Enhancing Effectiveness of Existing Weight Management Programs for Teens with Severe Obesity: a 6 Month Feasibility Pilot

NCT#: 03939494

7/22/19

TITLE OF STUDY: ENHANCING EFFECTIVENESS OF EXISTING WEIGHT MANAGEMENT PROGRAMS FOR TEENS WITH SEVERE OBESITY: A 6-MONTH FEASIBILITY PILOT

SHORT TITLE: HEALTHY WEIGHT FOR TEENS STUDY

Sponsor: NIH/NIDDK – R34DK118510

Study Sites: Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, OH'
Helen DeVos Children's Hospital (HDVCH), Grand Rapids, MI.

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1. ABSTRACT

The prevalence of obesity among adolescents (ages 12-19) continues to be a serious public health problem as the most recent national survey (NHANES: 2015-2016) reported 20.5% of adolescents have a BMI > 95th percentile. Especially concerning is the steady increase of severe obesity (≥ 120% of the 95th percentile for BMI) within this age group. Also the concurrent rise in obesity-related health complications, such as insulin resistance, dyslipidemia, and fatty liver disease, underscores this major health burden from severe obesity. The recommended treatment for adolescents with obesity is a pediatric weight management (PWM) program offered in a tertiary-care setting that combines dietary, physical activity and behavioral strategies, using a patient-centered model with frequent contact. However this approach often has poor adherence to treatment and high attrition rates. Providing at least 26 hours of contact over a 6-month treatment period was found to be most effective, but a recent survey of 29 PWM programs in POWER (Pediatric Obesity Weight Evaluation Registry) found most sites offer low-intensity interventions (<26 hours) due to limited resources and patient circumstances. To improve the effectiveness of PWM programs, this proposed study has identified a "bundle of program enhancements" (BPE) informed by a literature review, preliminary POWER outcomes, and evaluation of program characteristics of POWER's "top-performing" sites. The BPE components are: 1) Increasing provider contact hours in existing PWM programs to reach 26 hours during a 6-month treatment period by using remote interactive technologies to supplement standard-of-care clinic visits; 2) Identification of mental health problems during an individual program orientation prior to starting a PWM program, in order to initiate needed treatment as part

of a PWM program; and 3) Evaluation of “readiness to change” and “barriers to making lifestyle changes” with motivational interviewing during the orientation session, allowing for interventions tailored to the patient’s needs. The proposed study is a pilot pragmatic trial designed to test the feasibility, acceptance, and preliminary effectiveness of the BPE (*Intervention* group: N=40) vs. standard-of-care (*Control* group: N=20) for adolescents with severe obesity in PWM programs at two POWER sites. The primary aims are: 1) Test whether existing PWM programs can successfully implement the BPE for 80% of participants randomly assigned to the *Intervention* group and 2) Test whether 70% of participants in the *Intervention* group will complete 26 contact hours during 6 months of treatment. The secondary aims test whether the *Intervention* group has greater rates of participation and retention, plus better health outcomes compared to the *Control* group. If the results of this pilot study are promising, then a fully-powered multi-site clinical trial can be designed to evaluate the BPE’s efficacy in existing PWM programs. By developing more successful evidence-based interventions for PWM programs, this research can help reverse the adolescent obesity epidemic and prevent the onset or worsening of comorbidities.

2. INTRODUCTION

2.1. Background

The prevalence of obesity among adolescents (ages 12-19) continues to be a serious public health problem nationwide with 20.5% of adolescents having a body mass index (BMI) greater than the 95th percentile. 1 Though the rate of increase over the past decade has slowed, 2 there is a growing concern about the steady increase in severe obesity (BMI ≥ 120 percent of the 95th percentile for age and sex) within this age group. Based on NHANES survey from 1999-2014, the prevalence of adolescents with severe obesity doubled for girls (5.2% to 10.2%) and increased by one-third for boys (6.7% to 8.9%).3 In addition the concurrent rise in obesity-related health complications, such as insulin resistance, dyslipidemia, fatty liver disease, hypertension, obstructive sleep apnea and low self-esteem 4 emphasizes the extensive health burden resulting from severe obesity. Since obesity during adolescence is likely to persist into adulthood 5 developing effective intervention strategies is critically important. For adolescents with obesity who are unsuccessful with primary care management, the American Academy of Pediatrics recommends a structured multi-component pediatric weight management (PWM) program offered in a tertiary-care setting that combines dietary, physical activity and behavioral strategies, using a patient-centered model with more frequent contact.6 However this approach has had limited success, often characterized by poor adherence to treatment and high attrition rates.7-15 A systematic literature review of clinical trials of behavioral multi-component PWM interventions for youth with obesity reported that those offering a medium-intensity (26-75 provider contact hours) to high-intensity (>75 contact hours) intervention over a 6-month period were the most effective, consistently resulting in small to moderate improvements in weight status. 5 However a recent survey of 29 multi-component PWM programs participating in POWER (Pediatric Obesity Weight Evaluation Registry) from across the country reported the majority of sites only offered low-intensity (<26 contact hours) interventions. 16 Therefore

innovative strategies are needed to increase provider contact time and improve retention rates of multi-component PWM programs in order to improve their effectiveness in treatment of adolescents with severe obesity. *By developing a more intensive, yet practical evidence-based intervention strategy for multi-component PWM programs, we can help reverse the adolescent obesity epidemic and prevent the onset or worsening of obesity-related comorbidities.*

