ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☒ **Yes** ☐ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) or MR from Masonic Institute for the Developing Brain (MIDB) 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*	**each have their own application process.**
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core? Formerly the AHC Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: bpic@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham* *Pham0435@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact:* fencl003@umn.edu	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	Lisdexamfetamine for the Treatment of Severe Obesity in Children Aged 6 to 12 Years
Principal Investigator/Faculty Advisor	Name: Claudia Fox, MD, MPH
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	Department:
	Telephone Number:
	Institutional Email Address:
Scientific Assessment	I believe Scientific Assessment is not required.
IND/IDE # (if applicable)	162424
IND/IDE Holder	Claudia Fox, MD
Investigational Drug Services # (if applicable)	6151
Version Number/Date:	Version 10.0, dated 19Sep2025

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	29Mar2023	Revises the number of participants, revises the drug titration schedule, revises the statistical analysis section, adds in safety labs at the screening visit, adds in urine pregnancy testing at all in-person visits and adds in depression/suicide screening at all in-person visits. Restructures the dietary recalls that will be conducted during the study.	Yes
2	28Jun2023	Notes the tests within the basic metabolic panel to the footnote of the schedule of events.	Yes
3	12Sep2023	Revises the visit windows for the study, adds a sleep log and a dose log for the parent, provides trinket incentives for the parent to give the child for wearing the ActiGraph (stickers, pens, markers, etc.), adds a lifestyle visit at the Week 24 visit, updates the questionnaires, changes the footnote in the schedule of events for the NDSR, notes that parents may be offered a portion plate and updates the resting metabolic rate collection methods.	Yes
4	01Dec2023	Notes that the screening visit may be broken into two visits, allowing for participants who have difficulty with the pill swallow test to try a second time.	Yes

5	02Feb2024	Makes clarifications to the study inclusion and exclusion criteria. Revises protocol section 12.1 to expand the risks for elevated blood pressure, elevated heart rate and change in mental health status. Corrects references which had become corrupted during previous versions.	No
6	16Jul2024	Clarifies that pregnancy tests are to be done on all female participants, regarding of menstrual status, during the course of the study.	Yes
7	18Oct2024	Removes the EKG at Week 12. Removes the urine toxicology testing at screening, Adds in that medical history to be done at screening includes asking about a history of chemical dependency.	Yes
8	24Jun2025	Corrects an omission from protocol version 8, section 7.3. The urine collection at the Screening visit will NOT include a toxicology test	No
9	19Sep2025	We are adjusting the number of participants we will need to consent in order to randomize 44 participants.	No

Table of Contents

ABBREVIATIONS/DEFINITIONS

ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BIS/BAS	Behavior Inhibition and Behavioral Activation System
BMI	Body mass index
BMI_z	Body mass index z-score
BPIC	Best Practices Integrated Informatics Core
BPM	Beats per minute
BRIEF-2	Behavioral Rating Inventory of Executive Function
CDI-2	Children's Depression Inventory
CEBQ	Child Eating Behavior Questionnaire
CI	Confidence interval
CPOM	Center for Pediatric Obesity Medicine
C-SSRS	Columbia Suicide Severity Rating Scale
CTSI	Clinical and Translational Science Institute
DBP	Diastolic blood pressure
DXA	Dual x-ray absorptiometry
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICH GCP	International Conference on Harmonisation-Good Clinical Practice
ICS	Informatics Consulting Services
IDS	Investigational Drug Service
IE	Information Exchange
LDX	Lisdexamfetamine
LOC	Loss of control
mSv	Millisievert
NICHQ-Vanderbilt	National Institute for Children's Health Quality-Vanderbilt Scale
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NDS-R	Nutrition Data System for Research
PALS	Pediatric Adapted Liking Survey
Peds QL	Pediatric Quality of Life Survey
PWMC	Pediatric Weight Management Clinic
QOL	Quality of life
QR	Quick response
SAE	Serious adverse event
SBP	Systolic blood pressure
SDS	System Dynamics Statistics
SOP	Standard operating procedure
%BMI95p	BMI 95th percentile
U.S.	United States

1.0 Objectives

1.1 Purpose: This will be a single site, 24-week double-blind, randomized, placebo-controlled pilot and feasibility clinical trial designed to estimate the treatment effect and tolerability of lisdexamfetamine (Vyvanse™) for the treatment of severe obesity in children ages 6 to < 12 years. After careful screening, all eligible participants (n=44) will be randomized, 1:1, to either lisdexamfetamine plus lifestyle therapy or placebo plus lifestyle therapy for 24 weeks of intervention. Participants and their parent/guardian will attend 8 in-person and 6 virtual visits. Participants will undergo regular assessments of anthropometrics, blood pressure, heart rate, and side effects and interval assessments of body composition, bone age, Tanner stage, laboratory tests, and questionnaires.

2.0 Background

2.1 Significance of Research Question/Purpose:

Childhood severe obesity is a highly prevalent, serious, and chronic disease. Severe obesity in children (defined as a body mass index [BMI] ≥120 percent of the 95th age- and sex-specific percentile) is one of the most important public health challenges of the 21st century.[1] Affecting nearly 5% of the 6-11 year olds in the U.S.,[2] severe obesity, particularly in this early life phase, is a serious and chronic disease. The physical and psychological health sequelae of childhood obesity are substantial, including high rates of metabolic syndrome (50-61%), [3,4] non-alcoholic fatty liver disease (11-28%),[5] obstructive sleep apnea (11-78%),[6] depression (10-27%),[7] and low quality of life.[8,9] Furthermore, multiple studies indicate that obesity in childhood almost universally persists into adolescence and adulthood.[10-12] For instance, one longitudinal study reported that 85% of 7-year olds with obesity became adults with obesity.[13] Unsurprisingly, the consequences of obesity in childhood on future adult health and productivity are staggering and include increased rates of type 2 diabetes, coronary artery disease, hypertension, and many cancers,[14] as well as reduced education attainment and employment.[15] Thus, there is an urgency to intervene on obesity early and aggressively in childhood when there is a window of opportunity to improve, or even normalize, growth trajectories in order to reduce the immense social and financial burden childhood obesity has on society.

Lifestyle therapy alone has limited efficacy; adjunct anti-obesity medication may improve outcomes. While the cornerstone of obesity treatment in children is lifestyle therapy, the effectiveness [16-18] and long-term durability [19,20] of this singular strategy is questionable, even in young populations. This has been demonstrated in multiple randomized controlled studies, as in real world settings.[21] Even the gold standard of pediatric obesity treatment, family-based therapy, resulted in only 1/3 of children achieving a healthy weight.[18] Underlying

poor outcomes of lifestyle therapy is the failure of this approach to appropriately address the pathophysiology of obesity. Accordingly, anti-obesity medications, which target pathophysiology,[22] are recommended as an adjunct to lifestyle therapy when lifestyle therapy alone is insufficient for limiting weight gain or ameliorating comorbidities.[23-25] Indeed, this approach of combining anti-obesity medications with lifestyle therapy, when employed early in childhood, before puberty when obesity is all but "ingrained," has the potential to slow weight gain, thereby improving growth trajectories.

Presently, however, no anti-obesity medications are approved by the U.S. Food and Drug Administration (FDA) for children under 12 years of age. Liraglutide, a glucagon-like peptide-1 receptor agonist, is in a phase 3 study for the treatment of obesity in children 6-11 years of age, but its widespread utilization is likely to be low because it is expensive (approximately $15,000 annually), administered by daily injection, and unfamiliar to most pediatricians. Identification of safe, effective, easy to use, and affordable anti-obesity medications for children with obesity has the prospect of dramatically improving the outcomes of this high-risk population, ultimately leading to a reduction in future morbidity and accompanying, staggering health care costs, and premature mortality. One such class of medications that may meet these criteria are psychostimulants such as amphetamine and methylphenidate. Psychostimulants are FDA-approved for the indication of attention deficit hyperactivity disorder (ADHD) in children ≥ 6 years of age and are the second most frequently prescribed medication class in the pediatric population.[26] Psychostimulants have a long-standing, well-described safety profile[27] and because of their favorable impact on weight, they may serve as a useful adjunct to lifestyle therapy.

Psychostimulants may be an effective adjunct to lifestyle therapy.
Pharmacological treatments for obesity target homeostatic and non-homeostatic energy regulatory mechanisms. Homeostatic mechanisms induce food intake and decrease energy expenditure when energy reserves are depleted. This "physiologic hunger" is controlled by numerous hormones and neurotransmitters such as leptin, insulin, and norepinephrine. In contrast, non-homeostatic mechanisms involve reward, cognition, and emotional factors of eating, and are primarily driven by dopamine activity.[28-30] Dopamine is implicated in mediating the reinforcing value of food, and reduced brain dopamine activity is associated with both obesity and with pathological food intake, such as binge eating.[31] Psychostimulants are both norepinephrine and dopamine re-uptake inhibitors and therefore may be especially effective for weight management because they address both homeostatic and non-homeostatic pathways (see Figure 1).

