we estimate that a realistic dropout rate is 25%, based on 3 prior anti-obesity medication RCTs conducted in obese adolescents.[22,63,64] A realistic medication tolerability rate (% who do *not* discontinue medication because of adverse effects) is 85%, based on the single RCT of topiramate in adolescents and two larger RCTs of phentermine/topiramate XR in adults.[22,65,66] Dropout: With the minimum of 10 adolescent/young adult participants, if our observed dropout rate is 25%, we can be 68% confident that the enrollment rate estimate is accurate within 13 percentage points (or 90% confident that it is accurate within 20%). With 14 adolescent/young adult participants, if our observed dropout rate is 25%, we can be 68% confident that the enrollment rate estimate is accurate within 11 percentage points (or 90% confident that it is accurate within 18%). Medication tolerability: With 10 adolescent/young adult participants, if our observed medication tolerability rate is 85%, we can be 68% confident that the tolerability estimate is accurate within 9 percentage points (or 90% confident that it is accurate within 16%). With 14 adolescent/young adult participants, if our observed medication tolerability rate is 85%, we can be 68% confident that the tolerability estimate is accurate within 9 percentage points (or 90% confident that it is accurate within 15%). Given possible constraints around enrollment, the level of precision with 10 or 14 adolescents/young adults was deemed **acceptable to achieve protocol refinement for future RCT development.**

Planned analyses*:* Descriptive statistics will characterize the study population. Independent samples t-tests will be performed for continuous variables and chi-square for categorical variables to determine statistically significant differences between experimental and control groups. **Aim 1**: Feasibility of acceptability (adherence, tolerability, and satisfaction) will be descriptively assessed using differences in proportions between experimental and control groups. Feasibility of protocol implementation will be established by determining the proportions (rates) of recruitment, enrollment, randomization, and dropout. **Aims 2,3**: Estimated means and variability of continuous health outcome variables (e.g. % change in weight) and intra- and intersubject variability of repeated measures (e.g. loss of control eating) will be graphically presented and visually compared for experimental vs. control groups, as this aim is not powered to run inferential statistics.

G. Summarize Knowledge to be Gained:

The goal of this study is to establish the feasibility and initial efficacy of two common anti-obesity medications for adolescents who require additional risk reduction following bariatric surgery.

Adolescents with severe obesity who don't achieve optimal weight loss and co-morbidity improvement after bariatric surgery have few evidence-based treatment options to mitigate significant health risks through the remainder of adulthood. This study has the potential for substantial impact regardless of results, given that anti-obesity medications are currently being used in the post bariatric surgery setting without an evidence base. A recent international pediatric obesity webinar (4/2019) with contributors from leading adolescent bariatric surgery centers strongly expressed need and enthusiasm for studying the role of pharmacotherapy after surgery. **Our center's volume, interdisciplinary expertise, and existing IND to study these medications in this setting sets us apart as the best positioned adolescent bariatric surgery center to carry out this initial pilot**, with high potential for a subsequent larger multi-site RCT to evaluate safety and efficacy, mechanism of action, and predictors of response.