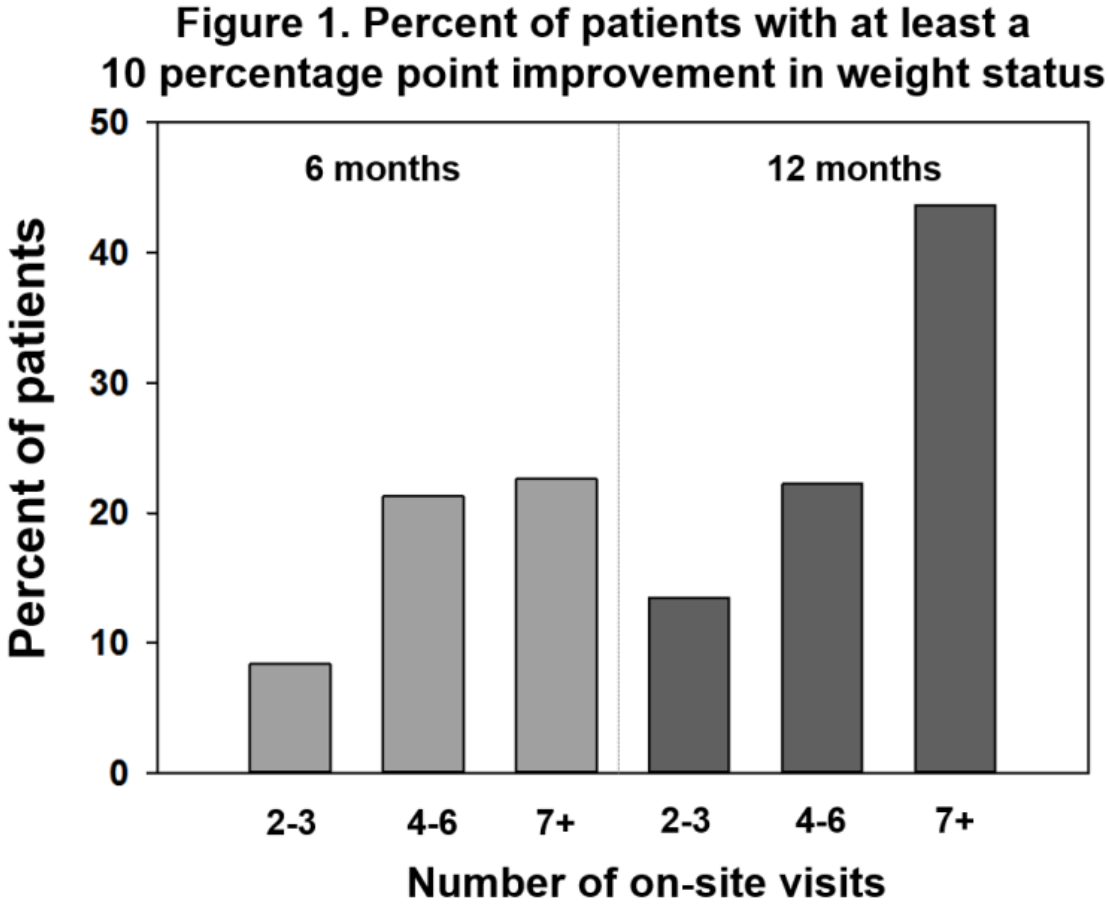
Preliminary Studies

POWER was established in 2013 to identify and promote effective intervention strategies for pediatric obesity within the tertiary care, specialty weight management program environment. Participating sites in POWER are multi-component PWM programs that collect a defined set of demographic, anthropometric, and laboratory data that are regularly sent to the POWER Data Coordinating Center.16 POWER now has data on 7200 patients with obesity aged 2-18 from 33 pediatric weight management programs). Patient enrollment began in May 2014 and is ongoing. Sites began enrolling patients into POWER after receiving approval from their local IRB. Sixty-three percent of patients have at least one on-site follow-up visit in addition to their baseline medical visit and 57% of patients have at least one follow-up lab. Nearly 50% of the patients enrolled in POWER are adolescents, 54% female, 54% white, 18% black, 31% Hispanic, and 59% publically insured. Seventy-four percent of patients present to the clinic with severe obesity.

The proposed study will enroll adolescents (12-18 years) that present with severe obesity. The demographics for adolescents in POWER are similar to the entire POWER population: 54% female, 56% Caucasian, 21% Black, 26% Hispanic, 62% publically insured and 61% with at least 1 follow-up visit. At the baseline medical visit, the median [IQR] weight status (measured by percent of the 95th percentile) is 141% [130%, 158%] and a high percentage present with abnormal (elevated) lab values: triglycerides (38%), non-HDL (20%), HbA1c (27%), fasting glucose (13%) and ALT (24%), underscoring the prevalence and severity of the comorbidities associated with severe obesity. This BMI metric is recommended for evaluating youth with higher levels of obesity.**17, 18** Modest changes in weight status have been observed in these adolescents during participation in the various pediatric weight management program in POWER; median [IQR] change in BMI: percent of the 95th percentile is -2.4 [-7.1, 1.0] at 6 months and -3.75 [-11.6, 1.4] at 12 months with 14.5 and 29 having at least a 10 percentage point improvement in percent of the 95th percentile at 6 and 12 months respectively.

For many PWM programs, provider contact with patients occurs only during on-site visits. The aims of this study are to determine if increasing contact hours by supplementing on-site visits and remote follow-up interactive contacts will lead to improved outcomes and a higher retention rate. Outcomes data from on-site visits that measure height and weight are captured in the POWER data base. The median [IQR] number of on-site visits for adolescent patients with severe obesity enrolled in POWER is 3 [3,5] at 6 months and 5.5 [4,7] at 12 months. The power data set shows a modest, yet statistically significant, correlation between an increased number of visits and a larger improvement in weight status at 9 and 12 months (9 months: $r=0.20$, $p<0.0001$;

12 months: r=0.22, p=0.0006). As the number of visits increases, the percentage of patients with improvement in weight status increases. Also, the longer patients stay in the PWM program with an increasing number of visits, the percentage of patients with improvements in weight status increases (Figure 1).



The POWER data set also shows significant correlations between improvement in weight status and improvement in laboratory values (ALT: r=0.46, p<0.0001; non-HDL: r=0.27, p=0.0022; HgA1c: r=0.27, p=0.0009; triglycerides: r=0.22, p=0.02) (Figures 2 and 3). A large percentage of patients with abnormal labs at baseline that achieved at least a 10 point improvement in weight status (i.e. percent of 95th percentile) at approximately 6 months also achieved normalized labs (alt: 57%; triglycerides: 46%; HgA1c: 62%; non-HDL: 43%).

