TITLE: **MOBILITY- M**ETFORMIN FOR OVERWEIGHT & **OB**ESE CH**IL**DREN AND ADOLESCENTS WITH B**I**POLAR SPECTRUM DISORDERS **T**REATED WITH SECOND-GENERATION ANTIPS**Y**CHOTICS.

FUNDER: PCORI

A. SPECIFIC AIMS

The specific aim of this study is to address the significant gap in the evidence base for metformin (MET) use in overweight and obese youth with Bipolar Spectrum Disorders (BSD).

The overall objective of this prospective, large, PRAGMATIC randomized trial is to study the impact of MET and healthy lifestyle intervention (LIFE) vs. LIFE alone on patient-centered outcomes of body weight, Second Generation Antipsychotics (SGA) adherence and satisfaction, psychiatric symptom burden (e.g. mood/anxiety), and quality of life (QoL). We will also examine metabolic outcomes.

Specific Aim 1: Assess the overall and subgroup-specific impact of MET+LIFE versus LIFE alone on short- (6mo) and long-term (24mo) **weight and metabolic health** in overweight and obese youth with BSD.

Hypothesis (H)1.1: Overall, assignment to treatment with MET will abrogate more weight gain and lead to fewer adverse metabolic outcomes than LIFE alone at 6 and 24 months.

H1.2 (Heterogeneity of Treatment Effects [HTE]): MET's effectiveness at abrogating weight gain and components of metabolic syndrome will vary with respect to the following factors (see Patient Population and Background for rationale and prior data): 1) Change in BMI z-score from SGA initiation to baseline (in patients already receiving SGA treatment); 2) Prior exposure to and duration of SGA treatment; 3) Baseline BMI z- score; 4) Baseline psychotropic weight burden (in SGA non-naïve patients; as defined in Measures below); 5) BSD as diagnosed by a structured interview; 6) Age; 7) Type of insurance (public/private); 8) Ethnicity (Hispanic/Non); 9) Baseline insulin resistance (HOMA-IR); 10) Race (African-American (AA) vs non-AA).

Specific Aim 2: Assess the overall and subgroup-specific impact of MET+LIFE vs. LIFE alone on short- (6mo) and long-term (24mo) **SGA adherence and treatment satisfaction,** including assessment of how these effects may be mediated by MET effects on weight gain.

***H2.1*:** Overall, assignment to treatment with MET will lead to better SGA adherence and greater treatment satisfaction than LIFE alone after both 6 and 24 months.

***H2.2*:** (HTE): MET effectiveness with regard to SGA adherence will vary with respect to: 1) Baseline weight acceptability; 2) Baseline psychotropic medication treatment acceptability; 3) Type of insurance (public/private).

***H2.3*:** The overall effects of MET treatment on SGA adherence will be mediated by degree of weight abrogation, and this relationship will be stronger among girls than boys. We anticipate a possibly complex relationship between abrogation of weight gain (associated with MET) and SGA adherence, because weight gain may also be avoided via SGA non-adherence (at the probable cost of sub-optimal psychiatric outcomes; see Specific Aim 3). A statistical framework (marginal structural models) to accommodate this possibility is described in the Statistical Analysis Plan.

Specific Aim 3: Assess the overall and subgroup-specific impact of MET+LIFE vs. LIFE alone on **psychiatric symptom burden, psychotropic treatment changes**, **and overall and weight-related QoL**, including assessment of how these effects are mediated by MET effects on weight gain and SGA adherence.

H3.1: Overall, assignment to treatment with MET will be associated with lower psychiatric symptom burden, decreased risk for symptom-driven treatment changes, and greater improvements in overall and weight-related QoL than LIFE alone at both 6 and 24 months, post-randomization.

H3.2: (HTE): MET effects on psychiatric symptoms will be smaller in patients who meet full DSM criteria for a BSD.

B. BACKGROUND AND SIGNIFICANCE

Overweight and Obese Youth with Bipolar Spectrum Disorders (BSD): 1 out of 3 youth in the United States is overweight or obese. The rising prevalence of obesity and associated metabolic problems has led to elevated healthcare costs, marked morbidity, and high mortality. Compared with the general population, individuals with BSD have higher rates of obesity, poor access to medical care and premature mortality, largely due to the greater incidence of cardiovascular disease.[1-3] BSD are common psychiatric illnesses characterized by periods of mania, hypomania, and depression. Epidemiological studies suggest that BSD most commonly begin during adolescence and have a prevalence rate of up to 5% in youth.[4-7] Youth with BSD have a relapsing and remitting illness course, with greater functional impairment, poorer quality of life (QoL), and greater economic burden than those with later-onset BSD as well as youth with chronic medical and behavioral illnesses (e.g., asthma, heart conditions, and depression).[11] A major factor contributing to poor outcomes is the high rate of overweight or obesity in youth with BSD. 12 Rates of overweight/obesity in youth with BSD vary in studies between 45-80%, more than double that of the general population.[12-14] Overweight or obese youth with BSD have a more severe illness course, with a greater number of hospitalizations and higher rates of substance use disorders and physical abuse than youth with BSD who are not overweight or obese.[15] Moreover, these youth typically become overweight or obese adults with more medical problems and higher rates of psychiatric symptom recurrence, hospitalizations, and suicidality[16-18] as well as elevated morbidity and mortality.[15,19] Therefore, prevention and intervention for weight gain in youth with BSD is of significant public health interest and clinical concern.

Treatment with Second Generation Antipsychotics (SGAs) is on the Rise for Youth with BSD: Maximizing mood stability and minimizing medication side effects are the primary treatment goals for improving overall outcome and QoL of youth with BSD.[20-22] Over the past decade, there has been an increase in evidence-based treatments for youth with BSD. There have been at least 10 double-blind randomized controlled trials demonstrating that SGAs are effective for treating mania and depression in youth with bipolar disorder.[20,23-25] These studies have led to the United States Food and Drug Administration's (USFDA) approval of four SGAs (olanzapine, risperidone, aripiprazole, and quetiapine) for the treatment of mania in youth and of olanzapine/fluoxetine combination as the only evidence-based treatment for depression associated with bipolar disorder in youth. Furthermore, in contrast to adults with bipolar disorder, several studies have recently demonstrated that youth with BSD have a significantly greater response to SGAs than to other mood stabilizing medications (e.g., lithium, valproic acid).[23,29-31] In fact, in the only double-blind placebo-controlled study of lithium for mania in youth, only 38% had a > 50% reduction in symptoms of mania, as compared to most studies of SGAs, which report response rates of 55-80%.[23] Without equally efficacious evidence-based options for treating BSD in youth, SGAs use will likely continue to increase. Although treatment with SGAs offers advantages over conventional antipsychotics (e.g., haloperidol), such as lower rates of extrapyramidal syndromes, there is significant concern about the dramatic increase in SGA prescriptions for youth, because younger patients are more susceptible to SGA-related side effects than adults[23] and discontinuing SGAs without an effective alternative medication is not a treatment option for many youth with BSD.

Treatment with SGAs often leads to considerable symptom improvement, but is very commonly associated with substantial weight gain early in treatment. A primary etiology of overweight/obesity in youth with BSD is SGA exposure.[32] SGA-induced weight gain increases their already elevated long-term risk of cardiovascular disease and premature mortality.[33,34] Furthermore, metabolic syndrome is a common, more immediate consequence of SGA treatment in youth.[35,36] The risk for SGA-induced weight gain is much greater in youth than in adults.[23,32,37] The weight gain associated with SGAs is often dramatic and places these youth at risk for dyslipidemias and insulin resistance, which may progress to diabetes. Weight gain typically begins immediately following SGA initiation. In a recent study, over 50% of 272 treatment-naïve youth gained >7% of their baseline weight within 12 weeks.[38,39] These data may underestimate the problem; recently, we determined that 80% of SGA-treated youth gained > 7% of their baseline weight over two months while hospitalized at our Academic Health Center. The so-called "appetite aggression" induced by SGAs[40,41] may lead to violent behaviors and medication refusal following food restraint.