Numerous studies indicate that psychostimulant treatment is associated with reduced weight gain in children with ADHD. A recent meta-analysis of 8 studies including nearly 5,000 children and adolescents with ADHD showed that

psychostimulant treatment, for at least 6 months, was associated with a consistent, significant pre-post difference in weight z-score of 0.33 (95% CI: 0.22-0.44, p <0.0001).[32] A subset of this meta-analysis, including only those studies that provided outcomes out to 18-24 months, showed a pre-post difference in weight z-score of 0.46 (95% CI: 0.29-0.62, p <0.0001). Although these findings are modest, though clinically significant, several large studies observed that children with higher baseline BMIs [33-34] and younger age [35] experience greater weight reduction. Combined with lifestyle therapy, the magnitude of change in BMI due to psychostimulants is likely to be much higher, particularly when considering their mechanisms of action.

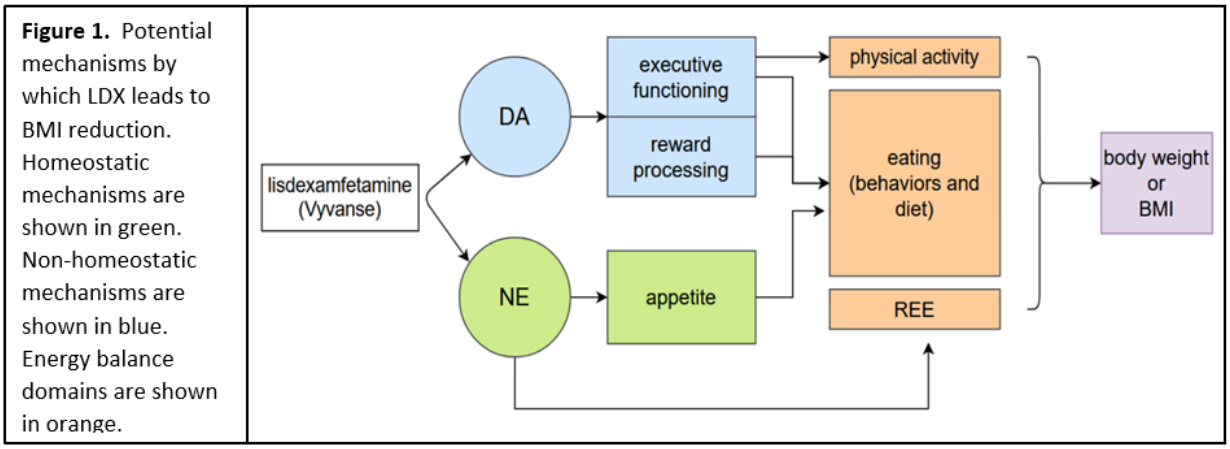

Figure 1. Potential mechanisms by which LDX leads to BMI reduction. Homeostatic mechanisms are shown in green. Non-homeostatic mechanisms are shown in blue. Energy balance domains are shown in orange.

Figure 1. Potential mechanisms by which lisdexamfetamine leads to BMI reduction. Homeostatic mechanisms are shown in green. Non-homeostatic mechanisms are shown in blue. Obesogenic behaviors are shown in orange.

There are likely multiple mechanisms by which psychostimulants promote weight loss (see Figure 1). One mechanism may be by their direct effect on appetite reduction and subsequent decrease in food intake, given their noradrenergic properties. This is supported by two studies that measured the acute effect of a common psychostimulant, methylphenidate, on eating in individuals with obesity who did not also have ADHD. In one of these studies, 22 adolescents with obesity received a single acute dose of methylphenidate or placebo before a test meal. The methylphenidate group compared to the placebo group consumed significantly less calories from fat (167 vs 203 kcal) and carbohydrate (311 vs 389 kcal).[36] In the other study, 9 adults were treated with a single dose of methylphenidate or placebo in a within-subject double blind laboratory study. Compared with placebo, those who had pre-meal methylphenidate consumed 34% fewer calories.[37] It is also conceivable that via its noradrenergic properties, psychostimulants may increase resting energy expenditure, which may directly lead to BMI reduction. While this has been demonstrated in a small (n=14) study

of healthy adults,[38] where resting energy expenditure increased by 7% over baseline after an acute dose of a psychostimulant, another study in children (n=31)[39] had null findings.

Other proposed mechanisms by which psychostimulants may promote weight loss are related to non-homeostatic processes including reward, cognition, and emotional factors, which are determined largely by dopaminergic pathways. These processes are controlled, in part, by executive functioning, which is positively affected by psychostimulants.[40-42] Executive functioning is an umbrella term that refers to a set of cognitive processes that aid in managing behavior, emotions, and thoughts with regard to a future goal or outcome. Executive functioning emerges in early childhood, continues to develop throughout adolescence, and plays a key role in self-regulation. Extensive literature supports a robust association between deficits in executive functioning and obesity.[43-45] Indeed, deficits in executive functioning lead to dysregulated eating patterns including more emotional overeating, more binge eating, and higher intake of high calorie snacks, as well as difficulty with delay of gratification for both food and non-food rewards.[44] Executive function skills are also needed to facilitate physical activity behaviors, such as sport or complex motor movements.[46] Finally, via dopaminergic pathways, psychostimulants may directly improve reward processing[1] and thereby decrease reward-based eating. In summary, by improving executive functioning and reward processing, psychostimulants may increase a child's ability to successfully engage in goal directed behavior such as healthy eating, reduced binge eating and reward-based eating, and regular physical activity, which in turn may lead to BMI reduction.

Lisdexamfetamine (LDX) may be better than other psychostimulants for treating obesity in children. The two primary types of psychostimulants are amphetamine-based, such as lisdexamfetamine (LDX), and methylphenidate-based, such as Ritalin. LDX is a long-acting (12 hour) psychostimulant that is dosed once daily. Multiple studies suggest that amphetamine-based psychostimulants,[49] and LDX in particular,[50] compared to methylphenidate-based psychostimulants perform better for ADHD treatment. Furthermore, LDX compared to other psychostimulants may be associated with more weight loss. In a head-to-head study of LDX versus a long-acting methylphenidate compound for treating ADHD in adolescents, those treated with LDX compared to methylphenidate experienced more frequent decreased appetite (53% vs 42%) and decreased weight (21% vs 13%).[51] Thus, it is possible that LDX, through its superior impact on improving ADHD symptoms, including executive dysfunction, may also have a superior effect on weight reduction compared to other psychostimulants.

In addition to ADHD, LDX, unlike other psychostimulants, is also FDA-approved for the indication of binge eating disorder in adults and may therefore be useful for

decreasing binge eating behaviors (and perhaps subsequent weight) in affected children. Binge eating disorder is characterized by recurrent episodes of consumption of larger amounts of food in a discrete period of time than is typical for most people, accompanied by a sense of loss of control over the food consumption and psychological distress.[2] A corollary to this eating disorder in children is loss of control (LOC) eating. LOC eating is described as the experience of LOC over what or how much one eats, regardless of the amount of food consumed.[3] Binge/LOC eating is highly prevalent in the pediatric population, affecting 22-31% of children and adolescents with overweight and obesity,[4] and is consistently associated with adverse physiological and psychological outcomes.[5] Furthermore, it has been proposed that binge/LOC eating may mediate the relationship between poor executive function and weight gain.[6] Perhaps not surprising is that in the phase 3 study of adults randomized to 11 weeks of LDX or placebo for binge eating disorder where weight loss was only a safety outcome and obesity was not an inclusion criteria, the mean weight loss was 4.9 kg for the treatment arm and 0.1 kg for the placebo arm.[7]

Finally, other advantages of LDX include its long half-life compared to other psychostimulants, which is associated with reduced abuse potential[8] and the fact that the manufacturer's patent has expired in February 2023, thus paving the way for less expensive, generic formulations. The latter is particularly important because many insurance plans do not cover anti-obesity medications so families must resort to paying out-of-pocket for their needed obesity treatment. It should also be noted that phentermine, the most commonly prescribed anti-obesity medication in adults, is also an amphetamine derivative.[9] However, although it is inexpensive, phentermine, in contrast to LDX, is only FDA-approved for 12 weeks of use rather than chronic use. Further, phentermine has relatively weaker dopaminergic properties. For these reasons, it seems logical to examine LDX, not phentermine, for the treatment of childhood obesity.