Cincinnati Children's Hospital Medical Center (CCHMC) and Helen DeVos Children's Hospital (HDVCH) will be the two PWM programs participating in this trial and these sites see approximately 929 and 564 new patients each year, respectively. CCHMC began enrolling patients into POWER in May, 2014 with HDVCH following in June, 2014. The demographics for adolescents with severe obesity for these two sites are very similar to the POWER population with the exception of a lower percentage of

Hispanic ethnicity (7%) and a higher percentage of Black race (31%). For these two sites, the median [IQR] number of visits by 6 months is 3 [3, 7] and the median [IQR] change in percent of the 95th percentile for BMI at 6 months is -1.7 [-4, 3] with only 6% achieving an improvement of 10 percentage points in the weight status measurement at 6 months. Significant correlations between improvement in weight status and improvement in laboratory values were also seen for patients from these two sites (ALT: r=0.36, p=0.02; HbA1c: r=0.31, p=0.048; triglycerides: r=0.34, p=0.03). Testing the feasibility and acceptability of the BPE in these two sites that are representative of the entire POWER population will provide the needed data, including estimates of treatment effects, to design a fully powered multi-site clinical trial to evaluate the efficacy of the BPE as an enhancement for existing multi-component PWM programs.

Rationale for the Study

POWER is uniquely positioned to evaluate characteristics of multi-component PWM programs that are associated with “favorable” health outcomes for treatment-seeking youth with obesity. The POWER Data Coordinating Center developed ranking reports of the 33 participating sites based on weight status change at 6 months. An in-depth review of program design of 4 “top-performing” sites was conducted. A unique feature identified was offering an individual program orientation session to patient-families prior to the start of the multi-component PWM program. This orientation helped patient-families better understand the program’s expectations, and offered an opportunity to evaluate readiness to change, barriers for making lifestyle changes, and mental health problems. This information was used to tailor the intervention to better meet the needs of participating patient-families. When a survey of program characteristics was conducted of the 33 participating sites, this “top-performing site” was the only one to offer such a program orientation session prior to patient-families starting the PWM program. Therefore this program feature was included as part of the “bundle of program enhancements” (BPE) for this proposed pragmatic pilot study.

Figure 2

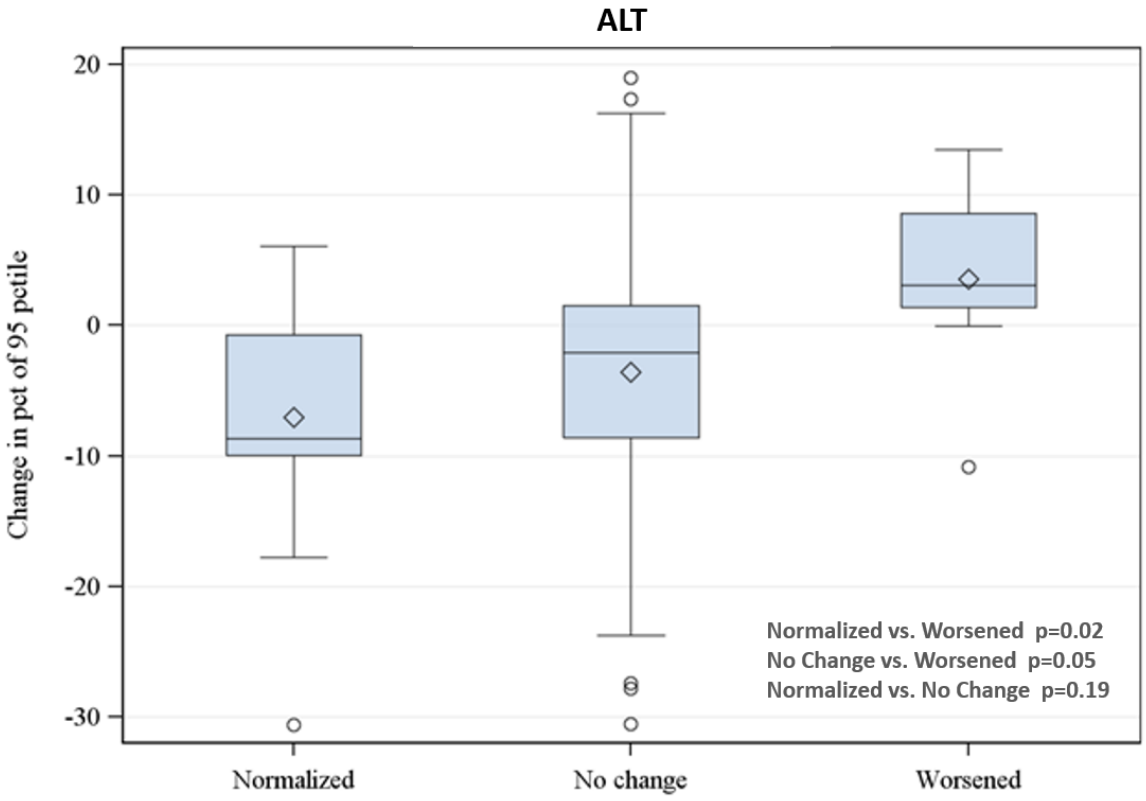
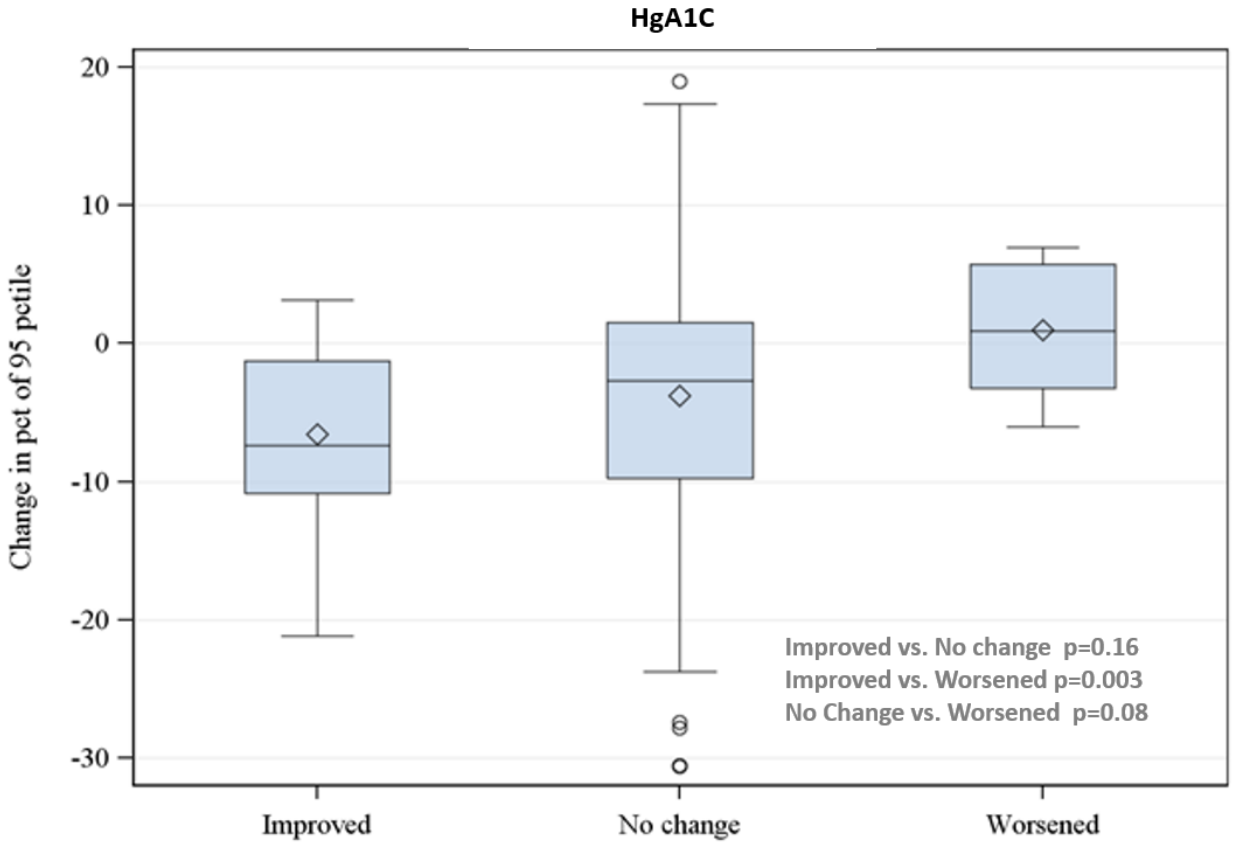