H. References:

1. Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of Obesity and Severe Obesity in US Children, 1999-2016. *Pediatrics*. Published online February 26, 2018. doi:10.1542/peds.2017-3459
2. Bureau USC. American FactFinder - Results. Accessed December 12, 2018. https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=PEP_2017_PEPSYASEX&prodType=table
3. Kelly AS, Barlow SE, Rao G, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation*. 2013;128(15):1689-1712. doi:10.1161/CIR.0b013e3182a5cfb3
4. Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. *J Pediatr*. 2007;150(1):12-17.e2. doi:10.1016/j.jpeds.2006.08.042
5. Pont SJ, Puhl R, Cook SR, Slusser W, SECTION ON OBESITY, OBESITY SOCIETY. Stigma Experienced by Children and Adolescents With Obesity. *Pediatrics*. 2017;140(6). doi:10.1542/peds.2017-3034
6. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. *Cochrane Database Syst Rev*. 2014;(8):CD003641. doi:10.1002/14651858.CD003641.pub4
7. Inge TH, Courcoulas AP, Jenkins TM, et al. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. *N Engl J Med*. 2016;374(2):113-123. doi:10.1056/NEJMoa1506699
8. Inge TH, Jenkins TM, Xanthakos SA, et al. Long-term outcomes of bariatric surgery in adolescents with severe obesity (FABS-5+): a prospective follow-up analysis. *Lancet Diabetes Endocrinol*. 2017;5(3):165-173. doi:10.1016/S2213-8587(16)30315-1
9. Sarwer DB, Dilks RJ, Spitzer JC, et al. Changes in Dietary Intake and Eating Behavior in Adolescents After Bariatric Surgery: an Ancillary Study to the Teen-LABS Consortium. *Obes Surg*. 2017;27(12):3082-3091. doi:10.1007/s11695-017-2764-9
10. Ryder JR, Gross AC, Fox CK, et al. Factors associated with long-term weight-loss maintenance following bariatric surgery in adolescents with severe obesity. *Int J Obes (Lond)*. 2018;42(1):102-107. doi:10.1038/ijo.2017.193
11. Rudolph A, Hilbert A. Post-operative behavioural management in bariatric surgery: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev*. 2013;14(4):292-302. doi:10.1111/obr.12013
12. Stewart F, Avenell A. Behavioural Interventions for Severe Obesity Before and/or After Bariatric Surgery: a Systematic Review and Meta-analysis. *Obes Surg*. 2016;26(6):1203-1214. doi:10.1007/s11695-015-1873-6
13. Pratt JSA, Browne A, Browne NT, et al. ASMBS pediatric metabolic and bariatric surgery guidelines, 2018. *Surg Obes Relat Dis*. 2018;14(7):882-901. doi:10.1016/j.soard.2018.03.019
14. Grieve E, Fenwick E, Yang H-C, Lean M. The disproportionate economic burden associated with severe and complicated obesity: a systematic review. *Obes Rev*. 2013;14(11):883-894. doi:10.1111/obr.12059
15. Finkelstein EA, Khavjou OA, Thompson H, et al. Obesity and severe obesity forecasts through 2030. *Am J Prev Med*. 2012;42(6):563-570. doi:10.1016/j.amepre.2011.10.026
16. Purnell JQ, Selzer F, Wahed AS, et al. Type 2 Diabetes Remission Rates After Laparoscopic Gastric Bypass and Gastric Banding: Results of the Longitudinal Assessment of Bariatric Surgery Study. *Diabetes Care*. 2016;39(7):1101-1107. doi:10.2337/dc15-2138