A.5. Tolerability of LDX for the treatment of severe obesity in children is unknown

Although psychostimulants, including LDX, have a long-standing, well-established safety profile,[10] the relative tolerability of these medications in children who do not have ADHD has yet to be established. Aside from decreased appetite, the most common side effects of psychostimulants in children with ADHD include insomnia, upper abdominal pain, and irritability. Particularly relevant to patients with obesity are the impact of psychostimulants on blood pressure, heart rate and linear growth, the effects of which tend to be dose dependent in children with ADHD.[10] Clinical trials of LDX for the treatment of ADHD in children report

mean increases in systolic blood pressure of 2-4 mm Hg and in heart rate of 3-7 bpm.[11] The clinical significance of this effect on the cardiovascular system is uncertain, especially for children with obesity who may be at higher risk of having underlying cardiovascular impairment such as hypertension. Importantly, in adults with obesity treated with phentermine, also a noradrenergic agent, blood pressure tends to *decrease* as a function of weight loss.[12] Thus, measuring the impact of LDX on blood pressure and heart rate in children with obesity is critical for assessing its utility as an adjunct treatment for obesity in this population. Regarding linear growth, psychostimulants have been shown to have adverse effects on height velocity at various stages of childhood, including pre-puberty.[13,14] However, final adult height does not appear to be impacted.[15] Similarly, obesity can effect growth and has been associated with taller stature during childhood but decreased growth velocity in adolescence; the net result again is no association between childhood weight status and adult height.[16] That said, as both psychostimulant use and obesity can affect growth velocities during the pre- and peri-pubertal periods, the net effect of both of these simultaneously during this stage of development is unclear and warrants further investigation.

2.2 Preliminary Data: To our knowledge, no randomized controlled trials have examined psychostimulants as an adjunct to lifestyle therapy for BMI reduction in children with obesity. At the University of Minnesota Pediatric Weight Management Clinic, where off-label use of medications for the treatment of obesity is guided by protocols developed by our team of pediatric obesity medicine physicians, we have used LDX as an adjunct to lifestyle therapy for the treatment of obesity in patients. We identified 65 patients, $\geq$6 years of age with severe obesity, who were treated with LDX plus our standard of care lifestyle therapy for at least 3 months. The mean absolute change in the percent of the 95th BMI percentile (%BMIp95) was -4.68 and -6.35 percentage points at 3- and 6-months, respectively (see Figure 2). In a sub-analysis including only patients ages > 6 to < 12 years (n=37), the mean absolute change in %BMIp95 was -5.94 and -8.41 percentage points at 3- and 6-months, respectively.

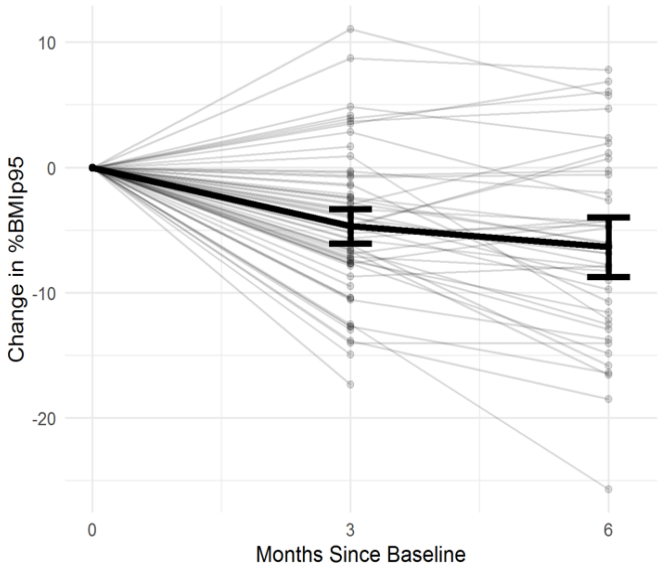

Figure 2. Change in %BMIp95 from baseline to 3- and 6-months with LDX and lifestyle therapy.

2.3 Existing Literature: Several case series and retrospective medical chart reviews describe the results of treating hypothalamic obesity (most often from brain tumors) in children with psychostimulants. These reports demonstrated BMI stabilization or reduction with dextroamphetamine or methylphenidate.[17-20] A case series of children with monogenic obesity due to mutations in leptin receptor or melanocortin-4 receptor also demonstrated favorable BMI outcomes with methylphenidate treatment.[21]

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: To estimate the treatment effect of LDX + lifestyle therapy vs. placebo + lifestyle therapy on changes in BMI (%BMIp95), body fat, cardiometabolic health and quality of life (QOL) from baseline to 24 weeks. We hypothesize that LDX compared to placebo will result in a greater mean decrease in %BMIp95 and body fat, improved cardiometabolic health and QOL at 24 weeks.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s): To generate estimates of the tolerability and safety of LDX used for the treatment of severe obesity in children. We hypothesize that at least 80% of participants will tolerate an LDX dose of at least 30 mg per day (the recommended starting dose) and that the LDX group compared to the placebo group will not demonstrate clinically significant increases in blood pressure or heart rate.

We will also examine the potential mechanisms by which LDX affects BMI in children with obesity, including its effect on executive functioning, reward processing, appetite, resting energy expenditure, and health behaviors (diet, eating behaviors, and physical activity). Study Intervention(s)/Investigational Agent(s)

3.3 Description:

LDX: LDX, a psychostimulant prodrug of dextroamphetamine, is FDA-approved for ADHD in children ≥6 years of age and for binge eating disorder in adults. It is available in capsules of 10, 20, 30, 40, 50, 60, and 70 mg. It is orally administered once daily and has a half-life of 12 hours. After a single dose, the pharmacokinetics are linear between 30 and 70 mg in children ages 6-12 years, and both the clinical efficacy for ADHD symptoms and weight loss side effects are dose dependent.[22] Following single doses of 30 mg to 70 mg, the weight/dose normalized area under the curve and maximal concentration values are the same in 6-12 year olds compared to adults. Per the package insert, the recommended starting dose for children ≥6 years of age with ADHD is 30 mg daily. The dose is adjusted by 10 or 20 mg increments at weekly intervals up to a maximum of 70 mg daily. The target dose is one that balances the clinical efficacy with tolerability. For binge eating disorder in adults, the recommended dose is 50-70 mg daily. To operate conservatively and allow for maximum tolerability, we will start at 30 mg daily for 2 weeks, then 40 mg daily for 2 weeks, then 50 mg daily for 2 weeks, then 60 mg daily for 2 weeks, then 70 mg daily for the remaining 14 weeks. We will not use a forced titration schedule. That is, for patients who do not tolerate the full dose escalation schedule, we will maintain the dose at the maximum tolerated dose for the remainder of the trial. Also, we will not escalate the dose after week 10, which is the end of the planned dose escalation schedule. A participant's dose may be decreased for medication intolerance anytime during the trial; the dose will be reduced by 10 mg at weekly intervals until a tolerable dose is achieved. If a participant cannot tolerate the smallest dose, 10 mg, then drug/placebo will be discontinued but the participant will remain in the trial. This flexible dosing will allow for maximal time on medication. Placebo capsules that are identical in appearance to the LDX capsules will be made by the University of Minnesota Investigational Drug Service Pharmacy, which will manage all trial product.

Lifestyle Therapy: Lifestyle therapy will focus on dietary and physical activity modification supported by behavior change strategies. The standardized curriculum will be based on a behavioral conceptualization of effective weight management that emphasizes: 1) identifying behaviors in need of change; 2) setting goals for change; 3) monitoring progress; 4) modifying environmental cues to facilitate change; and 5) modifying consequences to motivate change (e.g. positive reinforcement for goal attainment). Each session will be delivered by an

RD-trained research coordinator, who will follow a standardized format including a review of progress, new material, and a summary/plan for the upcoming session. A total of 13 sessions, each 30-60 minutes in length, will be delivered every 2 weeks, 7 in-person and 6 virtually (delivered by a secure virtual platform). Virtual visits may be conducted with the parent/guardian alone (without participant present) to allow for more flexibility in scheduling and to minimize time away from school.

3.4 Drug/Device Handling:

LDX will be purchased commercially. The University of Minnesota Investigational Drug Service (IDS) Pharmacy will be asked to prepare a matching placebo. Trial product will be managed by IDS and will be dispensed according to their operating policies. The IDS office specializes in storing and dispensing investigational drugs for clinical trials. Study physicians will write a prescription in order for IDS to dispense the study medication. IDS is a secure facility (behind two locked doors) and maintains refrigerators and freezers with temperature tracking to assure that the drugs utilized in this study will maintain stability. IDS will keep detailed records on the receipt of investigational product (including lot numbers) and detailed records on the dispensing of the product to each subject enrolled in the study. IDS is also equipped to destroy any medication that is returned at the end of the study when all drug accountability has been completed. The participants and their parents will be instructed on how to administer the medication and the dose escalation. Study staff members will perform drug accountability at each visit and estimate a percentage of missed doses as additional forms of compliance tracking.

3.5 Biosafety: Not applicable.

3.6 Stem Cells: Not applicable.

3.7 Fetal Tissue: Not applicable.

4.0 Procedures Involved

4.1 Study Design: This will be a 24-week, randomized, double-blind, placebo-controlled pilot and feasibility clinical trial of LDX plus lifestyle therapy versus matching placebo plus lifestyle therapy. We will enroll 44 children who have previously failed to lose weight with lifestyle therapy per parent report.