ALT
Change in pct of 95 pctile
20
10
0
-10
-20
-30
Normalized
No change
Worsened
Normalized vs. Worsened p=0.02
No Change vs. Worsened p=0.05
Normalized vs. No Change p=0.19

Figure 3.



Analysis of POWER data has also shown most participating sites have low provider contact hours compared to the recommendation of at least 26 provider contact hours over a 6-month treatment period, X particularly when resources, staffing, clinic space are limited, and circumstances of patient-families often prevent more frequent attendance at clinic visits. To address this gap in provider contact hours, an innovation in the proposed pilot study is the use of technology, such as telehealth19 to provide remote follow-up interactive encounters (FIEs). The sites in the proposed study have the capability to offer patient-families FIEs through a telehealth platform (Jabber®), email exchange, and/or phone calls. Furthermore the Twilio® text messaging platform will be used to send reminders to patient-families about scheduled FIEs. Twilio® will also be used to record FIEs scheduled and completed via the linked REDCap database. This feature of the BEP will be tailored to each participating site in order to achieve the goal of 26 provider contact hours over a 6-month treatment period from the combination of FIEs plus the standard-of-care clinic visits and group sessions (if offered).

3. PURPOSE OF THE STUDY

This pilot pragmatic trial is designed to test the feasibility, acceptance, and preliminary effectiveness of a “bundle of program enhancements” (BPE) vs. a standard-of-care control group for treatment-seeking adolescents with severe obesity. The BPE was

informed by a literature review of the effectiveness of pediatric weight management (PWM) interventions and evaluation of program characteristics of top-performing sites in POWER (Pediatric Obesity Weight Evaluation Registry). BPE components offer: 1) Increased contact hours with existing clinical staff of a multi-component PWM program to achieve a medium-intensity intervention (26 contact hours during a 6-month treatment period) using remote interactive technologies to supplement standard-of-care clinic visits; 2) Identification of mental health problems during a program orientation offered prior to starting a PWM program, in order to initiate needed treatment while participating in a PWM program; and 3) Evaluation of "readiness to change" and "barriers to making lifestyle changes" using motivational interviewing as part of the orientation session, allowing for tailored interventions to better meet patient needs. This proposed pilot study will involve 2 multi-component PWM programs, which both are participating in POWER.

Primary Aim 1 *(Feasibility)***: Test whether existing multi-component PWM programs can successfully implement the BPE for adolescents with severe obesity using existing clinical staff.** Successful implementation of the BPE will be defined as ≥80% of the *Intervention* group participants randomly assigned to the *Intervention* group and their parent/guardian attending the individual program orientation *prior to* the initial medical assessment visit of the PWM program. The program orientation will include: 1) Validated mental health questionnaires to assess cognitive, emotional and behavioral problems, anxiety, and binge eating disorder; 2) Clinical evaluation of "readiness to change" and barriers to lifestyle changes, using motivational interviewing; and 3) Scheduling of follow-up interactive encounters (FIEs: telehealth visits, phone calls, and/or email exchange) for the 1st month of the 6-month treatment period. For the remaining 5 months of treatment, participants in the *Intervention* group will be scheduled monthly for FIEs between clinic visits to achieve a total of 26 contact hours when combined with standard-of-care clinic visits and group sessions, if offered.

Hypothesis 1.1: 80% of participants in the *Intervention* group (N=40) will successfully complete all components of the BPE in the program orientation session (as described above), with existing clinical staff in their respective multi-component PWM program.

Hypothesis 1.2: 80% of participants in the *Intervention* group will successfully schedule FIEs between clinic visits for the remaining 5 months of the 6-month treatment period to achieve a total of 26 contact hours.

Primary Aim 2 *(Acceptability)***: Evaluate rates of retention and attrition among participants in the *Intervention* group**

Hypothesis 2.1: 70% of participants in the *Intervention* group will complete 26 contact hours (including standard-of-care clinic visits, group sessions, and FIEs between clinic visits) during the 6-month treatment period.

Hypothesis 2.2: 70% of the scheduled FIEs will be completed by participants in the *Intervention* group.

Secondary Aim 3 Test whether the *Intervention* group has greater rates of participation and retention in standard-of-care clinic visits and group sessions (if offered) compared to the *Control* group.