17. Kadera BE, Lum K, Grant J, Pryor AD, Portenier DD, DeMaria EJ. Remission of type 2 diabetes after Roux-en-Y gastric bypass is associated with greater weight loss. *Surg Obes Relat Dis*. 2009;5(3):305-309. doi:10.1016/j.soard.2009.02.007
18. Hamza N, Abbas MH, Darwish A, Shafeek Z, New J, Ammori BJ. Predictors of remission of type 2 diabetes mellitus after laparoscopic gastric banding and bypass. *Surg Obes Relat Dis*. 2011;7(6):691-696. doi:10.1016/j.soard.2010.03.292
19. Courcoulas AP, King WC, Belle SH, et al. Seven-Year Weight Trajectories and Health Outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) Study. *JAMA Surg*. 2018;153(5):427-434. doi:10.1001/jamasurg.2017.5025
20. Karlsson J, Taft C, Rydén A, Sjöström L, Sullivan M. Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. *Int J Obes (Lond)*. 2007;31(8):1248-1261. doi:10.1038/sj.ijo.0803573
21. Mitchell JE, Christian NJ, Flum DR, et al. Postoperative Behavioral Variables and Weight Change 3 Years After Bariatric Surgery. *JAMA Surg*. 2016;151(8):752-757. doi:10.1001/jamasurg.2016.0395
22. Fox CK, Marlatt KL, Rudser KD, Kelly AS. Topiramate for weight reduction in adolescents with severe obesity. *Clin Pediatr (Phila)*. 2015;54(1):19-24. doi:10.1177/0009922814542481
23. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311(1):74-86. doi:10.1001/jama.2013.281361
24. Khera R, Murad MH, Chandar AK, et al. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis. *JAMA*. 2016;315(22):2424-2434. doi:10.1001/jama.2016.7602
25. Sherafat-Kazemzadeh R, Yanovski SZ, Yanovski JA. Pharmacotherapy for childhood obesity: present and future prospects. *Int J Obes (Lond)*. 2013;37(1):1-15. doi:10.1038/ijo.2012.144
26. Ryder JR, Kaizer A, Rudser KD, Gross A, Kelly AS, Fox CK. Effect of phentermine on weight reduction in a pediatric weight management clinic. *Int J Obes (Lond)*. 2017;41(1):90-93. doi:10.1038/ijo.2016.185
27. Nor Hanipah Z, Nasr EC, Bucak E, et al. Efficacy of adjuvant weight loss medication after bariatric surgery. *Surg Obes Relat Dis*. 2018;14(1):93-98. doi:10.1016/j.soard.2017.10.002
28. Stanford FC, Alfaris N, Gomez G, et al. The utility of weight loss medications after bariatric surgery for weight regain or inadequate weight loss: A multi-center study. *Surg Obes Relat Dis*. 2017;13(3):491-500. doi:10.1016/j.soard.2016.10.018
29. Schwartz J, Chaudhry UI, Suzo A, et al. Pharmacotherapy in Conjunction with a Diet and Exercise Program for the Treatment of Weight Recidivism or Weight Loss Plateau Post-bariatric Surgery: a Retrospective Review. *Obes Surg*. 2016;26(2):452-458. doi:10.1007/s11695-015-1979-x
30. Toth AT, Gomez G, Shukla AP, et al. Weight Loss Medications in Young Adults after Bariatric Surgery for Weight Regain or Inadequate Weight Loss: A Multi-Center Study. *Children (Basel)*. 2018;5(9). doi:10.3390/children5090116
31. Srivastava G, Fox CK, Kelly AS, et al. Clinical Considerations Regarding the Use of Obesity Pharmacotherapy in Adolescents with Obesity. *Obesity (Silver Spring)*. 2019;27(2):190-204. doi:10.1002/oby.22385
32. Inge TH, Zeller M, Harmon C, et al. Teen-Longitudinal Assessment of Bariatric Surgery: methodological features of the first prospective multicenter study of adolescent bariatric surgery. *J Pediatr Surg*. 2007;42(11):1969-1971. doi:10.1016/j.jpedsurg.2007.08.010
33. Children's Hospital Colorado Bariatric Surgery Center. Accessed October 12, 2018. https://www.childrenscolorado.org/doctors-and-departments/departments/bariatric-surgery-program/
34. Ahmed SN, Siddiqi ZA. Antiepileptic drugs and liver disease. *Seizure*. 2006;15(3):156-164. doi:10.1016/j.seizure.2005.12.009
35. KVK-Tech, Inc. LOMAIRA (phentermine hydrochloride USP) tablets, CIV Prescribing Information. Published online September 2016. Accessed August 14, 2019. https://www.lomaira.com/Prescribing_Information.pdf
36. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, Wolraich M, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007-1022. doi:10.1542/peds.2011-2654
37. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5(9):727-738. doi:10.1016/S2215-0366(18)30269-4

38. Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017;102(3):709-757. doi:10.1210/jc.2016-2573
39. Rajjo T, Almasri J, Al Nofal A, et al. The Association of Weight Loss and Cardiometabolic Outcomes in Obese Children: Systematic Review and Meta-regression. *J Clin Endocrinol Metab*. 2017;102(3):758-762. doi:10.1210/jc.2016-2575
40. TOPIRAMATE FDA Approved Labeling Prescribing Information. Published online October 2012. Accessed January 1, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020844s041lbl.pdf
41. Wilding J, Van Gaal L, Rissanen A, Vercruysse F, Fitchet M, OBES-002 Study Group. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes Relat Metab Disord*. 2004;28(11):1399-1410. doi:10.1038/sj.ijo.0802783
42. Pandina GJ, Ness S, Polverejan E, et al. Cognitive effects of topiramate in migraine patients aged 12 through 17 years. *Pediatr Neurol*. 2010;42(3):187-195. doi:10.1016/j.pediatrneurol.2009.10.001
43. Aldenkamp AP, Baker G, Mulder OG, et al. A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. *Epilepsia*. 2000;41(9):1167-1178.
44. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95(2):297-308. doi:10.3945/ajcn.111.024927
45. Hendricks EJ, Srisurapanont M, Schmidt SL, et al. Addiction potential of phentermine prescribed during long-term treatment of obesity. *Int J Obes (Lond)*. 2014;38(2):292-298. doi:10.1038/ijo.2013.74
46. Radloff LS. The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. *J Youth Adolesc*. 1991;20(2):149-166. doi:10.1007/BF01537606
47. Stockings E, Degenhardt L, Lee YY, et al. Symptom screening scales for detecting major depressive disorder in children and adolescents: a systematic review and meta-analysis of reliability, validity and diagnostic utility. *J Affect Disord*. 2015;174:447-463. doi:10.1016/j.jad.2014.11.061
48. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-1277. doi:10.1176/appi.ajp.2011.10111704
49. The Columbia Lighthouse Project/Center for Suicide Risk Assessment. The Columbia Suicide Severity Rating Scale (C-SSRS) Support Evidence. Published online March 13, 2019. Accessed August 14, 2019. http://cssrs.columbia.edu/documents/c-ssrs-supporting-evidence/
50. Fox CK, Kaizer AM, Rudser KD, et al. Meal replacements followed by topiramate for the treatment of adolescent severe obesity: A pilot randomized controlled trial. *Obesity (Silver Spring)*. 2016;24(12):2553-2561. doi:10.1002/oby.21633
51. Modi AC, Zeller MH, Xanthakos SA, Jenkins TM, Inge TH. Adherence to vitamin supplementation following adolescent bariatric surgery. *Obesity (Silver Spring)*. 2013;21(3):E190-195. doi:10.1002/oby.20031
52. Modi AC, Quittner AL. Barriers to treatment adherence for children with cystic fibrosis and asthma: what gets in the way? *J Pediatr Psychol*. 2006;31(8):846-858. doi:10.1093/jpepsy/jsj096
53. Crawford PB, Obarzanek E, Morrison J, Sabry ZI. Comparative advantage of 3-day food records over 24-hour recall and 5-day food frequency validated by observation of 9- and 10-year-old girls. *J Am Diet Assoc*. 1994;94(6):626-630.
54. Stewart G. Trost. Measurement of Physical Activity in Children and Adolescents. *Am J Lifestyle Med*. 2007;1(4):299-314. doi:10.1177/1559827607301686
55. Modi AC, Zeller MH. The IWQOL-Kids(©): establishing minimal clinically important difference scores and test-retest reliability. *Int J Pediatr Obes*. 2011;6(2-2):e94-96. doi:10.3109/17477166.2010.500391
56. Kolotkin RL, Zeller M, Modi AC, et al. Assessing weight-related quality of life in adolescents. *Obesity (Silver Spring)*. 2006;14(3):448-457. doi:10.1038/oby.2006.59
57. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obes Res*. 2001;9(2):102-111. doi:10.1038/oby.2001.13
58. Bryant EJ, Thivel D, Chaput J-P, Drapeau V, Blundell JE, King NA. Development and validation of the Child Three-Factor Eating Questionnaire (CTFEQr17). *Public Health Nutr*. 2018;21(14):2558-2567. doi:10.1017/S1368980018001210
59. Shomaker LB, Tanofsky-Kraff M, Mooreville M, et al. Links of adolescent- and parent-reported eating in the absence of hunger with observed eating in the absence of hunger. *Obesity (Silver Spring)*. 2013;21(6):1243-1250. doi:10.1002/oby.20218

60. Moore CG, Carter RE, Nietert PJ, Stewart PW. Recommendations for planning pilot studies in clinical and translational research. *Clin Transl Sci*. 2011;4(5):332-337. doi:10.1111/j.1752-8062.2011.00347.x
61. Hertzog MA. Considerations in determining sample size for pilot studies. *Res Nurs Health*. 2008;31(2):180-191. doi:10.1002/nur.20247
62. Confidence interval for a proportion. Sample Size Calculators. Published May 13, 2014. Accessed September 30, 2018. http://www.sample-size.net/confidence-interval-proportion/
63. Chanoine J-P, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA*. 2005;293(23):2873-2883. doi:10.1001/jama.293.23.2873
64. Kelly AS, Metzig AM, Rudser KD, et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. *Obesity (Silver Spring)*. 2012;20(2):364-370. doi:10.1038/oby.2011.337
65. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)*. 2012;20(2):330-342. doi:10.1038/oby.2011.330
66. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9774):1341-1352. doi:10.1016/S0140-6736(11)60205-5