Although all SGAs cause some weight gain in youth, the amount of weight gain varies by specific SGA, prior exposure to SGAs, and the individual.[1,42] Treatment-naïve youth may be more susceptible to SGA-related weight gain.[1,38,43,44] Nonetheless, weight gain typically continues over the course of treatment. Indeed, we found 1 lb/week weight gain over 16 weeks in youth prescribed olanzapine, risperidone, or quetiapine for up to one year.[36,45] While it is unclear whether SGA-related weight gain is dose-dependent,[1,38,46,47] SGA polypharmacy may be associated with greater risk of metabolic syndrome compared to SGA monotherapy.[43]

SGA-related weight gain in this already overweight/obese population is particularly problematic, as most obese youth become obese adults.[48] In fact, studies report that approximately 70% of youth treated with SGAs are overweight or obese.[13,49] Although relatively few youth develop diabetes because of their large insulin reserves, 12-50% of youth treated with SGAs experience hyperinsulinemia and dyslipidemia,[50] which are related to the development of metabolic syndrome and cardiovascular morbidity and mortality.[51] Additionally, obesity during youth influences later morbidity and mortality to a greater extent than obesity present only during adult life [52,53] and the relationship of overweight, obesity, and metabolic abnormalities to poor cardiovascular outcomes is accelerated when age-inappropriate weight gain and metabolic abnormalities begin during development.[54] The immediate and dramatic nature of the anthropometric and metabolic effects is a common reason for SGA discontinuation,[55,56] is predictive of medication non-adherence in youth,[57] and has a negative impact on overall satisfaction with care and illness outcome.[58] Moreover, poor adherence in youth with BSD increases the likelihood of relapse[59,60] and is associated with substance use.[59]

Evidence-Based and Accessible Strategies for Managing SGA-related Weight Gain and Obesity in Youth with BSD are Urgently Needed. The mechanisms of SGA-related weight gain are likely multi-factorial, involving effects on central and peripheral hormonal, neuronal, and metabolic regulation of energy intake and consumption.[1,61-63] Regardless, the widespread and devastating impact of SGA-related weight gain on psychiatric symptoms, other health outcomes, and health care costs have led to an immediate need for standardized, evidence-based approaches to manage this common and serious side effect.[64]

Despite SGA-related medical concerns, these medications are highly effective for treating BSD[23] and thus, given a choice, patients and their families would prefer to effectively manage this side effect rather than change medications and risk relapse (see Significance). Nonetheless, discontinuation of SGAs or switching to a lower-risk SGA is a potential strategy to manage weight gain. Unfortunately, switching SGAs produces limited or inconsistent improvements in weight and metabolic outcomes, along with some psychiatric risk.[65] Indeed, in the recently completed IMPACT study,[66] youth treated with SGAs who were randomized to switching to an SGA with lower weight burden experienced significantly greater rates of psychiatric symptom exacerbation than those maintained on their original SGA with lifestyle intervention or metformin added.

Healthy Lifestyle Interventions promote physical activity and dietary lifestyle changes. Healthy lifestyle programs designed for youth, such as the "Healthy Eating Plan" associated with Healthworks!, developed and tested by Dr. Siegel (Co-Investigator), may lead to weight loss in obese youth.[67,68] However, some studies show only limited benefits and involve programs that are not easily accessible.[69,70] Studies of older adolescents and adults treated with SGAs found that healthy lifestyle interventions are effective for preventing weight gain and for weight loss, respectively, as well as for improving QoL, particularly when used early in the course of SGA treatment.[71-75] In general, 2-5% reduction in weight or 1-1.5 body mass index (BMI) units is reported in studies of healthy lifestyle interventions for patients with mental health disorders. However, these studies suffer from high dropout rates, small sample sizes, and short duration.[65,71-73,75]

Furthermore, the effects on weight and other metabolic parameters are small compared with pharmacological interventions.[65.] Despite these limitations, The American Medical Association (AMA) 2007[76] provides guidelines on interventions for youth ages 2-19 years old who meet CDC criteria for "at risk for overweight" and "overweight" (BMI% ≥85%ile) that involve simple education regarding diet and physical activity, i.e., healthy lifestyle intervention. Although these guidelines were not specifically developed for mentally ill youth, the approach has advantages for this population, including simple dietary guidelines and inexpensive strategies to reduce sedentary behavior. This approach is similar to the standardized Healthy Eating Plan and Physical Activity education (LIFE) that will be provided to each participant of the proposed trial.[67,76]

Metformin (MET) for Obesity in Youth. Pharmacological therapies, such as MET, supplement the effects of lifestyle interventions for weight loss. MET targets a molecular mechanism for weight gain, i.e., hypothalamic neuronal AMP kinase, a metabolic "fuel sensor". SGAs directly affect hypothalamic AMP kinase through histamine H1 receptors, decreasing leptin and insulin sensitivity.[77] MET is an oral anti-hyperglycemic, insulin- sensitizing agent that reduces hepatic gluconeogenesis and is noteworthy among diabetes treatments for not promoting weight gain.[78] MET is approved by the USFDA for treatment of type II diabetes in youth >10 years. MET decreases food intake in obese, non-diabetic individuals.[79] A recent meta-analysis[80] of 14 randomized clinical trials (N>1000) examining the effectiveness of MET for obesity in youth found an average BMI reduction of -1.38 (95% CI, -1.93 to -0.82) over 6 months compared with controls. Although a greater effect was seen for youth with a BMI > 35 at baseline, the authors concluded that a large trial is needed to determine the benefits to subgroups. Smaller meta-analyses report BMI reductions of -1.1 to -2.7 in obese youth compared with placebo or lifestyle intervention alone, in trials ranging from 6-12 months with MET dosages of 1000-2000mg/day.[81,82] Fasting insulin resistance, glucose homeostasis, and dyslipidemia improved after MET. In these studies of youth from 8-18 years old, MET was well-tolerated at up to 2000mg/day.[83-85]

MET is extremely safe in youth. Lactic acidosis is extremely rare, especially in the non-elderly and those with creatinine levels < 1.4, and the risk of neuropathy from chronic vitamin deficiency is low.[85] MET for Weight Gain in Patients Treated with SGAs. We chose MET over other evidence-based medications for weight loss (e.g., orlistat, sibutramine, or topiramate) because MET is the only medication that has been systematically studied for reducing weight in adults and youth treated with SGAs and because of its superior tolerability and safety profile when prescribed in conjunction with SGAs. Indeed, we first reported that MET is safe and effective for minimizing weight gain in youth taking SGAs.[36,86] Furthermore, in our randomized, placebo-controlled study, MET was associated with weight loss and improved insulin sensitivity, minimal discontinuation and no significant side effects other than transient gastrointestinal symptoms.[36] In contrast, 1 in 6 patients discontinued orlistat and 1 in 2 patients discontinued sibutramine because of side effects. Additionally, although topiramate is effective for weight loss, cognitive "slowing" commonly leads to discontinuation.[87] Subsequent to our studies, the utility of MET for weight loss in patients treated with SGAs has been confirmed in several RCTs and meta-analyses.[39,65,88-93] In fact, there are now seven meta-analyses of treatments for weight gain and/or cardiovascular risk factors in patients taking SGAs.

Most recently, Gierisch et al,[65] conducted a meta-analysis of studies of patients taking SGAs who were treated for weight gain and reported that adding MET was the only intervention studied to date that improves metabolic parameters, although, "comparative effectiveness studies are needed to test multi-modal strategies."[65] In another review of 11 MET studies (N=685) lasting on average 15.5 weeks, we determined that MET: 1) Produces statistically and clinically significant weight loss (-3.1 kg; 95% CI -4.5 to -1.6); 2) Improves lipid and glucose levels; 3) Is well tolerated; and 4) That weight gain resumes after stopping MET.[39] We also concluded that MET's effects might continue beyond 16 weeks, but noted there is a paucity of long-term studies.[94] Although MET may be even more effective for prevention (i.e.,

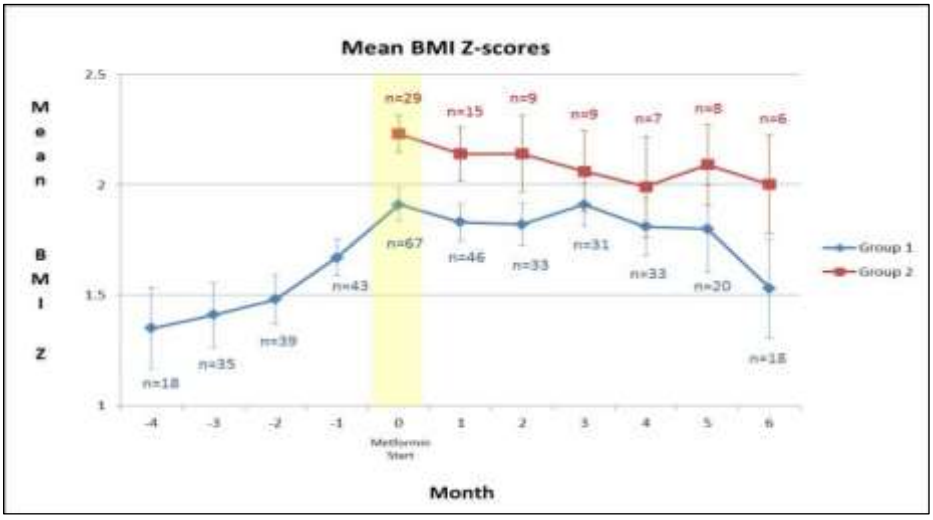
when MET is started concurrently with an SGA) rather than intervention (i.e., participants were started on MET when on a stable dose of SGA), there have been only 2 prevention studies. While these studies were both from China and are therefore difficult to compare to studies conducted in the U.S., their findings are highly consistent with our preliminary data. Therefore, based on our patient surveys and these data, we opted to include both treatment-naïve and non-naive patients in our proposed pragmatic trial. This would be the first study to directly examine differences in MET's effectiveness for prevention vs. intervention for weight gain in youth taking SGAs. Only one trial has compared MET alone, placebo plus healthy lifestyle intervention, and MET plus healthy lifestyle intervention: Wu et al.[95] reported significant weight reduction and improved glucose and insulin levels for combined MET plus healthy lifestyle intervention compared with either alone.[95] Based on these studies, the following recommendations were made: 1) The duration of future MET studies must be longer than 16 weeks to provide long-term efficacy data; 2) Larger studies are necessary to identify mediators and moderators; 3) Studies of MET in comparison to or combined with other strategies is much needed; 4) Because not all patients respond to MET, it is necessary to study heterogeneity of treatment effects (i.e., who is the best candidate for MET).[85,96,97]

In summary, meta-analyses confirm that treatment with MET is the strategy for which there is the most evidence for weight loss in patients taking SGAs.[65,90] However, each of the meta-analyses conclude that large- scale studies of MET in community settings and for long duration are urgently needed. We propose to conduct a pragmatic trial that addresses each of these gaps in evidence by investigating the long-term effectiveness of MET in obese and overweight youth with BSD, treated with SGAs in a community setting.