Hypothesis 3.1. Participants in the *Intervention* group will have a greater rate of participation in the standard-of-care PWM program as measured by percent of scheduled clinic visits and group sessions (if offered) attended over the 6-month treatment period, compared to those assigned to the *Control* group (N=20)

Hypothesis 3.2. Participants in the *Intervention* group will have a greater retention rate (percent of participants that complete the 6-month treatment period) than those in the *Control* group.

Secondary Aim 4 Test whether the *Intervention* group has better health outcomes when compared to the *Control* group after the 6-month treatment period. Health outcomes to be measured at baseline, 3-month, and 6-month assessment visits will include: 1) Weight status (BMI metric: percent of the 95th percentile); 2) Body composition (% body fat, skeletal muscle mass; fat-free mass); and 3) Blood pressure. Laboratory measures (HbA1c, ALT, non-HDL, TG, fasting glucose) will be obtained at baseline and 6-months.

Hypothesis 4. The *Intervention* group will have better health outcomes than the *Control* group.

Expected outcomes and impact: If the results of this pilot pragmatic study show that the BPE is feasible, acceptable and potentially effective, then we will have the information needed to design a fully-powered multi-site clinical trial to evaluate the efficacy of the BPE as an enhancement for existing multi-component PWM programs. If it is found that the BPE is efficacious, this evidence-based approach can then be widely implemented in order to improve the treatment of adolescents with severe obesity.

4. STUDY DESIGN

4.1. Study Description

A pilot pragmatic trial involving 2 multi-component PWM programs participating in POWER (Pediatric Obesity Weight Evaluation Registry) will be conducted to determine the feasibility of implementing a “bundle of program enhancements” (BPE) and its acceptability to 40 adolescents (ages 12-18) with severe obesity.

4.2 Study Duration

Each patient will participate in the study for approximately 6 months. Study is expected to last approximately 2 years.

5. SELECTION AND RECRUITMENT OF PARTICIPANTS

Participants will be drawn from the patient population of the multi-component PWM program selected to participate in the proposed study. Potentially eligible participants will be identified from clinic schedules for new patients who meet age criteria (12 to 18 years) and are scheduled at least 4 weeks in advance of the initial medical assessment visit. Name of patient and parent/guardian, current home address and contact phone numbers will be obtained for the identified patients, who will then be mailed the study's Introductory Letter. This letter will provide an overview of the study and inform them that a study staff member will be contacting them by phone with more details. The Introductory Letter will include a phone number and email address that will allow patient-families to opt out of the follow-up phone call. A standardized script will be used for the follow-up telephone interview. Details of the study will be explained and a screening questionnaire will be completed to further ascertain inclusion/exclusion criteria, and interest of the adolescent and parent/guardian to commit to the study. If the adolescent and parent/guardian meet the study's eligibility criteria based on information obtained during the telephone interview, they will be invited to schedule a screening visit with study staff to confirm eligibility criteria are met. The screening visit will be scheduled before they are seen for their scheduled initial medical assessment visit with the PWM program. Informed consent will be obtained in person at the screening visit.

5.1. Inclusion Criteria

Subjects who meet all of the following criteria will be eligible for the study:

- ≥ 12 years of age and ≤ 18
- Scheduled for a new patient clinic visit at the multi-component PWM program at CCHMC or HDVCH
- Severe obesity (≥ 120% of the 95th percentile for BMI based on age and gender at time of screening visit)
- Able to understand and complete the consent process
- Have access to a smart phone, device, or computer with a web camera
- Have access to the internet

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

- Lacking capacity to provide informed consent
- Non-English speaking
- Participating in any other weight management program or research study related to weight management
- Have a sibling participating in any other weight management program or research study related to weight management
- Currently taking anti-obesity medication (Phentermine, Orlistat, Qsymia, Naltrxone-Bupropion, Lorcaserin, or other medications that promote weight loss such as Victoza (liraglutide), Trulicity (dulaglutide), Byetta (exenatide), others at the discretion of the PI). Also, patients should not start these medications while enrolled in the study.

6. STUDY PROCEDURES

Screening Visit– Adolescents and their parents/guardians who appear to qualify for the study based on the telephone interview will be scheduled to attend a screening visit. At the screening visit, height and weight measurements for the adolescent will be obtained by a qualified member of the study staff, using a standardized protocol and demographic information (date of birth, sex, race, ethnicity, and type of health insurance coverage) will be obtained and recorded. Adolescents and their parents/guardians who meet all inclusion/exclusion criteria, and express interest in participating in the study, will engage with a qualified member of the study staff who will review the consent/assent with the participant and their parent/guardian to ensure information presented is understood prior to obtaining the appropriate signatures for the IRB-approved informed consent/assent form. At the screening visit, participants and their parents/guardians who have met all criteria and informed consent/assent was obtained, will be enrolled in the study. Enrolled subjects at the screening visit will then be randomly assigned to either the *Intervention* or *Control* group, using a 2 *Intervention*:1 *Control* randomization ratio. At the end of the screening visit, all participants will be given a reminder card about their scheduled initial medical assessment visit with the PWM program. The week prior to this clinic visit, they will also receive a reminder call. This initial medical visit with the PWM program will serve as the baseline assessment visit for the study.

Group Assignment – Subjects will be randomized to either the Intervention or Control group using a *2 Intervention:1 Control* randomization ratio. The randomization plan will be stratified by study site such that the 2:1 randomization ratio will be obtained within each study site. In addition, randomization will be stratified by baseline obesity status (Class 2, Class 3) to ensure the appropriate balance of obesity classes within each treatment group. A statistician independent from the study team will provide the

randomization plan so that the study team is blinded to the group assignment for each newly enrolled patient until that patient is randomized.