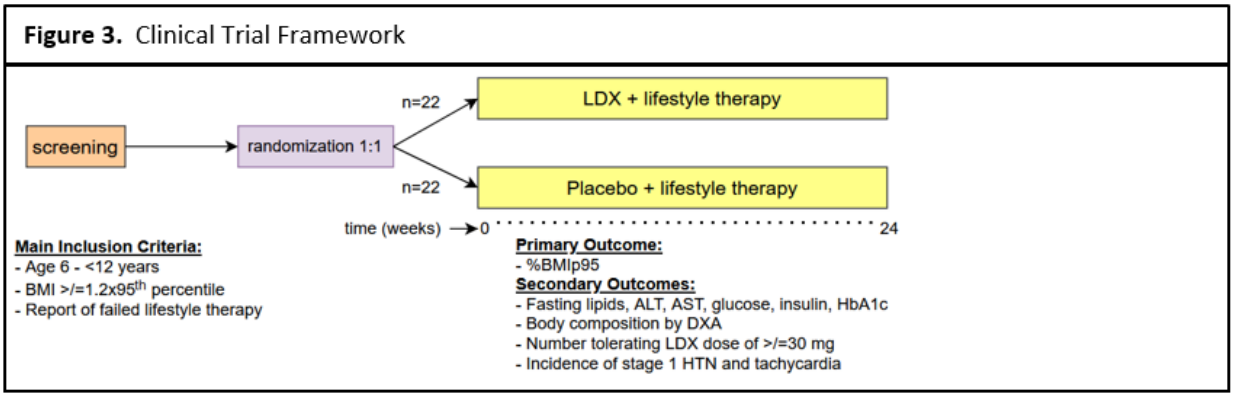

Figure 3. Clinical Trial Framework

The schedule of events shows the data that will be collected at each study visit. All participants will receive reimbursement for completing study visit assessments.

	Screening	Baseline/ Randomization +21d[7]	Week 2 ± 3d	Week 4 ± 3d	Week 6 ± 3d	Week 8 ± 3d	Week 10 ± 3d	Week 12 ± 7d	Week 14 ± 7d	Week 16 ± 7d	Week 18 ± 7d	Week 20 ± 7d	Week 22 ± 7d	Week 24 ± 7d
Informed Consent	X													
Inclusion/Exclusion[3]	X													
Demographics	X													
Medical history, including chemical dependency	X													
Height, weight, blood pressure and heart rate	X	X		X		X		X		X		X		X
Physical exam	X													
Tanner stage	X													X
ECG	X													
Basic metabolic panel[5], TSH	X													
Pregnancy test[1]	X	X		X		X		X		X		X		X
Suicide and Depression Screen • C-SSRS • CDI-2	X	X		X		X		X		X		X		X
Bone age		X												X
Indirect calorimetry		X												X
Fasting blood tests • Lipids • Glucose • Insulin • HbA1c • AST • ALT	X													X
DXA		X												X
Diet recall	X	X											X	X
Accelerometry[2]	X											X		
Questionnaires • Peds QL • NIH Toolbox • BRIEF-2 • NICHQ-Vanderbilt • CEBQ • VAS of Hunger • CBES • BIS/BAS[6]		X												X
Planned dose escalation (mg)		30	40	50	60	70								
Dispense study medication		X		X		X		X		X		X		
Compliance check			X	X	X	X	X	X	X	X	X	X	X	X
AE Review • AEs • Barkley Rating Scale[4] • Con Meds • Intercurrent Illness		X	X	X	X	X	X	X	X	X	X	X	X	X
Lifestyle therapy (in-person)		X		X		X		X		X		X		X
Lifestyle therapy (virtual)			X		X		X		X		X		X	

1. Blood or urine pregnancy tests can be conducted at the Screening and Week 24 visits. Urine pregnancy tests will be done at the Baseline/Randomization. Week 4, Week 8, Week 12, Week 16 and Week 20 visits.
2. Accelerometer will be worn 24/hours x 7 days between screening and baseline and again for 24/hours x7 days between Week 20 and Week 24
3. Participant may be given a placebo test capsule to ensure they are able to swallow the capsules for the study
4. Barkley Rating Scales will be performed every two weeks during the dose escalation through Week 10 and then at the in person visits (Weeks 12, 16, 20 and 24).
5. Basic metabolic panel to consist of anion gap, calcium, chloride, bicarbonate, creatinine, glucose, potassium, sodium, urea nitrogen
6. Only BAS will be utilized
7. Baseline/Randomization must occur within 21 days of the date blood was drawn at the Screening visit.

4.2 Study Procedures:

- *Height, weight, blood pressure, heart rate and pubertal development*. Height and weight will be measured by a calibrated, wall-mounted stadiometer and an electronic scale, respectively. Measurements will be obtained with participants in light clothing, without shoes. Two consecutive height and weight measurements will be obtained and averaged. If the first two values differ by more than 0.5 cm for height and/or 0.3 kg for weight, a third measurement will be obtained and the average of three measurements will be calculated. BMI will be calculated as the weight in kilograms divided by the height in meters, squared. Blood pressure will be obtained on the same arm using the same cuff size and equipment according to standardized procedures and the internal standard operating procedure. Tanner stage will be determined by trained personnel.
- *Medical history and history of chemical dependency*. Participants will be asked about their medical history at the screening visit and will be asked if they have a history of chemical dependency.
- *Bone age*. To estimate the maturity of the participant's skeleton, an x-ray of the left wrist will be taken.
- *Resting energy expenditure*. Resting energy expenditure will be measured by indirect calorimetry after participants have been fasting for $\geq$ 12 hours. Metabolic data will be collected using a ventilated hood. Participants will be instructed not to engage in intentional exercise or consume caffeine on the day prior to testing. Participants will be instructed to take their study medication the morning of their 24-week visit. Resting gas exchange measurements will be collected using a Parvo Medics TrueOne 2400 Metabolic Cart (Sandy,UT). After a 30-minute resting session, room air will be drawn through the hood at a rate of 25-40 L/min to match participant's respiration (dilution method). VO2 and VCO2 values will be collected over a 30-minute period in a semi-supine position to estimate resting metabolic rate. An estimate of metabolic rate will consist of an average of the 30-minute collection period minus the first 5-minutes and any movement and/or abnormal respiration. The metabolic cart will be calibrated for gas analyses and volume prior to each testing session.
- *Blood analyses*. Safety labs consisting of a basic metabolic panel and TSH at screening. Fasting blood ($\geq$ 12 hours) will be collected for measurement of lipids (total-, LDL-, and HDL-cholesterol and triglycerides), glucose, insulin,

hemoglobin A1c, ALT and AST (Fairview Diagnostics Laboratories, Minneapolis, MN).

- *DXA scan*. Total percent body fat, visceral fat, and lean mass will be determined by dual energy x-ray absorptiometry. The scanning table accommodates body sizes of up to 204 kg.
- *Diet recall*. Will be measured with two multi-pass 24-hour diet recalls on non-consecutive days using the Nutrition Data System for Research (NDS-R, Nutrition Coordinating Center, University of Minnesota).[66] The first set of two recalls will be completed at the screening and baseline visits. A second set of two 24-hour diet recalls will be completed over the phone at week 22 and in person at week 24. Respondents will use the Food Amounts Booklet to estimate portion sizes. Quality assurance checks will be conducted on at least 10% of recalls according to NDS-R standard protocols. Key dietary intake variables include total energy intake, percent calories from fat, Healthy Eating Index, and intake of specific food types (e.g., sugar-sweetened beverages).
- *Accelerometry.* Objectively measured participant physical activity and sleep will be assessed using ActiGraph (GT3X+) accelerometers (ActiGraph LLC, Pensacola, FL), which provides reliable and valid assessments of physical activity in school-aged children.[68-70] Children will be asked to wear the accelerometer 24 hours/day for 2 seven-day sessions (between screening and baseline/randomization and between weeks 20 and 24), with the exception of water activity (e.g., bathing). The ActiGraph GT3X+ measures acceleration in three individual orthogonal planes using a vertical axis, horizontal axis and a perpendicular axis and is set to collect data at a 40-Hertz frequency. The minimum valid wear time criteria are four days (3 weekdays, 1 weekend day) of at least 6 hrs of activity between 5:00am and 11:59pm. Devices will be wrist worn, as recent studies have found better compliance with wrist-worn actigraph[70] without compromising measurement of physical activity.[71] Minutes spent in *moderate-to-vigorous physical activity* will be primary activity endpoint of interest. Vigorous, moderate, light, and sedentary activity will also be calculated using ActiLife software. Child sleep will also be measured using the same wrist-worn ActiGraph (GT3X-BT) device, which has been shown to have acceptable reliability and validity in sleep-wake detection compared with laboratory-based polysomnography.[72] Nighttime *sleep efficiency* defined as the portion of time dedicated to sleep that is spent asleep, sleep latency, sleep duration, and awakenings after sleep onset will be examined. All indexes will be calculated using ActiLife software. A 7-day sleep diary will also be maintained by the parent. Parents will be given small gifts to provide to the child (stickers, pens, markers) to give to the child upon completion of wearing the ActiGraph for a 7-day period.
- *Questionnaires.* Appetite will be gauged by a visual analog scale obtained in a fasting state [73,74] and by the Child Eating Behavior Questionnaire (food

responsiveness subscale).[75] Executive Function will be assessed with brief subtests of the NIH Toolbox (including Flanker test of inhibition, Dimensional Change Card Sorting Test of cognitive flexibility and List Sorting Working Memory Test), and the parent report Behavioral Rating Inventory of Executive Function (BRIEF)-2. ADHD will be measured by the NICHQ Vanderbilt Assessment Scale. Reward responsiveness will be measured by the parent-reported Behavioral Inhibition System/Behavioral Approach System (BIS/BAS) scales for children. Specifically, we will use the 13-item BAS subscales. Reward based eating will be measured by the Child Eating Behavior Questionnaire (enjoyment of food subscale)[75] and Pediatric Adapted Liking Survey.[76] Binge eating will be measured by the Children's Binge Eating Scale, a 7-item structured, interviewer administered scale validated to measure binge eating disorder in children ages 5-13 years.[67]