C. PRELIMINARY STUDIES

Pilot naturalistic study: 47 youth with a BMI > 85%ile and prescribed an SGA were treated with MET at CCHMC's residential treatment facility, using a MET dose titrated to 850 mg 2x/day over 2-4 weeks, with a further increase to 1000 mg 2x/day by 2 months if weight gain continued. BMI z score was the primary outcome measure. Electronic medical record data from two groups of these MET-treated patients were analyzed (MS submitted for publication): Group 1 (SGA non-naïve) was taking SGAs for at least 2 months (mean ± SD = 9.2 ± 7.2 months, range= 2.3 - 24.9) prior to MET initiation (n=29, 47% girls, age=13.9 years ± 2.5); Group 2 (SGA naïve) started on MET and SGAs simultaneously (n=18; 59% girls, age=14.2 years + 2.8). The groups were similar, and, as in our previous report, 40% received > 1 psychotropic medications. 80% of the SGA non-naïve patients had weight gain > 7% over the 2 months prior to MET initiation and exhibited a 0.45 sd increase in their BMI z score (Figure 1). Surprisingly, more of the SGA naïve (94%) than the SGA non-naïve (78%) patients had a BMI > 95%ile at MET initiation. BMI Z score was stabilized by MET in both groups, but there was a significant group by month interaction (p=0.003, generalized linear model), even after controlling for the higher baseline BMI z score (p=0.002).

Figure 1: MET prevention and intervention effects SGA-induced weight gain in youth Group1=SGA-non-naïve Group 2= SGA-naïve



This group difference resulted in part from the immediate decrease in BMI z score in the SGA naïve group (BMI z score decreased by 0.23). BMI z score of the SGA non- naïve group decreased by 0.27+0.5 during the 6 months on MET. SGA naïve patients responded at lower MET doses than SGA non-naïve patients (764 ± 225 mg/d vs. 834 ± 285). Additional determinates of MET response were: 1) Higher baseline BMI z score ($p<0.0001$); 2) Longer length of SGA treatment prior to MET initiation ($p=0.049$); and, 3) A > 7% increase in weight over the 2 months prior to starting MET ($p=0.0007$). These data confirm our previous results that MET abrogates SGA-induced abnormal weight gain in youth and also adds concerning information that a larger proportion of youth on SGAs are affected by weight gain than previously reported.

IMPACT Study: Most recently, Dr. Correll completed a large rigorously controlled NIMH-supported study of youth with psychiatric disorders and BMI > 85%ile and SGA-related weight gain. Participants were randomized to 1 of 3 arms: 1) continuation of current SGA (control arm) (N=44); 2) switch from current SGA to lower-risk agent (LRA) (N=30) or 3) co-treatment with MET + continuation of current SGA (MET) (N=46).

Sample characteristics were as follows: Age: 13.7 (7.6-19.9; <18=88%) Male=65% Hispanic:12% Black: 28%. At 12 and 24 weeks there was a significant decrease in BMI Z-scores in the MET (-0.034, -0.088, respectively) and LRA (-0.051, -0.112) groups compared with the control group (+0.026, +0.040). Additionally, at 24 months weight gain in the control group was 8.5lbs and 0.3lbs in the LRA group. In contrast, the MET group had an average decrease of -0.4lbs. 14.9% in the MET lost >5% of weight compared to 2.3% in the control group and 10.0% in the LRA group (Fisher's exact, $p=0.059$). Importantly, dropout rates in the LRA (39%) and control (28%) groups were higher than in the MET (24%) group. The most common (58%) reason for discontinuation in the LRA group was "inadequate therapeutic effect."

These findings confirm those of prior studies, including our own.[36,90] However, these, along with previous studies, have been conducted in academic settings, typically with many rigorous study criteria. Findings from such studies may not be generalizable to BSD youth treated in community settings where access to these interventions (e.g. healthy lifestyle strategies and medications) is often limited. Moreover, patient-centered outcomes were not assessed in these studies.

D. INVESTIGATOR EXPERIENCE

Principal investigator Dr. Melissa P. DelBello and lead Co-investigator Dr. Christoph Correll are international experts in BSD research and treatment. Both have been involved in numerous clinical trials of SGAs in youth with BSD and have ardently studied and warned about the metabolic side effects of SGAs in youth. These efforts led investigators to seek out effective methods to minimize these side effects, including the initial studies of SGAs and MET. This proposal is the culmination of these endeavors, seeking to collaboratively expand from clinical efficacy to field effectiveness studies with the ultimate goal of providing relevant and immediate information to patients, their family members, clinicians and policy makers to enable them to make informed and patient-centered decisions regarding SGA and MET use. Both investigators have exceptional track records for study oversight, completion and budget management of large projects supported by the National Institutes of Health, industry, and foundations.

The project team also includes: 1) Scientific experts in the field of community child and adolescent mental health (Michael Sorter, MD; Brian Kurtz, MD; Victor Fornari, MD), pharmacoepidemiology (Stephen Crystal, PhD) pediatric endocrinology (Nancy Crimmins, MD, Phyllis Speiser, MD, Steven Chernausek, MD) bipolar disorder and psychopharmacology (John Kane, MD; Stephen Strakowski, MS; Rodrigo Patino, MD), pediatric healthy lifestyle management (Robert Siegel, MD), complex database management (Jeffrey Welge, PhD;Yuanfang Xu, PhD; Thomas Blom, MS), regulatory oversight (Jeremy Corsmo, MPH), psychometrics and patient-centered outcomes (Adam Carle, PhD), treatment adherence and QoL (Avani Modi, PhD; James Varni, PhD) and biostatistics (Jeffrey Welge, PhD;Bing Huang, PhD) and 2) Key stakeholders representatives from parents and patients with BSD (Avraham Goldstein, Elaine Nowery, Dan Nowery, Adam Schwarber, Bev Schwarber, Sharde Scott-Manning, Barbara Portugal, Cindy Starr, Barbara Valerius), advocacy organizations (NAMI-Heather Turner; DBSA-Ingrid Deetz), professional organizations (AACAP-Carmen Head; Endocrine Society-Steven Chernausek) and payers (Medicaid-Mary Appelgate, MD and Humana-Nick Patel, PharmD, Vinit Nair, B-Pharm, MS). This research team was assembled with the ultimate goal of ensuring the project 1) Answers key clinical questions that are important to patients and families; 2) Is completed on schedule, within budget; and 3) Holds to the principles of good clinical practice, human subject protection and scientific rigor.

E. EXPRIMENTAL DESIGN & METHODS

a. Methods and Procedures

Study Overview: We propose a prospective, large, PRAGMATIC, randomized trial to study the impact of MET and healthy lifestyle intervention (LIFE) vs. LIFE alone on patient-centered outcomes of body weight, SGA-adherence and satisfaction, psychiatric symptom burden (e.g. mood/anxiety), and QoL. We will also examine metabolic outcomes.

The focus of the pragmatic trial is to determine which intervention is most effective through observation of care as usual conditions or in "real-world clinical settings" rather than under controlled experimental circumstances. Information should be collected when available as part of routine clinical practice rather than through study-specific procedures, with minimal interference to clinical practice. Adherence to protocol recommendations from practitioners and patients are observed and documented throughout the study.

Subjects: We propose to recruit approximately 1800 overweight/obese youth with BSD who are prescribed SGAs from at least 40 public and private mental health practices (approximately 900 each from sites under the coordination of University of Cincinnati, Midwestern center and from within the sites under the Northwell Health East Coast coordinating center), to participate in the proposed patient-centered large pragmatic trial examining the effectiveness of MET and LIFE vs. LIFE alone. Patients will be **eligible** for study participation if they are:

1. Inpatient or outpatient age 8-19 years inclusive*;* participants must live with a parent, guardian, or caregiver;
2. Fluent in English;
3. Diagnosed or told by a clinician that they have any of the following bipolar spectrum disorders (BSD): bipolar I, bipolar II, unspecified bipolar and related disorders, Disruptive Mood Dysregulation Disorder (DMDD), cyclothymic disorder, other specified bipolar and related disorders, as well as mood disorder not otherwise specified (if diagnosed in the past as per DSM-IV);
4. Body mass index ≥85%ile for age and sex by standard growth charts;
5. Received a new or ongoing prescription for at least one SGA (i.e., olanzapine, clozapine, risperidone, quetiapine, aripiprazole, ziprasidone, iloperidone, lurasidone, paliperidone, brexpiprazole or cariprazine) that is not prescribed as a PRN medication

Additionally, patients will be excluded by the following:

1. Patients will be excluded if they have had exposure to a total daily dose of MET 1000 mg bid for at least 2 weeks in the past 3 months;
2. Patients will be excluded if they could not tolerate MET during the recommended titration schedule outlined in the protocol;
3. Major neurological or medical illnesses that affect weight gain (e.g., unstable thyroid disease) or require a systemic medication that might impact weight or glucose regulation (e.g., diabetes mellitus [insulin], chronic renal failure [steroids]);
4. If lab results are available in the last 6 months, then a fasting serum glucose ≥ 126 mg/dL on two occasions prior to or during screening, indicating need for prompt treatment.
5. If lab results are available in the last 6 months, then a serum creatinine ≥1.3 mg/dL on two occasions during screening and/or follow-up, indicating potential impairment of renal functioning
6. Pregnant or breast feeding;
7. Based on their clinician's assessment, children and caregivers who are unable to complete screening/baseline assessments for any reason;

The enrollment rate will be approximately 1-2 patients/month/site for a recruitment time of 57 months.