Program Orientation – Immediately after the screening visit, participants assigned to the *Intervention* group will attend an individual Program Orientation session. This will include the following: 1) Detailed site-specific description of the PWM program; 2) Assessment of "readiness to change" and barriers to lifestyle changes using motivational interviewing strategies, including "confidence rulers"; 3) Completion of selected validated mental health assessment questionnaires; and 4) Scheduling of FIEs between clinic visits. The frequency, time spent, and type of FIE will take into consideration the needs of each patient-family enrolled in the study. The adolescent and parent/guardian will determine whether they will participate together during a FIE, do them separately or have a combination of the two. The frequency of contact between clinic visits will be determined by the number of contact hours provided by clinic visits as part of the "standard-of-care" over a 6-month treatment. The goal for the *Intervention* group is to have a total of 26 provider contact hours over the 6-month treatment period. After accounting for the contact hours from clinic visits as part of the "standard of care", the balance of the 26 contact hours will consist of FIEs scheduled between clinic visits. At the end of the Program Orientation, the subject and parent/guardian will schedule FIEs and use tracking calendar booklet provided to keep record of their scheduled clinic visits and FIEs for the first month of treatment. A summary of the findings from the mental health assessment measures, assessment of "readiness to change" and barriers to lifestyle change for each subject in the *Intervention* group will be reviewed with the clinical team at each site prior to the initial medical visit with PWM program (Table 1). Baseline Assessment - Each participant *(Intervention and Control groups)* will complete at their initial medical visit with the PWM program a baseline assessment that includes the following measures: 1) Anthropometric measurements (height and weight); 2) Body composition assessment (% body fat, skeletal muscle mass, fat-free mass); and 3) Blood pressure (systolic and diastolic). Fasting blood work (plasma lipids, glucose, liver enzymes, and hemoglobinA1c) will be obtained up to 3 months prior to the initial medical visit or up to 6 weeks after the initial medical assessment visit. Fasting blood samples will be drawn for the laboratory analyses by qualified staff at a certified medical laboratory affiliated with CCHMC and HDVCH. Standardized methods and analytic procedures will be done for each blood parameter. The results of all clinical measurements and laboratory values, and referrals and/or additional clinic visits made to address mental health concerns will be recorded on the study's source document, specific for each subject. In addition contact time and provider types involved in the initial medical visit will also be recorded (Table 1).

Height will be measured with a calibrated wall-mounted stadiometer by qualified clinical staff following a standardized protocol.

Body Weight will be determined using the same calibrated, electronic digital scale for all subjects at each site to eliminate mechanical variation between and within subjects.

Body Composition will be measured using the InBody 270® that is based on bioelectrical impedance analyses. When scheduling female patients for their study assessment visits, consideration will be given to avoiding the time period of their menstrual cycle. In the event a subject has her period when attending a study assessment visit, the subject will return to obtain a body composition measurement when their menstrual period is done.

Blood Pressure will be measured using a standardized protocol33 by qualified clinical staff at each site. Blood pressure (BP) will be measured in the right arm unless specific subject conditions prohibit the use of the right arm. Upper arm circumference may be measured to ensure proper cuff size. Three consecutive blood pressure readings are obtained, using the same arm.

Six-month Treatment Period: *Intervention group* – Subjects will be scheduled for clinic visits and program group sessions (if offered) in accordance with the "standard of care" for the PWM program at each clinic location. Scheduling of remote FIEs (telehealth, phone call and/or email exchange) between clinic visits will be done on a monthly basis for the duration of the 6-month treatment period. The projected contact hours accumulated for the scheduled interactive encounters between clinic visits, when combined with the planned clinic visits and group sessions (if offered) is targeted to achieve 26 contact hours for the 6-month treatment period. These scheduled FIEs will be entered in the Twilio text messaging platform, which will automatically provide text message reminders of the scheduled FIEs. Twilio is also integrated with REDCap, which can provide reports on the FIEs scheduled, completed FIEs and time spent, provider type at encounter, and who participated (adolescent alone, parent/guardian alone and/or adolescent and parent/guardian together. *Control group* - Subjects will only receive the "standard of care" for weight management at their clinic location. Treatment data collection - Each clinic visit and group session attended, type of interactive encounter completed between clinic visits, and time spent by provider type, will be recorded on the study's source document, specific to each subject. In addition referrals made and additional clinic visits completed to address mental health concerns, as indicated, will be recorded as well (Table 1).

Table 1. Key Outcome Measures for Primary Aims (in bold font) and Secondary Aims		
Aim	**Variable**	**Source**
1	% of subjects attending program orientation	Program Orientation Session *(Intervention Group only)* Tracking form for attendance and completion of assessment measures, and documentation of scheduled FIEs
	% of subjects completing mental health assessment questionnaires	
	% of subjects completing "readiness to change" clinical assessment	
	% of subjects that complete scheduling of follow-up interactive encounters (FIEs) between clinic visits for 1st month of treatment	
1	% of subjects that complete scheduling of FIEs between clinic visits to achieve a total of 26 contact hours when combined with standard-of-care clinic visit over the 6-month treatment period	6-month Treatment Period Tracking form for completion of clinic visits and FIEs between clinic visits, time spent, and provider type.
2	% of scheduled FIEs between clinic visits completed *(Intervention Group only)*	
	% of subjects that achieve 26 hours of contact time *(Intervention Group only)*	
3	% of scheduled standard-of-care clinic visits attended *(Intervention and Control Groups)*	
	% of subjects that complete 6-month treatment period *(Intervention and Control Groups)*	
4	Anthropometric measurements (height, weight) BMI outcome metric: % of the 95th percentile for BMI	Clinical Assessment Visits *(Intervention and Control Groups)* Baseline, 3-, and 6-month assessments Tracking form for anthropometric and body composition measurements, and blood pressure.
	Body composition (% body fat, skeletal muscle mass, fat-free mass)	
	Blood pressure (systolic, diastolic)	
4	Laboratory values* (fasting) (HbA1c, ALT, glucose, non-HDL cholesterol, and TG)	Clinical Assessment Visits *(Intervention and Control Groups)* Baseline and 6-month assessments Tracking form for laboratory measures

Three-month and Six-month Assessments: Participants will be assessed following the same procedures as for the baseline assessment, with measurement of height, weight, body composition, and blood pressure. If the participant is at Tanner stage I, II, or III at the baseline visit, Tanner staging will be assessed again at the six-month visit. Fasting blood work will be obtained at the 6-month assessment visits. The results of all clinical measurements and laboratory values will be recorded on the study's source document, specific for each subject (Table 1). Completion of the 3-month and 6-month reassessment clinic visits can occur 2-weeks prior or 4 weeks after the 3-month and 6-month time points.