- Quality of Life will be measured by the parent report on the Peds QL.[77]
- *Tolerability and Safety Outcomes.* The feasibility of conducting the larger clinical trial will depend on whether or not participants can tolerate LDX at doses that are effective for inducing BMI reduction. We will define tolerability as being able to tolerate a dose of at least 30 mg daily (the recommended starting dose) for the duration of the study. Importantly we will also measure outcomes of children taking doses less than 30 mg daily (i.e., 20 mg or 10 mg) as this information will be important for informing the dosing of the larger, definitive trial. We anticipate that participants taking LDX will have side effects at the same rate as patients who take LDX for the treatment of ADHD, so we will not define tolerability as not having any side effects whatsoever. Rather, the parent/guardian and participant will subjectively decide if the side effects, if present, are severe enough to warrant discontinuation of the study medication or reducing the dose below 30 mg daily. From an objective standpoint, every two weeks during dose escalation and every 4 weeks for the remainder of the study we will administer the Barkley's Side Effect Rating Scale which was developed specifically to monitor side effects from psychostimulants. This questionnaire, completed by the parent/guardian (and sometimes with the child's help) requests feedback on 17 items on a 9-point Likert scale including typical physical side effects (e.g., decrease appetite, insomnia, stomachaches, and headaches) and behavioral symptoms (e.g., irritability, anxiety).[78.] Other measures of tolerability will include incidence of developing stage 1 hypertension and tachycardia, measured by blood pressure and heart rate. Stage 1 hypertension is defined as SBP and/or DBP $\geq 95^{th}$ percentile on three separate occasions and will be confirmed by a 24-hour ambulatory blood pressure monitor.[79] Tachycardia in childhood is defined as heart rate $\geq$ 120 bpm at rest measured on three separate occasions.[80]

- *Lifestyle therapy.* Lifestyle therapy will focus on dietary and physical activity modification supported by behavior change strategies. The standardized curriculum will be based on a behavioral conceptualization of effective weight management that emphasizes: 1) identifying behaviors in need of change; 2) setting goals for change; 3) monitoring progress; 4) modifying environmental cues to facilitate change; and 5) modifying consequences to motivate change (e.g., positive reinforcement for goal attainment). Each session will be delivered by an RD-trained research coordinator, who will follow a standardized format including a review of progress, new material, and a summary/plan for the upcoming session. A total of 13 sessions, each 30-60 minutes in length, will be delivered every 2 weeks, 7 in-person and 6 virtually (delivered by a secure virtual platform). Virtual visits may be conducted with the parent/guardian alone (without participant present) to allow for more flexibility in scheduling and to minimize time away from school.

4.3 Study Duration: Individuals will be enrolled in the study for up to 27 weeks, including 24 weeks of intervention and up to 3 weeks between screening and start of intervention.

We anticipate that it will take 2.5 years to recruit and enroll the 44 participants needed for this pilot trial and that data collection will be completed after 3.5 years. We anticipate it will take 1 year to analyze the data.

4.4 Use of radiation

This study will consist of two bone age x-rays and two DXA scans, all of which will utilize ionizing radiation. None of these tests are considered part of standard medical care. The DXA scans each consist of exposure to 0.01 mSv. The bone age x-rays each consist of exposure to 0.001 mSv. A participant who completes both DXA scans and both bone age x-rays will be exposed to 0.42 mSv. The average amount of radiation that the average person would receive from these procedures is less than 2% of that received from natural sources of radiation by a Minnesota resident in one year. Parents will be asked if their child has participated in a research study that used radiation within the past 12 months so that the amount of radiation the child has been exposed to can be reviewed.

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

5.0 Data and Specimen Banking

Not applicable.

6.0 Sharing of Results with Participants

6.1 Laboratory results will be posted to the participant's medical record.

6.2 Sharing of genetic testing: Not applicable.

7.0 Study Population

7.1 Inclusion Criteria:

- Children ages 6 to < 12 years at study entry.
- Severe obesity defined as BMI $\geq$ 1.2 times the 95th percentile at the screening visit.
- Prior failed attempt of lifestyle therapy per parent/guardian report.
- Written informed consent of parent/legal guardian and written assent of participant

7.2 Exclusion Criteria:

- Contraindications to lisdexamfetamine, including current or recent (< 14 days) use of monoamine oxidase inhibitor and known hypersensitivity to amphetamine products.
- Family history of sudden death or ventricular arrhythmia in any first or second degree relative with any of the following: sudden or unexplained death including sudden infant death syndrome, cardiomyopathy, heart transplant, familial arrhythmia (such as Wolff-Parkinson-White syndrome, long QT interval, or implantable defibrillator).
- Any history of fainting or seizure from exercise, startle or fright
- Clinically significant congenital or structural heart disease or arrhythmia.
- BMI < 1.2 times the 95th percentile at the baseline/randomization visits
- Hypertension defined as SBP and/or DBP $\geq$95th percentile (on 3 separate occasions) at the screening OR baseline/randomization visits.
- Tachycardia defined HR $\geq$120 bpm (on 3 separate occasions) at the screening OR baseline/randomization visits.
- Current or recent (< 3 months) use of psychostimulant or sympathomimetic amine.
- History of chemical dependency.
- Diabetes mellitus (type 1 or 2).
- Current or recent (< 3 months) use of anti-obesity medication(s).
- Previous bariatric surgery.
- Recent initiation or change in dose (< 3 months prior) of anti-hypertensive or lipid medication(s).
- TSH > 1.5x ULN.
- AST or ALT > 3x ULN.
- Fasting glucose $\geq$ 126 mg/dL
- History of mania, schizophrenia, bipolar disorder, or psychosis.
- Unstable depression or anxiety that has required hospitalization in the past 12 months.
- Any history of suicide attempt.

- Columbia Suicide Severity Rating Scale (C-SSRS) with a score of Moderate or High at the screening or baseline/randomization visits.
- Children's Depressive Inventory 2 (CDI-2) score $\geq$ 70 (based on parent or child report) at the screening or baseline/randomization visits.
- Concomitant use of tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), lithium, fentanyl, tramadol, triptans, tryptophan, buspirone, and St. John's wort at any time during the study.
- Refusal to use adequate contraception (double barrier method or stable hormonal contraception plus single barrier method, tubal ligation, or abstinence) in girls of childbearing potential.
- Inability to swallow test capsule (participants will have two opportunities)

7.3 Screening (in person visit):

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

- Review of inclusion/exclusion criteria
- Review of medical history including chemical dependency
- Demographic information collection
- Height, weight, blood pressure and heart rate
- Physical exam
- Tanner staging
- ECG
- Fasting blood draw for basic metabolic panel, TSH, lipids, glucose, insulin, HbA1c, AST and ALT
- Urine collection for pregnancy test
- Suicide and depression screening (C-SSRS and CDI-2)
- Diet recall
- Demonstration of ability to swallow capsule

An accelerometer will also be worn for one week (7 days x 24 hours/day) between the screening and baseline visit. The parent will be provided with a sleep log and small gift to give the child upon completion. This visit may be broken into two parts, to give participants who have difficulty swallowing the capsule an opportunity to practice at home (by swallowing tic tacs, etc.) and return for a second attempt.