Randomization: We will randomize 1800 patients (1:1 ratio) to either MET + LIFE or LIFE alone. All patients will receive a lifestyle intervention (LIFE) of brief standardized education. Once a patient is determined to meet the above criteria and has provided appropriate informed consent/assent, site staff will assign the participant a patient ID number. The site staff will then log on to the study's REDCap site and enter the Patient ID, and the following stratification factors: site, overweight or obese, previous SGA exposure, and sex of patient (transgendered patients will be randomized according to sex assigned at birth). REDCap has a built in mechanism that prevents duplication of subject ID numbers.

Once all stratification factors have been entered, the REDCap randomization module will return the next assignment for the appropriate strata.

OUTCOME MEASURES:
Due to MOBILITY being a pragmatic and largely observational study, any participant who is deemed eligible by the above criteria will be enrolled in MOBILITY. These criteria, along with providing appropriate informed consent/assent, are the necessary criteria for participation in MOBILITY. We will continue to collect data in a naturalistic manner from all patients who have met these criteria regardless of whether they begin the intervention to which they have been randomized or have not attended all of their clinical follow up appointments. Patients will have follow-up study visits and data collected concurrent with their existing CLINICAL visit schedule.

Primary Outcome Measure: BMI z-score will be computed from measurement of height and weight. Raw BMI is calculated as (weight (kg)/ height $(m)^2$). Normalized BMI (z-score, adjusted for age and sex), will be calculated using the program provided by the USDA/ARS Children's Nutrition Research Center at Baylor College of Medicine (http://www.bcm.edu/cnrc/bodycomp/bmiz2.html). At each site weight will be measured with a Seca scale, model 813, calibrated to the nearest 0.2 kg per manufacturer instructions annually using standard weights. A standard operating procedure on weight and height measurement will be made available to each site, and staff will be trained in its application. Scales will be zeroed before each individual measurement and the patient will be instructed to remove their outer clothing, shoes, backpack, coat, and any other extra heavy clothing. Weight will be recorded to the nearest 0.1 kg. Height will be measured with a wall-secured stadiometer. The stadiometer is not required to be calibrated as stated by manufacturer instructions. Height will be measured without shoes while standing on a flat surface with chin parallel to the floor. The patient's height will be recorded to the nearest 0.1 cm.

Secondary Outcome Measures:
Metabolic Health and Nutrition: As per clinical standards, blood pressure will be measured after 5 minutes of sitting at each patient visit. A minimum of 8-hour fasting total cholesterol, low-density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides, glucose, insulin, and glycosylated hemoglobin (HbA1c) will be recommended for collection (see Table 2). For HTE analyses the homeostatic model assessment for insulin-resistance (HOMA-IR) will be computed as: (Insulin [IU/mL] x Glucose [mg/dL] /405). Following the modified ATPIII guidelines,[130-132] metabolic syndrome is defined when ≥3 of the following: 1) abdominal obesity (BMI >90%ile, as in NHANES study of metabolic syndrome in youth[133]; 2) blood pressure ≥90%ile for height, age, sex; 3) fasting triglycerides ≥150 mg/dL; 4) low HDL cholesterol (males <40 mg/dL and for females <50 mg/dL); 5) fasting glucose ≥100 mg/dL Fulfillment of individual criteria and metabolic syndrome will be outcome measures.

Adherence and Treatment Satisfaction Outcomes:
Self-Reported Adherence and Barriers: Caregivers and children will answer standardized questions related to adherence and adherence barriers to taking SGAs, MET (if applicable), and LIFE. Information on missed and partial doses of each medication in the past week will be ascertained. Questions prefaced by non-judgmental language that normalizes non-adherence to treatment will be used. A time period of one week will be used to maximize respondent recall and minimize memory decay.

MEMS®6 TrackCap/SimpleMed PillBox: The Medication Event Monitoring Systems (MEMS) [AARDEX Corporation] and the SimpleMEd PillBox are electronic monitoring systems that measure the dosing histories of oral medications. They will be used to monitor adherence to SGAs or MET in a sub-sample of 300 patients at a subset of sites. They consist of a standard plastic vial or box with a threaded opening and a closure for the vial that contains a micro-electronic circuit to register the dates and times the bottle/pillbox is opened and closed. Data from the MEMS TrackCap will be downloaded at each study visit. Patients randomized at an inpatient site to MEMS monitoring will only receive this monitoring if they are scheduled to be followed at an outpatient site that was selected for MEMS monitoring; otherwise, the MEMS aspect of the randomization should be disregarded.

Treatment Acceptability: A single-item 5-category Likert-type patient report of satisfaction with psychotropic medication regimen (0=not at all satisfied to 4=very satisfied).

International Physical Activity Questionnaires (IPAQ):[140] The IPAQ is an instrument for cross-national monitoring of physical activity and inactivity with good reliability and validity for monitoring population levels of physical activity in diverse settings to assess adherence to LIFE physical activity recommendations.

We will also assess food choices and eating habits using questions selected from the Healthworks Nutrition Screener, Satiety and Food Responsiveness using items from the Child Eating Behavior Questionnaire, and Uncontrolled Eating and Cognitive Restraint using items from the 3-factor Eating Questionnaire.[167-168]

Psychiatric Outcome Measures:
PROMIS (Patient-Reported Outcomes Measurement Information System) measures undergo a standardized, extensive measure development process which includes literature review, expert meetings, qualitative interviews with families, item development, cognitive testing of the item content, confirmatory factor analyses to establish construct validity, and item response theory to establish psychometric properties. We will use items from the validated short-form assessments of Anxiety, Depression and Anger as well as Global Health and Peer Relationships (the latter two are HRQoL instruments; see next section).

PROMIS Anxiety Short Form: focuses on fear (e.g., fearfulness), anxious misery (e.g., worry), and hyperarousal (e.g., nervousness). Marginal Cronbach's $\alpha > 0.85$

PROMIS Depression Short Form: focuses on negative mood (e.g., sadness), anhedonia (e.g., loss of interest), negative views of the self (e.g., worthlessness, low self-esteem), and negative social cognition (e.g., loneliness, interpersonal alienation). Marginal Cronbach's $\alpha > 0.85$

PROMIS Anger Short Form: assesses angry moods (e.g., irritability and reactivity) and aggression (verbal and physical). Marginal Cronbach's $\alpha > 0.80$

Clinical Global Impressions Scale-Severity (CGI-S): Single-item assessments of symptom severity. Severity is rated from 1 (not at all ill) to 7 (among the most severely ill patients).

Young Mania Rating Scale (YMRS): 11-item clinician-rated instrument that assesses symptoms of mania.

Children's Depression Rating Scale (CDRS)-Revised selected items: a clinician-rated scale used for assessing severity of depression and change in depressive symptoms.

Quality of Life (QoL) and Functional Outcomes: We will ask patients and caregivers the number of days that they missed from school and work, respectively, in the last month and will use items from the following scales:

PROMIS Global Health: assesses physical, mental, and social health. Cronbach's $\alpha=0.88$.

PROMIS Peer Relationships: measures understanding and communication; companionship; and quality, reciprocity, and size of patients' social network Cronbach's $\alpha> 0.80$.

Children's Global Assessment Scale (CGAS): A single-item index of overall functional capacity. Scores range from 1 (indicating severe impairment) to 100 (indicating superior functioning).

Sizing Me Up & Sizing Them Up: self-report and parent-proxy measures of obesity-specific HRQoL for youth, with subscales measuring Emotional, Physical and School Functioning, Teasing/ Marginalization, Positive Social Attributes, Mealtime Challenges, and Social Distress/Avoidance, and a Total QoL score. Excellent documented internal consistency, test-retest reliability and convergent validity.

Body Weight, Image and Self-esteem Evaluation (B-WISE®): scale designed to capture and quantify weight satisfaction, ability to control food intake, self-esteem and other the psychosocial consequences of weight gain, scored on a 3-point Likert scale from 1 (never)-3 (all the time), Cronbach's α=0.79.

Caregiver Strain Questionnaire-Short Form 7 (CGSQ-SF7): Routine assessment of objective and subjective internalized caregiver strain, scored on a 5-point Likert scale from 1 (not at all)-5 (very much a problem), with good validity and reliability.

Laboratory Measures:
Site staff will collect and report any lab results that are obtained as part of the patient's clinical care. Laboratory tests will be suggested according to clinical practice guidelines, but will not be required for patients enrolled in MOBILITY, with the exception of a pregnancy test for all girls who have reached menarche and who are randomized to metformin. Additionally, since patients receive their treatment at mental health treatment facilities throughout the country and MOBILITY is a pragmatic study, patients may have laboratory tests performed at any laboratory facility that they typically would as part of their routine clinical care. We will collect the results of the laboratory tests once they are available in medical records. Therefore, we will not require CLIA certificates or other regulatory documents for each laboratory facility. Table 2 (at intervals that reflect standard clinical care) indicates the recommended lab measures according to practice guidelines.