Table 1 Schedule of Procedures

Elapsed Time	Screening Visit	Baseline Medical Visit	#Month 3 Medical Assessment	#Month 6 Medical Assessment	Telehealth/Phone/Email remote encounters between visits	Other clinical in-person encounters
Randomization	X					
Height and Weight	X	X	X	X		X
Body Composition (%body fat, skeletal muscle mass, fat-free mass)		X	X	X		X
Blood Pressure		X	X	X		X
Demographics	X					
Program orientation session detailing site-specific description of pediatric weight management program	X*					
Mental Health Assessments	X*					
Readiness to change assessment	X*					
Schedule Follow-up Interactive Encounters		X*	X*		X*	X*
Review Medical History		X	X	X		X
Physical Exam		X	X	X		X
Blood for serum chemistry		X		X		
Assess for adverse events		X	X	X	X	X
Medication Review		X	X	X		X

*Intervention Group Only

-2 weeks/+4 weeks

6.1. Process of Obtaining Informed Consent

A waiver of documentation of consent will be in place to collect patient height and weight to determine subject eligibility prior to the patient being consented. Consent, parental permission and/or assent will be obtained from all patients before any other study related procedures are performed. Written assent will be obtained from participants 12 years of age and older. The investigator will be available to answer any questions that the participant or parent may have regarding procedures, risks and alternatives. The consent process will be documented on the informed consent progress note. A copy of the signed consent(s) will be kept in the patient's medical record.

The study team will monitor the age of each participant. If a participant turns 18 during their study participation, the investigator or study coordinator will approach the participant during a routine clinic visit to confirm they would like to continue their participation in the study. The participant will be asked to sign a fresh consent form, documenting their consent.

7. DATA COLLECTION AND MANAGEMENT

7.1. Data Management

The Data Management Center (DMC) at CCHMC will provide full data management support to the project. The DMC will develop the data capture system using a web-based data collection system, REDCap, as the primary source of data entry and storage. Data will be recorded on study specific case report forms (CRFs) and entered into the REDCap data base. Some data may be entered directly into the REDCap data base from source documents. Participants will be given a study identification number that will be reported on all CRFs. REDCap is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data developed by Vanderbilt University, with collaboration from a consortium of institutional partners including the University of Cincinnati, Academic Health Center. The DMC will develop, test and maintain the REDCap data entry system, the data management plan, data quality checks and query management, and preparation of the data for analysis.

The REDCap system provides a secure, web-based application that is flexible and provides: 1) an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry; 2) HIPAA-compliant and 21 CFR Part 11-ready audit trails for tracking page views, data manipulation and export procedures; 3) record locking and electronic signature functions; 4) fine grained control of user rights to view and manipulate data, and tool to sequester data access for multiple sites; 5) a report builder for reporting, monitoring and querying patient records; and 6) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

REDCap is hosted on a network specially designed to support the rigorous security and compliance requirements of basic, clinical and translational research projects. Administered by the Division of Biomedical Informatics (BMI), this network features

multiple firewalls as well as a central facility for managing hosted systems and users. The result is another layer of access control and audit capability on top of what REDCap already provides. For example, a user's ability to access a REDCap study or even a specific questionnaire can be monitored and controlled at the network level without making any changes within REDCap itself. These capabilities are available to authorized BMI network administrators and REDCap study owners only, and all user access changes are documented by an automatic audit trail.

8. DATA ANALYSIS

8.1. Study Endpoints

Demographic and clinical characteristics will be summarized overall and within each center using frequency and percent for categorical data and median and interquartile range for the continuous measurements. For each aim below, the two-sided 95% confidence intervals will be calculated using the Score Confidence Interval.34 All comparisons between the intervention and control groups will be tested at the two-sided, 5% level of significance.

Aim 1: For patients in the intervention group only, percentages and two-sided 95% confidence intervals will be presented for the each of the components of the "Bundle of Program enhancements (BPE)": a) percent of participants attending the program orientation; b) percent of participants completing each of the mental health questionnaires; 3) percent of participants completing the "readiness to change" clinical assessment; 4) percentage of participants that complete scheduling of interactive encounters (FIE) between clinic visits for 1st month of treatment; and 5) Percent of participants that complete scheduling of FIE between clinical visits for each of months 2-6 of treatment. Each confidence interval will be examined to determine if the hypothesized value of 80% is contained within the interval.

Aim 2: For patients in the intervention group only, the percentages and two-sided 95% confidence intervals will be calculated for the intervention group only for the percent of patients that complete at least 26 contact hours during the 6-month treatment period. The confidence interval will be examined to determine if the hypothesized value of 70% is contained within the interval. In addition, the mean and 95% confidence interval will be presented for the percent of FIE completed by each patient and also for the total number of contact hours completed by each patient. These measures will also be provided for the subset of patients in the intervention group that are identified with mental health problems and descriptively compared to the subset of patients in the intervention group without mental health problems.

Aim 3: The rate of participation in on-site scheduled visits (i.e. clinic visits, group sessions) will be calculated for each patient in both the intervention group and the control group as the percentage of all scheduled visits during the 6-month period that was attended by the patient. These percentages will be compared between groups using the mixed effects model with treatment as a factor and site as a random effect. Additional covariates in the model may include baseline weight status as measured by percent of the 95th percentile, sex, race, ethnicity, socioeconomic status, and distance from clinic site. To the extent possible, interactions of covariates with treatment group will be examined and discussed if significant at $p<0.10$ level of significance. Transformations will be used (e.g. arcsin square root, log, rank) if needed to satisfy the assumptions of the model. The percentage of patients that complete the 6-month program will be analyzed using the same approach discussed above. In addition to doing hypothesis testing, treatment differences (unadjusted and also adjusted for covariates) and 95% confidence intervals will be presented.

Aim 4: Health outcomes measured by weight status, body composition, and blood pressure will be compared between the intervention and control groups using the repeated measures mixed effects analysis with center as a random effect. The outcome metric for weight status in the proposed study will be the change in percent of the 95th percentile for BMI (based on age and sex).

For each outcome, change from baseline will be calculated and included as the dependent variable. Terms in the model will include treatment, month (i.e. 3, 6 month) and the interaction of treatment by month. If the interaction is not significant at the two-sided $p<0.10$ level, it will be removed from the model. Appropriate contrasts will be used to compare the treatment groups at 3 months and at 6 months. Covariates in the model may be the same as those listed in Aim 3. The respective baseline measure may also be included as a covariate in the model for each health outcome. Laboratory measures will be measured at baseline and at 6 months of treatment. The mixed effects model using change in laboratory measure as the dependent variable and treatment as independent variable and center as random effect will be used. Covariates may include those listed for Aim 3 and the respective baseline laboratory measure.