Baseline/Randomization (in person visit):

- Height, weight, blood pressure and heart rate
- Bone age x-ray
- Indirect calorimetry
- DXA scan (with urine pregnancy test for females)
- Suicide and depression screening (C-SSRS and CDI-2)
- Questionnaires
- Diet recall
- Medication/placebo dispensed and medication log provided to parent
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- In-person lifestyle therapy visit and offer of a portion plate

Week 2 (virtual visit):

- Compliance check
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- Dose escalation (if tolerated)
- Virtual lifestyle therapy visit

Week 4 (in person visit):

- Height, weight, blood pressure and heart rate
- Urine pregnancy test
- Suicide and depression screening (C-SSRS and CDI-2)
- Compliance check and return unused study medication
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- Dose escalation (if tolerated) and study drug dispensing
- In-person lifestyle therapy visit

Week 6 (virtual visit):

- Compliance check
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- Dose escalation (if tolerated)
- Virtual lifestyle therapy visit

Week 8 (in person visit):

- Height, weight, blood pressure and heart rate
- Urine pregnancy test
- Suicide and depression screening (C-SSRS and CDI-2)

- Compliance check and return unused study medication
- Dose escalation (if tolerated) and study drug dispensing
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- In-person lifestyle therapy visit

Week 10 (virtual visit):

- Compliance check
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- Virtual lifestyle therapy visit

Week 12 (in person visit):

- Height, weight, blood pressure and heart rate
- Urine pregnancy test
- Suicide and depression screening (C-SSRS and CDI-2)
- Compliance check and return unused study medication
- Study drug dispensing
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- In-person lifestyle therapy visit

Week 14 (virtual visit):

- Compliance check
- Review adverse events, concomitant medications, and intercurrent illness
- Virtual lifestyle therapy visit

Week 16 (in person visit):

- Height, weight, blood pressure and heart rate
- Urine pregnancy test
- Suicide and depression screening (C-SSRS and CDI-2)
- Compliance check and return unused study medication
- Study drug dispensing
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- In-person lifestyle therapy visit

Week 18 (virtual visit):

- Compliance check
- Review adverse events, concomitant medications, intercurrent illness and
- Virtual lifestyle therapy visit

Week 20 (in person visit):

- Height, weight, blood pressure and heart rate
- Urine pregnancy test
- Suicide and depression screening (C-SSRS and CDI-2)
- Compliance check and return unused study medication
- Study drug dispensing
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale
- In-person lifestyle therapy visit
- Instructions for Accelerometer and sleep log

Week 22 (virtual visit):

- Compliance check
- Review adverse events, concomitant medications, intercurrent illness and Virtual lifestyle therapy visit
- Dietary recall

Week 24 (in person visit):

- Height, weight, blood pressure and heart rate
- Tanner stage
- Bone age x-ray
- Indirect calorimetry
- DXA scan (with pregnancy test for females)
- Suicide and depression screening (C-SSRS and CDI-2)
- Fasting blood draw for lipids, glucose, insulin, HbA1c, AST and ALT
- Questionnaires
- In-person lifestyle therapy visit
- Dietary recall
- Compliance check and return unused study medication
- Review adverse events, concomitant medications, intercurrent illness and Barkley Side Effect Rating Scale

8.0 Vulnerable Populations

8.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study.
Children	Primary focus of the research
Pregnant women/fetuses/neonates	Excluded
Prisoners	Excluded
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded
Non-English speakers	Excluded
Those unable to read (illiterate)	Excluded
Employees of the researcher	Excluded
Students of the researcher	Excluded
Undervalued or disenfranchised social group	included but not the focus
Active members of the military (service members), DoD personnel (including civilian employees)	Excluded
Individual or group that is approached for participation in research during a stressful situation	Excluded

such as emergency room setting, childbirth (labor), etc.	
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included but not the focus
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Excluded
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Included but not the focus
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded

8.2 Additional Safeguards, if any, to ensure inclusion is appropriate: Not applicable.

9.0 Local Number of Participants

9.1 Local Number of Participants to be Consented: 65 (Our goal is to randomize 44 participants. From previous experience, we expect no more than 15% to fail in-person screening after consent is obtained.)

10.0 Local Recruitment Methods

10.1 Recruitment Process: Recruitment will be achieved by a number of methods. These include mailing letters or sending electronic messages to potentially eligible participants within the MHealth Fairview Health System and our research partners, Children's Hospitals and Clinics of Minnesota and Health Partners/Park Nicollet health system. Direct recruitment of University of Minnesota Pediatric Weight Management clinic patients by Center for Pediatric Obesity Medicine CPOM clinician-scientists will also be conducted.

10.2 Identification of Potential Participants: Participants will be identified by using the University of Minnesota CTSI, Best Practices Integrated Informatics Core (BPIC) to identify patients in the MHealth Fairview health system based on age

and BMI. Both the recruitment mailing and the electronic messages will request that the interested parties contact the research staff for additional information. If the interested party and the research staff do not connect on the first try, the research staff will attempt to contact the interested parties with up to three follow-up phone calls and/or three emails.

10.3 Recruitment Materials: A recruitment letter and recruitment flyers will be created for this study and approved by the IRB before use.

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

- Baseline visit: $75 for the visit and $25 when the accelerometer is returned
- Week 4: $75
- Week 8: $75
- Week 12: $75
- Week 16: $75
- Week 20: $75
- Week 24 visit: $100 for the visit and $50 when the accelerometer is returned

Participants who complete all of the virtual lifestyle therapy visits will receive a $100 bonus at the Week 24 visit. Therefore, participants will be eligible to receive a total reimbursement/compensation of $725.

11.0 Withdrawal of Participants

11.1 Withdrawal Circumstances: Participants will be allowed to withdraw from the study at any time. Participants will be asked to return for one final visit and to return any study medication. Participants may be withdrawn from the study at any time based upon investigator judgement.

11.2 Withdrawal Procedures: Any participant who is removed from the study by the principal investigator will be asked to return for one final visit to assess adverse events and to collect any unused study medication and do a final study medication compliance.

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

11.4

12.0 Risks to Participants

12.1 Foreseeable Risks:

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

Risks of exposure to ionizing radiation: The DXA scans and the bone age scans involve exposure to a very low dose of ionizing radiation. The average amount of radiation that the average person would receive from the bone age scan and DXA scans used in this study is less than 2% (3 mrem) of that received from natural sources of radiation by a Minnesota resident in one year (300 mrem).

Risks of Lisdexamfetamine: Adverse reactions occurring in ≥5% and at a rate at least twice that of placebo in children include anxiety, dry mouth, diarrhea, nausea, vomiting, upper abdominal pain, irritability, insomnia and dizziness. Rarely reported adverse events include hypertension and tachycardia. Additionally, suppression of linear growth is a known class effect, though final adult height is not impacted.

- Although not recommended as a routine practice, baseline ECG will be obtained on all participants to screen for underlying arrhythmia. If SBP and/or DBP is ≥95th percentile or ≥130/80 (whichever is lower), blood pressure will be measured again on a separate visit within 2 weeks. If BP remains elevated on 3 separate visits, the participant will undergo a 24 hour ambulatory blood pressure monitor (ABPM) to confirm or rule out a diagnosis of hypertension.

  If elevated BP emerges and is confirmed on 2 additional occasions during lisdexamfetamine dose escalation, further dose escalation will halt until the results of a 24 hour ABPM are available.

  If hypertension is confirmed, lisdexamfetamine dose will be reduced until blood pressure normalizes.

  - If SBP and/or DBP is ≥95th percentile+12 mmHg or ≥140/90 (whichever is lower) and the participant is symptomatic, lisdexamfetamine will be discontinued and the participant will be referred to emergent care.
  - If heart rate is ≥140 bpm, an EKG will be obtained and the participant will be assessed for the need for emergent or non-emergent medical intervention, including the need to reduce or discontinue lisdexamfetamine dose.

  Risks of indirect calorimetry: Potential risks include feeling claustrophobic from the mask/hood.

Risks of Accelerometry: Potential risks include emotional distress from wearing the device 24 hours per day.

Risks of lifestyle therapy: Potential risks related to lifestyle therapy is sadness or frustration related to difficulty adhering to dietary and activity plans. Participants may experience injury related to increased physical activity. In our experience, participants tolerate lifestyle therapy without difficulty.

Risks of neuropsychological assessments and eating questionnaires: Potential risks include emotional distress and possible "test fatigue."

Risks of changes in mental health status: Individuals whose C-SSRS levels increase to a Moderate or High risk or whose CDI-2 values increase to a level of $\geq$ 70 (by either child or parent report) after the screening and baseline/randomization visits will have these values reported to a peds psychologist (either Dr. Gross or Dr. Kunin-Batson) and they may be referred to their mental health professional (if one is pre-existing) or provided with names of a mental health professional if one is not already in place.

12.2 Reproduction Risks: Exposure to ionizing radiation may cause harm to an unborn fetus. Therefore, all females will have a pregnancy tests before they undergo the bone age x-ray or the DXA scan.