Other outcome measures:

Patient Health Questionaire-9 (Item 9):[152] Assesses current suicidality; 0 (not at all), 3 (nearly every day) scale.
Zucker Hillside Side Effects Form:[119,153] Assesses intensity (1=not present, 4=severe) of adverse events in five domains (behavioral, neurological, cardiovascular, autonomic, GI side effects). Open ended AE (adverse event) questions at every visit.

STUDY SCHEDULE AND TREATMENT
Since MOBILITY is a pragmatic study, we will collect the above information, when possible, and in conjunction with patients' clinical visits. We will allow for data collection approximately monthly for the first three months, followed by every three months thereafter, for a total duration of 24 months. However, these visits and timeline are just guidelines. Data will be collected through information acquired during clinical visits. There is no minimum number of visits required for patients to continue to participate in MOBILITY and have their data collected. However, sites should not schedule patient appointments exclusively to conduct study specific visits or procedures. Therefore, it is anticipated that **not all study visits or procedures will be completed for every patient. However, we will emphasize the importance of collecting Month 6 and 24 data since those are primary outcomes.** Labs tests that are recommended in the Schedule of Events are based upon standard clinical practice guidelines, but will not be required for continuation in the study.

Each site will have a copy of the MOBILITY Projected Visit Dates Spreadsheet (also found on the website: MOBILITYstudy.org). The site coordinator will enter the patient's baseline visit date where indicated, and the recommended visit schedules will auto-populate. However, once patients are randomized at baseline, MOBILITY is primarily an observational pragmatic study, therefore, data will be collected only at clinical appointments.

Screening/Baseline Procedures: At screening and following informed consent/assent and review of initial study criteria, we will obtain demographic and clinical information as follows:

Demographic and Clinical Characteristics: Site staff will record patients' date of birth, sex, type of insurance, contact information, and prior type and duration of psychiatric treatments. Patients will report current daily nicotine intake (packs/day) and whether they currently use other drugs (checking all that apply from a list of common drugs). Data on treatments and substance use will also be collected at six-

month intervals.

Screening laboratory tests recommended include renal and hepatic function tests, electrolytes, CBC and thyroid stimulating hormone (TSH), as per Table 2. However, we will collect any results of labs performed within the last six months, if available. The only mandatory test for screening will be a pregnancy test in girls of menarche.

Every attempt will be made to encourage clinicians to obtain laboratory testing prior to starting metformin, however, patients who have not had baseline labs will continue to be followed in MOBILITY.

Kiddie-SADS-Present and Lifetime (K-SADS-PL 2013): After discussion with our patient/parent partners and site clinicians, we determined that the appropriate study population is all patients who receive a clinical diagnosis of a BSD, as these patients will typically receive SGA treatment regardless of whether they meet full DSM criteria. However, it was decided that using a structured research interview would provide an opportunity to examine concordance of clinical and research diagnoses and to assess HTE (i.e., do youth with a research diagnosis respond to MET differently than those with only a clinical diagnosis because risk for overweight/obesity and metabolic disorder may be higher for those with a research BSD diagnosis). Therefore, BSD diagnoses will be confirmed with the mood modules of the K-SADS-PL, a semi-structured diagnostic interview with established test-retest reliability.[128] (Interviewers will be trained by qualified personnel. Trained staff at the respective coordinating centers who are not associated with the clinical sites will administer the interview separately to guardians and patients, if > 12 years old). Based on feedback from the clinical sites, we determined that having their staff administer the K-SADS-PL might create diagnostic confusion, therefore, we will develop a mechanism that clinicians will be provided with the K-SADS-PL diagnoses after participants have reached Month 6 of study participation.

Table 1. Metformin (MET) Titration

	<50kg AM/PM	**≥50kg AM/PM**
Week 1	0/500mg	0/500mg
Week 2	0/500mg	0/500mg
Week 3	500/500mg	500/500mg
Week 4	500/500mg	500/500mg
Week 5	500/1000mg	500/1000mg
Week 6	500/1000mg	500/1000mg
Week 7	500/1000mg	1000/1000mg
Week 8	500/1000mg	1000/1000mg

Type and duration of current/prior SGA treatment and weight gain during SGA treatment: Prior data suggest that the effect of MET may depend on the extent of weight gain during SGA treatment prior to study entry. Site personnel will document weight and height prior to any SGA treatment, specific SGAs received and duration of treatment with each (i.e., by obtaining medical records). For *a priori* analyses of potential heterogeneity of treatment effect (HTE), we will then distinguish SGA-naïve patients (no current or prior SGA treatment as of baseline visit) versus those with any current or prior SGA treatment. Within the latter group, we will compute change in BMI z-score from the start of SGA treatment until baseline and perform HTE analyses to determine whether MET effectiveness varies based on the duration of SGA treatment and/or amount of excess (relative to normal development) weight gained during treatment.

Classification system for psychotropic treatments: We anticipate substantial variation in the specific psychotropic medication regimens prescribed at baseline, and that these treatments will vary over time. SGAs may be prescribed singly or in combination at varying doses, and concomitant treatment with antidepressants, non-SGA mood stabilizers (e.g., divalproex and lithium) and/or stimulants (e.g., for the subset of patients with co-morbid ADHD) will also be common. For our *a priori* analyses of potential HTE depending on pharmacologic treatments other than MET, we have reduced this large set of options to three groups based on available data regarding their weight effects. Our data will provide considerable additional observational evidence about the impact of specific regimens, and we will conduct detailed analyses that may suggest useful *post-hoc* alternative classifications.[1,129] Our survey data indicate that

risperidone, aripiprazole, and quetiapine will be the three most common SGAs prescribed.

(1) Mild to Moderate Risk of Weight Gain: Monotherapy with lurasidone, ziprasidone, or aripiprazole.

(2) High Risk of Weight Gain: Monotherapy with asenapine, iloperidone, paliperidone, quetiapine or risperidone. SGA-naïve patients receiving monotherapy with a group (1) SGA and patients prescribed divalproex or lithium plus a group (1) SGA will be assigned to this group.

(3) Severe Risk of Weight Gain: Monotherapy with clozapine or olanzapine. SGA-naïve patients receiving monotherapy with a group (2) SGA and patients prescribed divalproex or lithium plus a group (2) SGA will be assigned to this group.

Note that we have not incorporated dose effects because dose-dependent weight gain has not been consistently demonstrated for most SGAs. We will examine association of dose and dose adjustments with weight change and other outcomes, though exploratory analyses of such observational relationships will require careful consideration of confounding factors.

(See Next Page)

Table 2. Schedule of Events.

The Table of Events is an approximation for when routine clinic visits might occur. In order to adhere to the pragmatic nature of the study, data will only be collected during the patient's regularly scheduled clinical visits and a participant should not be brought in exclusively to conduct study specific visits. No specific study labs will be mandated for study participation, with the exception noted above (i.e., pregnancy test) The lab tests noted in the Schedule of Events are suggested in accordance with clinical practice guidelines for patients receiving SGAs.

Measures	**Visit (Approximate Months)**										
	SCREEN/ BASELINE	**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
Demographics & Clinical Characteristics (P, Y)	X										
Structured Diagnostic Assessment (K-SADS)[a] (C)	X										
Medication List (C)	X	X	X	X	X	X	X	X	X	X	X
Weight/Metabolic											
Body Mass Index [height and weight] (C)	X	X	X	X	X	X	X	X	X	X	X
Recommended Metabolic Labs [insulin, lipid profile, glucose, hemoglobin A1C] (C)	X[b,d, e]				X		X		X		X
Treatment Satisfaction											
Treatment Acceptability Questionnaire (Y)	X	X	X	X	X	X	X	X	X	X	X
Adherence											
Adapted Adherence Measure (P & Y)	X	X	X	X	X	X	X	X	X	X	X
International Physical Activity Questionnaire (P & Y)	X	X	X	X	X	X	X	X	X	X	X
Nutrition, Satiety, and Appetite Measures (P & Y)	X	X	X	X	X	X	X	X	X	X	X
MEMs Cap/ SimpleMed Pillbox Upload [300 patient subset] (C)		X	X	X	X	X	X	X	X	X	X
Mood/Anxiety											
PROMIS[c] Anxiety Short Form (P & Y)	X				X						X
PROMIS[c] Depression Short Form (P & Y)	X	X	X	X	X	X	X	X	X	X	X
PROMIS[c] Anger Short Form (P & Y)	X				X						X
Children's Depression-Revised/Selected Items (C)	X				X						X
Young Mania Rating Scale (C)	X	X	X	X	X	X	X	X	X	X	X
Clinical Global Impression-Severity (C)	X	X	X	X	X	X	X	X	X	X	X
Quality of Life (Weight & General)											
Body Weight, Image & Self-Esteem Evaluation, B-WISE (Y)	X				X						X