8.2. Sample Size Calculation

Sixty subjects will be enrolled in this study across the two sites with 40 subjects randomized to the Intervention group and 20 subjects to the Control group. This is a pilot study and therefore confirmatory hypothesis testing will not be done. Therefore, formal power calculations were not done. Table 2 shows the width of the two-sided 95% confidence intervals for various percentages and sample sizes. Table 3 provides the treatment effects that are detectable with various sample sizes.

Table 2. Sample Size and 95% Confidence Intervals for an Observed Percentage for Study Aims 1 and 2				
	Sample Size			
Observed Percentage	N=40		N=30	
	Lower 95% CL	Upper 95% CL	Lower 95% CL	Upper 95% CL
50%	35%	65%	33%	67%
65%	49%	78%	47%	79%
80%	65%	89%	63%	90%
95%	83%	99%	81%	99%

Table 3. Sample Size and Treatment Effect						
Sample size Intervention/Control	Detectable Treatment Effect					
	80% Power		70% Power		50% Power	
	p<0.05	p<0.10	p<0.05	p<0.10	p<0.05	p<0.10
40/20	0.8	0.7	0.7	0.6	0.5	0.5
30/15	0.9	0.8	0.8	0.7	0.6	0.5

9. RISKS AND BENEFITS

9.1. Potential Benefits

There is potential for direct benefit for participating in this study. The intervention may help participants to lose weight, which has well documented emotional and physical health benefits. In addition, the information learned from this research study may benefit other patients in the future.

9.2. Potential Risks

The potential risk to patients include an individual's frustration with efforts at weight loss.

There is also a potential loss of confidentiality, though study staff will work

9.3. Risk/Benefit Analysis

The proposed study has minimal risks associated with it, which are reasonable in relation to the knowledge that will be gained and used to create interventional programs in this high-risk population.

10. ADVERSE EVENTS

Events that are unexpected and considered to be related or possibly related to the study procedures as well as breaches of confidentiality, and protocol violations must be reported to the site PI and the site's IRB as soon as possible. The site is responsible for

informing the PI at CCHMC of the adverse event in a prompt and timely manner. The IRB at CCHMC will be notified of the event in a prompt manner after discovery of the event.

11. DATA SAFETY AND MONITORING PLAN

For the proposed pilot study, participants randomly assigned to the *Intervention* or *Control* group will be participating in a multi-component pediatric weight management (PWM) program for a 6-month treatment period. The PWM program for this study will be offered at two sites: Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, OH and Helen DeVos Children's Hospital (HDVCH), Grand Rapids, MI. Robert Siegel, MD at CCHMC and William Stratbucker, MD at HDVCH, both serving as Co-Investigators for the proposed study, will be responsible for the oversight of the clinical management of study participants, their data collection, and address any medical issues that arise.

In addition as a requirement of all NIH-sponsored clinical trials, a Data and Safety Monitoring Board (DSMB) will be established to 1) evaluate all physiological and psychological data obtained for indications of adverse reactions; 2) investigate potential adverse events reported by the participants and/or clinical staff of the proposed study; and 3) evaluate the potential impact of these adverse events on the participants' health status and their continuation in the proposed study. The DSMB, an independent group of experts from Cincinnati Children's Hospital Medical Center (CCHMC) and the Connecticut Children's Medical Center, will be reviewing the data from this research throughout the study at both participating sites (CCHMC and Helen DeVos Children's Hospital (HDVCH), Grand Rapids, MI. The DSMB will be comprised of a physician, psychologist and biostatistician. The DSMB will meet via conference call at 3 months into the study and every 6 months thereafter, or more often as deemed necessary by the occurrence of adverse events. The "GoToMeeting" platform will be used in order to review documents during these conference calls. During the program orientation session for participants assigned to the *Intervention* group, and during the 6-month treatment period for the Intervention and Control groups of the proposed study, participants will be screened for adverse events by members of the multi-disciplinary clinical team when seen for clinic visits as part of the PWM program at each participating site, and during follow-up interactive encounters for participants in the *Intervention* group. Any adverse event will be appropriately documented and reported to the Principal Investigator, Shelley Kirk, PhD, RD, LD who will in turn forward all reports to the DSMB as well as the respective Institutional Review Board for CCHMC and HDVCH.

All recommendations by the DSMB will be communicated to the Principal Investigator, Shelley Kirk, PhD, RD, LD who will then take appropriate action as indicated. The DSMB will operate independently of the study investigators. The investigator will keep participants informed about any new information from this or other studies that may

affect the health, welfare, or their willingness to remain in the study. The individuals listed below have agreed to be members of the DSMB.

Stavra A. Xanthakos, PhD, MD
Associate Professor of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition
Cincinnati Children's Hospital Medical Center
Director, Steatohepatitis Center;
Medical Director, Surgical Weight Loss Program for Teens
Associate Director, Gastroenterology Fellowship Program
Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, OH

Melissa Santos, Ph.D.
Assistant Professor of Pediatrics
University of Connecticut School of Medicine
Clinical Director of the Pediatric Obesity Center
Senior Pediatric Psychologist,
Connecticut Children's Medical Center, Hartford, CT

Jessica G. Woo, MSHA, PhD
Professor of Pediatrics, Division of Epidemiology and Biostatistics
Cincinnati Children's Hospital Medical Center
Department of Pediatrics
University of Cincinnati, College of Medicine, Cincinnati, OH

12. PRIVACY & CONFIDENTIALITY

The privacy and confidentiality of patient information will be maintained in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations. All research personnel who work on this study must complete HIPPA and the Collaborative Institutional Training Initiative module on human research with direct subject interaction. No identifying data will be used in any publications that were a result from this work.

13. PARTICIPATION COST AND PAYMENTS

There is no cost to participate in this study. Participants will not be charged for the tests that are done for research purposes however, participants will still be responsible for the usual costs of medical care. Participants will be compensated for time and expenses incurred after completing the 3-month assessment ($25.00) and the 6-month assessment ($50.00). Payment will be made using "Clin-Card", a type of debit card.

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