12.3 Risks to Others: Not applicable.

13.0 Potential Benefits to Participants

13.1 Potential Benefits: Participation in the study will be restricted to children ages 6 to <12 years who have severe obesity and have a parent report of failing to lose weight with lifestyle therapy. Participants may benefit from participation in this study through close contact with the study staff and counseling on diet and physical activity which may result in weight loss. Participants randomized to active treatment will have access to experimental intensified treatment, lisdexamfetamine, which has been shown to cause weight loss in children treated for ADHD. The side effect profile of lisdexamfetamine is acceptable and the proposed study tests are not more than minimal risk.

14.0 Statistical Considerations

Data Analysis Plan: Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations, median and range for continuous variables and frequencies with percentages for categorical variables. Safety analyses (including Barkley's Side Effect Rating Scale and incidence of hypertension and tachycardia) will be primarily descriptive reporting the number and percentage of adverse events during participation in the study. All safety outcomes will be evaluated and monitored throughout the study. Confidence intervals (Cis) and P-values for all analyses will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$.

Aim 1: Estimate the treatment effect of LDX plus lifestyle therapy vs placebo plus lifestyle therapy on changes in BMI (%BMIp95 primary endpoint), body fat, cardiometabolic health and quality of life (QOL) from baseline to 24 weeks.
H1: We hypothesize that LDX compared to placebo will result in a greater mean decrease in %BMIp95 and body fat, and improved cardiometabolic health and QOL at 24 weeks.

The primary outcome measurement will be absolute change in percent of the BMI 95th percentile abbreviated %BMIp95. Although we will report on other metrics of BMI change including absolute BMI change and percent BMI change, we chose %BMIp95 as the primary outcome measurement because of its clinical utility in measuring changes in BMI in young children who have severe obesity and a consensus in the research community that expressing BMI change relative to the 95th percentile is preferred over other metrics such as BMI standard deviation score a.k.a. z-score. The limitation of BMIz is explained by the flattening of BMIz curve at values significantly above the 95th percentile, despite the wide variance of BMIs in youth with severe obesity, which therefore leads to an underestimation of clinically significant improvement in weight status). The primary outcome will be the mean change in %BMIp95 from baseline to 24 weeks follow-up compared between treatment groups, while adjusting for baseline value for added precision. See Table 1 for examples of changes in BMI and corresponding changes in %BMIp95.

Table 1. Examples of changes in BMI and corresponding changes in %BMIp95

Example Participant	Starting BMI (kg/m^2)	Starting %BMIp95	Ending BMI (kg/m2)	Ending %BMIp95	Absolute change in BMI (kg/m2)	Absolute change in %BMIp95
6 yo girl	26.37	140% of 95th percentile	25.2	134% of 95th percentile	-1.17	-6 percentage points
10 yo boy	39.8	135% of 95th percentile	28.7	130% of 95th percentile	-1.1	-5 percentage points

Power Analysis: Given this is a pilot and feasibility study, the sample size is not driven by a power analysis stemming from a formal statistical evaluation of a hypothesis test associated with the primary endpoint the trial.[83] Instead, the objectives of this study revolve around identifying key information on execution of the study and experience of participants to best inform the design of a subsequent, larger study to examine efficacy and effectiveness.

Secondary endpoints for Aim 1 are also continuous and will be evaluated in a similar fashion, with adjustment for baseline value. These include percent body fat, lab measurements of glucose, insulin, lipids (total-, LDL-, HDL-cholesterol, and

triglycerides), hemoglobin A1c, ALT, AST, and PedsQL. We will also report on other metrics of BMI change, including absolute BMI change and percent BMI change.

Aim 2: Generate estimates of the tolerability and safety of LDX used for the treatment of severe obesity in children.

H2: We hypothesize that at least 80% of participants will tolerate an LDX dose of ≥30 mg daily (recommended starting dose) for 24 weeks and that the LDX group compared to the placebo group will not demonstrate clinically significant increases in blood pressure or heart rate.

We will define feasibility to conduct the larger trial if, in this pilot study, >80% of participants randomized to LDX tolerate a dose of >30 mg daily, the recommended starting dose, for 24 weeks and there are no statistically significant differences between the LDX group and placebo group in incidence of developing stage 1 hypertension or tachycardia. Outcomes will be captured for all regardless of tolerability and will inform inclusions/exclusion criteria and dose escalation schedule for the subsequent trial. Safety outcomes will be monitored carefully and include instances of stage 1 hypertension (defined as SBP and/or DBP ≥95th percentile on 3 separate occasions) and confirmed by 24 hour ambulatory blood pressure monitor) and tachycardia (defined as heart rate ≥120 bpm at rest measured on 3 separate occasions). The Barkley Side Effect Rating Scale will also be measured at every 2 weeks during dose escalation and then every 4 weeks for the remainder of the study and will be used to help identify reasons for limited tolerability should this occur. Height velocity in cm/year will be determined by the difference in measured height between the baseline and 24-week assessments and will be used to calculate a height velocity SDS (z-score). Given the potential for LDX to disrupt sleep and the impact of sleep on obesity, participant sleep will be measured objectively using accelerometry with the ActiGraph (GT3X-BT) device, which has been shown to have acceptable reliability and validity in sleep-wake detection compared with laboratory-based polysomnography.[72] Nighttime sleep efficiency, defined as the portion of time dedicated to sleep that is spent asleep, will be evaluated as the primary sleep endpoint of interest, with higher scores representing more efficient sleep. All indexes will be calculated using the ActiLife software. Participant mental health will be monitored by the Columbia-Suicide Severity Rating Scale (C-SSRS) and Children's Depressive Inventory-2 (CDI-2).

Exploratory Aim: Examine potential mechanisms by which LDX reduces BMI in children with obesity. To do this, we will examine the effect of LDX on executive functioning skills, reward, appetite, resting energy expenditure and health behaviors (diet, eating behaviors, and physical activity). We expect that over the

24-week intervention, LDX compared to placebo will be associated with greater gains in executive functioning (measured by BRIEF-2 and NIH Toolbox), reduced reward responsiveness (measured by BIS/BAS), and reduced appetite (measured by visual analogue scale), which in turn will lead to more BMI reduction. Further, LDX compared to placebo will be associated with increased resting expenditure (measured by indirect calorimetry), leading to greater BMI reduction. Finally, we hypothesize that LDX compared to the placebo will be associated with greater reduction in calorie intake (measured by NDSR), binge eating (measured by (measured by CBES) and reward-based eating (measured by CEBQ), and a greater increase in physical activity (measured by accelerometry).

The exploratory evaluation of associations between treatment groups and exploratory endpoints will follow the same approach as in Aim 1 looking at mean differences in change from baseline. All endpoints are continuous and will have baseline measurements which will be used for baseline value adjustment for added precision in estimating contrasts between treatment groups and use robust variance estimation for the confidence interval and P-value. The results of these analyses will inform the larger definitive study in which these mediating relationships could be further defined.

14.1 Data Integrity: Impacting all aims, despite best efforts, it is possible that some data will be missing, which could limit the interpretation and generalizability of results. If the data are missing at random, conditioned on measured covariates, then supplementary analyses adjusting for these covariates will produce unbiased results. For potential missing data mechanisms beyond measured covariates, we will examine the extent to which results may be affected. Imputation techniques will be considered for missing data issues (e.g., multiple imputation). In particular, we will incorporate multivariate imputation by chained equations to handle missing data in follow-up visits.[85] The imputation models will include baseline values and change from baseline. Additional variables for inclusion in the model include age, race, sex, Tanner stage, BMI, and LDX dose. We will also examine results without imputed values. If the analyses with and without multiple imputed values differ substantially, then exploratory analyses will be performed to evaluated factors that may have contributed to the differences.

15.0 Health Information and Privacy Compliance

15.1 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.

X I am requesting that all research participants sign a HIPCO approved HIPAA

Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

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

Appropriate Use for Research:

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

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

X 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

X 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.

X 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:

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

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

Practitioners within the Pediatric Weight Management Clinic may approach patients who they feel might qualify for the study and discuss the study with the patient. The patient may be provided with a flyer with the study name and a QR code to submit a request for additional information.

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

15.5 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.

X 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. Potential participants who request information via use of the QR code will be contacted via phone or via email. Potential participants will be asked to accept email that is encrypted or, if unwilling, sign the email permission to send emails that are not encrypted.

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

This has been explained in other sections of the protocol.

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

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

X Store ☐ Analyze ☐ Share

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

☐ Store ☐ Analyze ☐ Share

X In REDCap (recap.ahc.umn.edu)

X Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

X In OnCore (oncore.umn.edu)

X Store ☐ Analyze ☐ Share

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

X Store ☐ Analyze ☐ Share

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

☐ Store ☐ Analyze ☐ Share

X In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices: 20200305, 20200303, 20191753, 20191752 20191431, 20191182, 20191181, 20190950, 20190949, 20190208, 20190091, 20181963, 20181819, 20221301 20180940, 20180861, 20180790, 20180789, 20170466, 20161203, 20160775, 20140912, 20140482, and 20140295.

x Store x Analyze x 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 a tablet or smartphone not previously listed

15.8 Consultants. Vendors. Third Parties. None.

15.9 Links to identifiable data: We will strive to maintain absolute confidentiality. All data will be stored in locked offices and will not be released without consent of participants. Data to be used in scientific presentations or publications will not contain identifiers.