"Sizing Me Up"/"Sizing Them Up" (P & Y)	X				X						X
Height Weight Self for Viewpoint- Items 5 & 6 (wt. acceptability) (Y)	X	X	X	X	X	X	X	X	X	X	X
PROMIS[c] Pediatric Peer Relationships- Short Form (P & Y)	X				X						X
PROMIS[c] Global Health Scale (P &	X	X	X	X	X	X	X	X	X	X	X
Clinical Global Assessment Scale (C)	X	X	X	X	X	X	X	X	X	X	X
Number of School/Work Days Missed [past 30 days] (Y & P)	X	X	X	X	X	X	X	X	X	X	X
Caregiver Strain Questionnaire (P)	X	X	X	X	X	X	X	X	X	X	X
Other recommended measures											
Vital Signs [blood pressure, heart rate] (C)	X	X	X	X	X	X	X	X	X	X	X
Other recommended laboratory measures:[d,e] thyroid, renal and liver panels, pregnancy test, CBC, and Vitamin B12 (C)	X				X						X
Suicidality, Patient Health Questionnaire (PHQ)-Item 9 (C)	X	X	X	X	X	X	X	X	X	X	X
Zucker Hillside Side Effects Form (C)	X				X						X
Total Time/Visit for Youth Questions[f] (minutes)	15-20	5	5	5	15-20	5	7	5	7	5	15-20
Total Time/Visit for Caregiver Questions[f] (minutes)	15-20	5	5	5	15-20	5	7	5	7	5	15-20

P= Caregiver; Y= Youth, C= Clinician. Kiddie-SADS-Present and Lifetime-PL 2013;
[a]KSADS will be performed at any time point after enrollment.
[b]Baseline fasting serum glucose is highly recommended, however, results within the past six months will be acceptable.
[c]Items from the PROMIS=Patient Reported Outcome Measurement Information System;
[d]Any labs completed within the past 6 months are acceptable except for pregnancy test;
At baseline a negative serum or urine pregnancy test is required in girls who have reached menarche prior to prescribing metformin.
[e]Labs are recommended, however these are not required to start or continue in the study.
[f]Clinician and other assessments (e.g. labs, vitals) are part of a routine clinical visit and therefore, do not add time.

Our population will be ≥ 85%ile BMI (weight of such 8- and 9 year-olds will likely be comparable to an average 10-year-old child); 2) MET has a favorable side effect profile; and 3) prior reports as well as the investigators' previous experiences with the safe and well-tolerated use of MET in patients ≥ 8 years old.[125] All patients will have a renal panel prior to starting MET to evaluate for renal impairment that would preclude use of MET.

Participants randomized to treatment with MET will start at a recommended dose of 500 mg orally at night and slowly titrated in 2-week intervals to ensure that each patient achieves maximum insulin-sensitizing effects of the drug while minimizing the chance of side effects (see Table 1). We selected 50kg as the weight at which we felt comfortable increasing to a maximum total daily dose of 2000mg (1000mg twice daily). These youth will be at a low-end adult-comparable weight. We anticipate that most participants ≥10 years old will be >50kg, which is the 95%ile for weight for 10-year-olds of both sexes. Children <50kg, likely those patients <10 years, will have a reduced maximum daily dose of 1500mg. If

patients exhibit untoward gastrointestinal side effects while taking MET, clinicians will have the option to switch to an equivalent dose of the once-daily extended-release form of MET, which may alleviate side effects.[126] If a patient does not tolerate a specific dose, the clinician will also have the option of reducing that dose by 500mg/day to a minimum recommended daily dose of 500mg twice daily. At Week 8, the dose for the <50kg group may be titrated to the maximum of 2000mg/day (1000mg twice daily) if tolerated and strategy, in general, MET will be at steady-state target levels well before key outcomes are assessed at Month 6. We will also recommend that MET be taken with food to minimize side effects. If a participant's BMI percentile <5% (=underweight) his/her treatment with MET will be discontinued**.** Although the risk of low vitamin B12 while taking MET is associated with age > 50 years and having type II diabetes, we will monitor B12 levels and a CBC throughout study participation.[127]

Clinicians and patients must be willing to be randomized to either treatment arm. However, the clinician may choose to initiate or continue (for those on a subtherapeutic dose) metformin at their clinical discretion regardless of randomization following a recommended initial 3 month period of treatment. These patients' data will be considered in a different analytic group regardless of randomization.

Comparators: Healthy Lifestyle Intervention (LIFE): This healthy lifestyle intervention (LIFE) consists of introducing participants and families to a healthy eating plan and physical activity. Prior to study initiation, study site staff will participate in a live (or taped) training session from a dietician to become educated with LIFE. At baseline visit patients and caregivers will watch a standardized video about LIFE that was developed by Dr. Siegel and his group. The video explains the concept of a Traffic Light Plan (TLP) that is a classification system for food and activity (GREEN, YELLOW, RED). This plan encourages participants to limit RED foods (high-calorie, low-nutrient) and RED activity (sedentary), replacing them with GREEN foods (low-calorie, high-nutrient) and GREEN activity (moderate-to-high intensity). Participants will also receive a Food Reference Guide and Activity Reference Guide, categorizing food and activities in the TLP framework that was adapted from the Healthworks! Youth Fitness 101 program developed specifically for overweight and obese children by Dr. Robert Siegel. The baseline session will include a brief discussion of diet and physical activity instruction. At least 150 minutes/week of physical activity will be recommended. A link to the LIFE video and all handouts will be available on the study websites at www.mobilitystudy.org and offers a standardized, home-based exercise component for patients. At follow-up visits, patients and caregivers will have the option to watch the video again, and study staff will briefly reinforce nutritional guidance, remind participants about the need for 150 minutes of physical activity/week, and be available to answer any general questions on healthy lifestyle habits. Prior studies indicate that 33% of youth will decrease BMI with this LIFE intervention.[67]

b. Data Analysis and Data Monitoring:

Drs. Welge and Huang will conduct and/or supervise and have final responsibility for all analyses. Drs. Modi and Carle will conduct and/or supervise portions of the analysis that fall under their specific areas of expertise. Under the direction of the senior statistical team, Dr. Mara, Mr. Blom and Ms. Liu will carry out portions of the programming and analysis, which will begin within 6 months of the start of the trial (see Milestones). Analysis of short-term data will be complete by month 68 (when the last patient will have been followed for six months), and analysis of the long-term data will be completed by month 69 (when all 24- month follow-up will be complete), which will allow graphical and tabular summaries and narrative interpretation of the results to be completed by Month 72. No interim efficacy analyses or adaptive features are planned. Model fitting performed before all outcome data are available will be provisional, for the purpose of verifying code and making limited modeling decisions (e.g., determining from early data whether parameters, such as residual variance or scale reliability, may vary among subgroups). The Data Management and Biostatistics Committee will receive regular updates on progress in completing the statistical analysis plan, discuss any additional or modified analyses, and report to the Steering Committee as necessary.

Data Analyses: MOBILITY will use REDCap[154] for patient-reported outcomes. REDCap is a software toolset and workflow methodology for collection and management of clinical research data developed by Vanderbilt University, in collaboration with institutional partners including the University of Cincinnati Academic Health Center. This secure, flexible, web-based application provides: 1) an intuitive interface

for data entry and real time validation (e.g., automated data type and range checks); 2) HIPAA-compliant and 21 CFR Part 11- ready audit trails for tracking data manipulation and exports; 3) record locking and electronic signature functions; 4) control of view/edit rights; 5) a tool for reporting, monitoring and querying patient records; and 6) automated export to common statistical packages. REDCap is hosted on a network specially designed to support the rigorous security and compliance requirements of clinical research projects. Administered by the CCHMC Division of Biomedical Informatics, this network features multiple firewalls and a central facility for managing hosted systems and users, creating another layer of access control and audit capability on top of what REDCap already provides (e.g., user access can be monitored and controlled at the network level without making any changes within REDCap itself). These capabilities are available to authorized network administrators and REDCap study owners only, and user access changes are documented by an audit trail. The data management team will monitor the database throughout the study to assure that data are complete and accurate.

Analyses of Specific Aims: Each specific aim involves assessment of domains that are hypothesized to be affected by MET either directly or indirectly through other domains. Our approach to potential HTE distinguishes effect moderators from mediators of distal outcomes. Moderators include fixed patient characteristics and pre-treatment covariates values. Mediators include variables that are hypothesized to be affected by MET treatment and that may in turn affect other outcomes. We will utilize generalized linear mixed models (GLMM), which allow for outcomes from a range of distributions and will include random effects to account for unspecified causes of variation among sites and patients, and subgroup-specific coefficients to assess HTE.

The basic model for outcomes will be a GLMM with change from baseline to either 6- or 24- months as the dependent variable. Independent variables will include fixed-effect terms for randomized treatment group (MET), baseline value of the outcome, and random site effects. For HTE analyses, a baseline value-by-MET interaction (to assess HTE due to baseline status) will be included, and for particular domains additional continuous or categorical covariates and treatment-by-covariate interaction terms will be added to assess HTE. Outcomes within each domain will share the same set of HTE terms, specified in the Specific Aims. Because the subgroups are in general correlated (e.g., duration of SGA treatment, weight gain history and psychotropic weight burden will be correlated with baseline BMI), we will include multiple first-order HTE terms simultaneously (to assess heterogeneity independently attributable to each moderator), but will also fit separate models for each term to gauge the impact of this correlation on our conclusions. Higher-order treatment-by-covariate interactions will not be included a priori, but will be explored with rigorous adjustment for multiple testing, using step-down testing (removing highest-order interaction terms first) or information criteria based on penalized likelihoods to guide model selection.

Marginal Structural Modeling for Causal Inference: SA1 concerns the overall and sub-group specific effects of MET on abrogation of weight gain (with changes in BMI z-score from baseline as outcomes) and metabolic health, particularly metabolic syndrome and its component criteria. BMI and adherence measures are obtained at all study visits, so our models for these measures will use all available observations by treating the longitudinal series of changes in these variables and SGA treatment as dynamically dependent on each other. We will use marginal structural models[156] to address this bi-directional dependence, computing the probability of SGA treatment regimen change at each visit within weight gain treatment regimen groups and using appropriately normalized versions of the inverse of the probability as the stabilized weights.