15.10 Sharing of Data with Research Team Members. Team members will have access to Box, REDCap and OnCore.

15.11 Storage of Documents: Electronic documents are stored in password protected files that have two-factor authentication. Paper documents will be stored in locked offices and will not be released outside the study team without consent of participants.

15.12 Disposal of Documents: Disposal of paper documents will not happen until six years after the study analysis has been completed (to satisfy HIPAA requirements) or, in the event the study needs FDA oversight, until two years after the closure of the IND for this specific purpose, whichever is longer.

16.0 Confidentiality

16.1 Data Security: Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released outside of the study team without the consent of the participant. Data that is collected will be entered into REDCap and OnCore, which re only accessible by the study team via two-factor authentication. Data to be used in scientific presentations or publications will not contain participant identifiers.

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

17.1 Data Integrity Monitoring. Because this study requires FDA oversight, the study will undergo regular monitoring (at least annually) of the facility, staff, and study documents by clinical research associates in the University of Minnesota Clinical Trials Monitoring Service, which specializes in regulatory compliance for clinical trials associated with the Food and Drug Administration. This service provides regulatory monitoring of all research-related activities and is offered free of charge through the University of Minnesota Clinical and Translational Science Institute (CTSI). Monitoring of fidelity to the protocol (e.g., protocol deviations) will be performed at each monitoring visit. Monitoring staff will present a summary report to the PI after each monitoring session. If necessary, corrective action plans will be devised and implemented by the PI to address deficiencies.

Monitoring will be initiated shortly after IRB approval (before participants are enrolled) and then every six months. Consent and eligibility will be reviewed on 100% of subjects. Data will be reviewed on 10% of participants. Study monitoring will review the findings with the staff at the conclusion of the visit and the staff have 10 days to resolve the findings before the final report is generated. The monitoring report will be generated on Day 10 after the visit. Following written Standard Operating Procedures (SOPs), monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and

applicable regulatory requirements. The investigational site will provide direct access to source data/documents, and reports for the purpose of monitoring, auditing, and inspection by local and regulatory authorities.

17.2 Data Safety Monitoring. An independent Data and Safety Monitoring Board (DSMB) will be established to oversee participant safety in the clinical trial and provide overall monitoring of interim data and safety issues. An independent medical safety officer (medical monitor) with experience in pediatric obesity pharmacotherapy will review all serious adverse events. This individual will also serve on the DSMB. The DSMB will include a pediatric cardiologist, a pediatric psychologist and a biostatistician. DSMB members will not be affiliated with the study. At the first meeting, the DSMB (and medical monitor) will review the protocol and potentially recommend modifications. Subsequently, the DSMB will monitor and review recruitment, adverse events, data quality, outcome data, and overall trial performance. The DSMB will have the responsibility to review interim data and final data, and recommend whether the protocol should be modified, and, at each meeting, whether the study should be continued or should be terminated early. Review materials for the DSMB will be prepared and presented by the study biostatistician. The DSMB and medical monitor will review data every six months during the trial, beginning six months after enrollment of the first participant, to review data and evaluate participant safety. A charter for the DSMB will be developed and approved by the DSMB members along with a plan for frequency of data review prior to the commencement of the trial. 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 NIDDK program officer.

Adverse events (AEs), inter-current illnesses, and medications will be reviewed and documented at each in-person study visit, i.e., monthly throughout the study. Additionally, adverse events will be reviewed and documented every two weeks during dose escalation. Participants will be instructed to contact study staff immediately if any serious adverse event (SAE) is experienced.

Review of AEs: We will administer a standardized tool, the Barkley's Side Effect Rating Scale, which was developed specifically to monitor side effects from psychostimulants. This questionnaire, completed by the caregiver (and sometimes with child's help) requests feedback on 17 items on a 9-point Likert scale, including typical physical side effects (e.g., decreased appetite, insomnia, stomach aches, and headaches) and behavioral symptoms (e.g., irritability, anxiety).

Inter-current Illnesses/Medications: Participants will also be queried about any other new symptoms, inter-current illnesses, clinic or hospital visits, or medication changes.

- All AEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.
- Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.
- The study staff will record all reportable events with start dates occurring any time after informed consent is obtained until the final study visit. Any non-serious AEs that are not resolved at the final visit will be followed for an additional 7 days and any serious AEs that are not resolved at the final visit will be followed for an additional 30 days after the final visit. At each study visit, the study staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.
- All adverse events (AEs) will have their relationship to study intervention assessed by the PI who will remain blinded to intervention assignment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

    - **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
    - **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Adverse Event Reporting: The PI will be notified of all AEs within 7 days of identification; the PI will be notified of serious AEs (SAEs) within 24-hours of identification. A report of all SAEs will be sent to the FDA, the external medical monitor, DSMB,IRB, and NIH NIDDK program officer as soon as possible, but no later than five working days after the PI's initial receipt of the information. Reports of all adverse events, both serious and non-serious, will be provided to the external medical monitor and DSMB for review at their next regularly scheduled meetings.

Stopping Rules: In the event that a participant has an SAE that is deemed related to the study medication and/or procedures by the external medical monitor, DSMB, PI, and/or NIDDK, the participant will be required to immediately discontinue the study medication. However, the participant may be invited to stay in the study for lifestyle therapy if this seems beneficial to the participant and the SAE is not related to lifestyle therapy. Participants will be instructed that they may withdraw from the study at any time and for any reason. The overall study may be stopped at any time at the request of the external medical monitor, DSMB, PI, and/or NIDDK. Participants will be instructed that they may withdraw from the study at any time and for any reason.

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy: Please see HIPCO ancillary review.

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

19.0 Compensation for Research-Related Injury

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

19.2 Contract Language: Not applicable*.*

20.0 Consent Process

20.1 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 consent forms will be given to the participants and the parents/guardians.

20.2 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.

20.3 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.

20.4 Non-English Speaking Participants: It is typical for the children to be seen in the Pediatric Weight Management Clinic to speak English. At times, the parent feels more comfortable with the Spanish language. Should we receive a large number of families where the parent is a native Spanish speaker, we would amend the protocol to note that Spanish language parental consent forms will be used after IRB approval.

20.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): Participants who will enroll in this study will be aged 6 to <12 at study entry. Assent will be obtained from children who are aged 8 to <12 at study entry and a parent will also be needed to provide consent. Children aged 6 and 7 will not be asked to sign an assent form at study entry, but a verbal dissent to participate will be honored. Participants who turn 8 during the course of the study will be asked to sign the assent form. Participants will not reach the age of majority to require adult consent during their enrollment in the study.

Single parent consent will be secured. As this study has a potential for benefit, we believe it falls under 21CFR46.404 which allows single parent consent.

20.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: Not applicable.

20.7 Adults Unable to Consent: Not applicable.

- Assent: Children aged 6 to <12 at study entry will be approached about participating in the project.
    - Children aged 6 to <8 years of age will be asked to consent verbally. Dissent will be honored and noted in the record. Individuals who turn 8 during the course of the study will be asked to sign an assent form. A single parent will be asked to sign a parental consent form.
    - Children aged 8 to <12 at study entry will be asked to sign an assent form if they would like to participate in the study. A single parent will be asked to sign a parental consent form.
- Dissent: Dissent will be honored from the children who are approached about participating in this study.

21.0 Setting

21.1 Research Sites

- Study activities will take place at the University of Minnesota within the building located at 717 Delaware Street SE. All research procedures will be performed in this building.

21.2 International Research: Not applicable.

22.0 Multi-Site Research

Not applicable.

23.0 Coordinating Center Research

Not applicable.

24.0 Resources Available

24.1 Resources Available:

- When designing the study, the University of Minnesota CTSI, Best Practices Integrated Informatics Core (BPIC) identified 2,512 in our health care system (MHealth Fairview). Additionally, the clinician-scientist members of CPOM are all active in recruiting their patients from the University of Minnesota Pediatric Weight Management Clinics, where 600 new patients with severe obesity are seen annually. By harnessing the support of CPOM and the extensive pool of participants, we are confident in our ability to realistically recruit and retain the number of participants (n=44) proposed for this project.

- The implementation of research protocols within CPOM involves the PI and sub-investigators, the study coordinator, dietician and the regulatory manager who have regular meetings to refine the protocol before it opens for enrollment. The study, when close to opening for enrollment, will hold a protocol training for the CPOM staff where the protocol will be reviewed. Team members who are unable to attend will be provided with a slide deck overview of the study to familiarize themselves with the project. Many activities (lifestyle modification, bone age, DXA, ECG, indirect calorimetry, questionnaires, blood draws, measurement of height, weight, blood pressure and heart rate and the collection of adverse events) are seen in most of our projects so staff are quite familiar with procedures that will be conducted in this study.

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