Adjustment of Self-Reported Adherence: Adherence rates for self-report and MEMS (where available) will be calculated as number of treatments/day divided by number of prescribed daily treatments. Truncated MEMs adherence rates (maximum of 100%) will be used in analyses to reduce inflation as a result of overuse or extra openings due to prescription refills. This method has been used successfully in studies assessing electronic monitoring (EM) adherence.[157,158] Self-reported adherence vastly underestimates adherence as measured by EM.[159] While it is not feasible to use EM for all patients and medications, we will use the statistical relationship between EM and self-reported adherence in a subsample of 300 patients (equal numbers per treatment group, i.e., 100 for SGA adherence who are also taking MET, 100 for SGA adherence who are not taking MET, and 100 for MET adherence, who are

randomly selected the 8 randomization strata) to estimate EM adherence from self-report in the remaining patients. We will regress EM adherence on self-reports, using standard diagnostics to ensure that non-linearity, heterogeneity of variance across the range of adherence, or subgroup-specific regression relationships are included as needed. Predictions that accurately reflect the residual uncertainty can then be generated by multiple imputation, and the resulting complete-sample datasets will be used in primary analyses involving SGA adherence, with sensitivity assessed by parallel analyses using self-report directly.

Data and Safety Monitoring plan: The Cincinnati site will provide an independent certified study data monitor who will visit each site prior to study initiation and approximately every 6 months thereafter. The monitor will follow a monitoring plan that includes source data verifying and ensuring compliance with good clinical practices (GCPs), the IRB-approved protocol and other applicable regulatory guidelines, and will report any problems to the site PI and the other clinical staff members. Additionally, adherence to inclusion/exclusion criteria, completion of scheduled assessments, withdrawal/termination procedures, and maintenance of training and certification for all research personnel will be continuously monitored. The monitor will provide written recommendations following each visit to each site. All reports will be reviewed by members of the Steering Committee.

Safety and tolerability data will be monitored by an independent Data Safety Monitoring Board (DSMB), the study investigators, and the CCHMC and NS/LIJ IRBs. The function of the DSMB is to protect the safety of the study participants. The DSMB members are: Tobias Gerhard, PhD, pharmacoepidemiologist with focus on SGA risks; Avraham Goldstein, adult diagnosed with BSD as an adolescent; Robert Parker, PhD, biostatistician; Boris Birmaher, MD, child psychiatrist; David Repaske, MD, pediatric endocrinologist; and Robert Gardiner, parent of youth with BSD. Members will disclose and resolve any potential conflicts of interest prior to each meeting.

At their initial meeting (prior to study initiation), the DSMB members will select a Chair, who will provide written meeting minutes and recommendations and will review the study protocol and consent forms for safety and validity. Biannually, they will evaluate whether recruitment goals are being met and monitor the occurrence of adverse events and early withdrawals or terminations. All serious adverse events will be reported to the site's IRB and the DSMB within 7 days of knowledge of occurrence and will be followed until resolution, permanent outcome of the event, or stabilization. The DSMB will provide recommendations based on this review (e.g., to terminate the study or recommend modifications, including additional safety or tolerability measures). Dr. DelBello, in conjunction with the DSMB, will be responsible for ensuring that DSMB reports are filed with the IRBs and PCORI. The DSMB will also provide the investigator with a summary report that includes their recommendations. Adverse event reports will be collected systematically at patient visits, any rated as severe will be documented and reported. All adverse events will be reviewed by the DSMB biannually and reports will be sent to the FAC and Steering Committees.

c. <u>Data Storage and Confidentiality</u>:

Information will be obtained from clinical assessments and confidential HIPAA compliant online questionnaires that will be completed on the tablet. Access to activate tablets will be limited to study staff and password protected. Patient and their caregivers will confirm their identity by answering a personal security question at the end of each session. Specific materials obtained in the study will include patient and caregiver reports from behavioral, adherence, treatment satisfaction and QOL assessment tools.

Other information, such as medical history and clinician symptom ratings also will be collected by site staff from clinician notes and/or medical records or directly entered into password protected online databases by the clinicians or patients/caregivers. The following samples will be collected: urine in girls for a pregnancy test, if they confirm menarche. As recommended in standard clinical practice an 8-hour fasting blood draw for serum glucose, insulin, liver function tests, renal panel (including electrolytes),

TSH, HbA1c, and lipid profiles. The results of pregnancy test will be given to parents of minors at the discretion of the clinician. Blood pressure, and anthropometrics including height, weight, BMI, and BMI %ile will be recorded.

As with any study, there is a potential risk of loss of confidentiality. Consistent with the Federal guidelines, all patients and guardians will be informed of the federally mandated reporting laws for child abuse and neglect, verbally and in the written consent form. Therefore, if abuse or neglect is suspected the Department of Human Services will be called. Risks associated with this include embarrassment, legal consequences, and removal of the child from the parents'/legal guardians' home.

d. Setting: Assessments will be conducted at the participating community-based private and public mental health treatment centers in the East Coast and Midwest Regions. The participating site personnel will be made up of a real-world clinical trial team that includes members with varied training and experience with appropriate support from a qualified physician and centralized study trial team. Site staff who will be obtaining informed consent, reviewing medication lists, and collecting and assessing adverse events must complete Human Participants Protection and Good Clinical Practice (HPP and GCP) training prior to involvement in the study. These essential study staff will be documented via a site specific delegation of authority (DOA) log**.** DOA logs will be reviewed by the study monitor at each site visit to ensure that all new essential study staff have been added.

e. Laboratory methods and facilities: Participants will be sent for blood work, at the clinician's discretion, to any laboratory facility. No specific laboratory test will be mandated, as it is expected that laboratory procedures will take place in settings where everyday care happens, such as community clinics, hospitals and health systems. It is recommended that clinicians adhere to practice guidelines and labs are ordered through the patient's medical practice by their clinicians.

f. Estimated Period of Time to Complete the Study: The following is a timeline for the 72-month period of the proposed study: Months 1-2: Train study personnel; Months 3-57: Recruit an average of approximately 1-2 patients/site/month from 40 sites over 54 months for a total sample size of 1800 patients, we expect 25% of the sample recruited by M10-11; 50% recruited by M30; 75% by M45 and the final patient recruited by M57; Months 34-68: Complete subject participation, data entry, and analyses. Final analyses will be completed M70- after the last patients have completed 6 and 24 months of follow-up.

F. HUMAN SUBJECTS

a. Description of Subjects

We will recruit a total of 1800 youth, (approximately 900 each from ~20 Midwest sites and ~20 East Coast mental health treatment sites) to participate in the proposed patient-centered large pragmatic trial examining the effectiveness of MET and LIFE vs. LIFE alone. Subjects will be eligible to enroll and randomize if they are ages 8-19 years old (inclusive) at the time of screening, overweight or obese (BMI $\geq$ 85%), continuing or starting treatment with at least one SGA (i.e., olanzapine, clozapine, risperidone, quetiapine, aripiprazole, ziprasidone, iloperidone, lurasidone, paliperidone, or asenapine), have a clinical diagnosis of BSD (bipolar I or II disorder, cyclothymia, or bipolar or mood not otherwise specified, or other specified bipolar or mood disorder) and are living at home with their caregivers.

Based on feedback from our advisory board and our consultants including children and adolescents who are in state custody is essential so that our sample is not biased as SGA exposure in this population is extremely high, Therefore, we will allow children and adolescents who are under the custody of DHS to enroll. We will seek the approval of a legally authorized individual from the county (e.g. Hamilton or Butler). This may be the county caseworker or it may be their supervisor. It will NOT be the case manager from the private agency that is handling the placement. But, the private agency case manager

will know who the appointed county JFS social worker. The foster parent(s) will NOT have the authority to authorize enrollment into a research study. We will need the foster parent(s)' approval to ensure that study visits will be attended and compliance with study requirements is manageable. Consents may be faxed for signature to the legally authorized individual as specified from each county. A fully signed copy of the consents will be offered back to JFS after the consenting process occurs.

For youth who reside in Northern KY and are in the custody of the Cabinet for the Commonwealth of Kentucky, we will obtain the permission of the assigned Cabinet Social Worker who is assigned to the individual. That person will determine if they have the authority to grant permission for participation or whether they need to seek higher approval.

For youth in the custody of New York City foster care, the investigator will submit a proposal along with our IRB approval and relevant consent forms to the Administration for Children's Services (ACS). ACS will review, process, and approve the proposal. Once approved the proposal will go to the State Office of Children and Family Services (OCFS) for their review and approval.

b. Sample Size

Eighteen hundred (1800) children will participate in the study. Each site will enroll up to 90 participant's total or 1-2 participants/month for a total study enrollment period of 57 months (some sites completed regulatory requirements well into the recruitment period)

c. Inclusion Criteria

1. Inpatient or outpatient age 8-19 years inclusive*;* participants must live with a parent, guardian, or caregiver;
2. Fluent in English;
3. Diagnosed or told by a clinician that they have any of the following bipolar spectrum disorders (BSD): bipolar I, bipolar II, unspecified bipolar and related disorders, Disruptive Mood Dysregulation Disorder (DMDD), cyclothymic disorder, other specified bipolar and related disorders, as well as mood disorder not otherwise specified (if diagnosed in the past as per DSM-IV);
4. Body mass index $\geq$85%ile for age and sex by standard growth charts;
5. Received a new or ongoing prescription for at least one SGA (i.e., olanzapine, clozapine, risperidone, quetiapine, aripiprazole, ziprasidone, iloperidone, lurasidone, paliperidone, brexpiprazole or cariprazine) that is not prescribed as a PRN medication;

Exclusion Criteria:

1. Patients will be excluded if they have had exposure to a total daily dose of MET 1000 mg bid for at least 2 weeks in the past 3 months;
2. Patients will be excluded if they could not tolerate MET during the recommended titration schedule outlined in the protocol;
3. Major neurological or medical illnesses that affect weight gain (e.g., unstable thyroid disease) or require a systemic medication that might impact weight or glucose regulation (e.g., diabetes mellitus [insulin], chronic renal failure [steroids]);
4. If lab results are available in the last 6 months, then a fasting serum glucose $\geq$ 126 mg/dL on 2 occasions prior to or during screening, indicating need for prompt treatment.
5. If lab results are available in the last 6 months, then a serum creatinine $\geq$1.3 mg/dL on 2 occasions during screening and/or follow-up, indicating potential impairment of renal functioning
6. Pregnant or breast feeding;
7. Based on their clinician's assessment, children and caregivers who are unable to complete screening/baseline assessments for any reason;

If a patient does not have fasting glucose or renal lab results within 6 months prior to their baseline visit, then every attempt will be made to obtain labs prior to starting metformin. However, patients will not be excluded from the study if they are unable to get serum creatinine or glucose. Renal dysfunction is extremely rare in otherwise healthy children and adolescents, and in a clinical setting renal panels are not typically done prior to starting metformin, unless there is a reason to suspect kidney disease.

The initial rationale for requiring normal glucose prior to starting metformin was that patients who are hyperglycemic may need to receive metformin + LIFE rather than LIFE alone. However, if a patient does not have a normal glucose available prior to randomization, but meets all other study criteria, we will continue to collect data from the patient and administer the treatment to which they have been randomized, so that at a minimum they will receive LIFE. We will also strongly encourage their clinician to emphasize the importance of obtaining fasting glucose levels. If, however, lab results are available in the last 6 months, patient with a fasting glucose ≥ 126 mg/dL on 2 occasions will be excluded and referred to their primary care clinician for prompt evaluation for Type II diabetes. Including these patients, rather than waiting until they get their glucose level checked, will ensure that at least the patient will receive LIFE while we encourage the clinician to engage the patient to get fasting metabolic labs. At any point in the study of a patient has a fasting glucose ≥ 126 mg/dL on 2 occasions, they will be immediately referred to their primary care physicians and possibly endocrinology.

d. Intended Demographics

We propose to recruit 1800 inpatient or outpatient youth (ages 8-19 years, inclusive) who have a BMI ≥ 85%ile (i.e., overweight or obese) and are prescribed SGAs as either ongoing or new treatment. There will be no barriers to inclusion based on sex, race, ethnicity or clinical status with the exception that otherwise eligible patients with current or prior therapeutic MET exposure will be excluded. We anticipate equal recruitment by sex, and based on US census reports from the recruitment regions, approximately 25% non-White (20% African American/Black and 5% Asian) and 15% Hispanic youth. Because the diagnosis of BSD and the use of SGAs is more controversial in younger patients and there are little safety data regarding the use of MET in patients younger than 8 years old, we restrict our sample to 8-19 year olds.

Process for consenting Spanish speaking caregivers: If it is determined that a caregiver cannot be properly consented in English, the caregiver will receive a consent document translated into Spanish. A qualified translator will be present to answer any questions the caregiver may have about the study. A qualified translator can be a bilingual study staff member, or a certified translator. A progress note will be written indicating a qualified translator was present at time of consent. The progress note will remain attached to the signed consent form.

e. Study Population Source

Participants will be recruited from approximately 40 community-based mental health treatment centers, some of which have multiple locations.

f. Recruitment Plans

Because our study is a large pragmatic patient-centered trial, we have minimal eligibility requirements, which should facilitate the feasibility of recruitment. Each selected clinical site is a large mental health practice that has more than 100 youth eligible for study participation. Therefore, we should have no difficulty reaching our proposed rate of recruitment of 1-2 patients/month/site at 40 sites and over the course of 57 months. In general, study visits will coincide with clinical visits, so we anticipate that retention will be at least as good as in our prior naturalistic outcome studies (~90%) over 2 years. Each week study sites will send their screening logs to the lead site that identify potential patients and will collect ethnicity information.

We will create a study website that will have the address of www.mobilitystudy.org. This website will be used as a communication tool to post important study related material and information to committee/stakeholder members, study sites, and patients enrolled in the study. A Login username and password will be required to view study specific material related to interventions, meeting material, and videos. There will be information about the study that will be available for the public to view, including information about the study, metformin, and bipolar spectrum disorders.

We will have a study Twitter account for the MOBILITY study that will be used to disseminate information about the study. This will not be used as a means of recruitment. We will use the handle name @MOBILITY_Trial, to communicate information about the study to likely followers, including clinicians, researchers, members of the media and study participants and their families. The account will not provide medical or health advice or recommendations. It will provide background information about the study; background information about Metformin; and information about any publications or webinars related to the study. It could provide links to other research that is published during the next 5 years related to Metformin, SGAs and bipolar disorder in adolescents. We anticipate posting one tweet per week. Tweets will be reviewed prior to publication by Melissa DelBello, MD, or a study-related personnel designated by her.

G. RISK TO SUBJECTS

a. Level of Risk Description

Potential risks from study participation include possible risks from MET treatments, and other risks associated with any study participation (e.g. loss of confidentiality and fatigue and frustration from repeated evaluations):

Confidentiality: As with any study, there is a potential risk of loss of confidentiality. Consistent with the Federal guidelines, all patients and guardians will be informed of the federally mandated reporting laws for child abuse and neglect, verbally and in the written consent form. Therefore, if abuse or neglect is suspected the Department of Human Services will be called. Risks associated with this include embarrassment, legal consequences, and removal of the child from the parents'/legal guardians' home.

Healthy Lifestyle Intervention (LIFE): There is little to no risk associated with LIFE, although patients may become bored, fatigued or develop anxiety by the weight monitoring and recommendations. The exercises recommended may result in muscle soreness or strains, as there may be an increase in activity levels.

MET: All patients, guardians and clinicians will be made aware that MET is not approved by the USFDA for the treatment of overweight or obese youth or for SGA-related weight gain. Risks associated with MET include: Common side effects (≥5%): diarrhea, nausea, and vomiting. Less likely (<5%): abdominal pain/abdominal distension, constipation, dizziness, dysguesia, dyspepsia, flatus, headache, and upper respiratory infection. Rare: Lactic acidosis, 47 cases out of 1 million patients taking MET. Very rare: Vitamin B12 deficiency. Clinicians will be educated that youth who develop symptoms of lactic acidosis, such as hyperventilation, myalgia, malaise, and somnolence should stop taking MET and notify their treating clinician immediately. Additionally, we will educate all study-related clinicians about the very rare side effect of Vitamin B12 deficiency and associated potential clinical manifestations of vitamin B12 deficiency (i.e., peripheral neuropathy and pernicious anemia).

Blood Draws: Although blood draws are not required for participation in MOBILITY, they are highly encouraged in accordance with clinical practice guidelines. No study specific blood draws will be performed. Risks of blood draws include discomfort and/or bruising at the blood draw site. Less commonly, fainting, the formation of a small blood clot, swelling of the vein and surrounding tissue,

bleeding from the puncture site or infection may occur. Other potential risks include possible fatigue and frustration from repeated evaluations and the potential for additional weight gain, worsening of lipids, and increased insulin resistance. Since only patients prescribed SGAs as part of their clinical care will be approached for participation and no patient will be started on an SGA for the purpose of the study, we do not consider other risks associated with SGA treatment as study specific risks. Additionally, patients may experience exacerbation of BSD symptoms during study participation.

Protection Against Risks. The final protocol will be approved by the Steering and Family Advisory Committees, the CCHMC and NS/LIJ IRBs, and the study data and safety monitoring board (DSMB) prior to recruiting. Patients/parents will be clearly informed they are free to terminate participation at any point during study participation. Furthermore, to minimize risks associated with the study, all personnel will be thoroughly trained as previously described prior to having any contact with patients or data.

Breach of confidentiality: All data will be entered into electronic case report forms (eCRF) or directly into databases (e.g. patient/parent questionnaires) that are 21 CFR Part 11 and/or HIPAA compliant. We will train all study-related personnel to follow HIPAA regulations for research to ensure confidentiality of all data and that the rights of the patients/guardians are protected. All data will reside on password-protected computers, with only the investigators and key members of the research team having access. A variety of other measures will be taken to protect confidentiality, including: We will 1) assign and use a unique ID number to each patient to label all components of the protocol, instead of patient names, 2) restrict access to the key linking names and ID numbers to key staff and the PI at each site, 3) store of any paper with data at each site in a locked file cabinet, 4) if necessary, only send de-identified from clinical sites to the data coordinating site. Patients and caregivers will directly enter information regarding adherence, treatment satisfaction, mood, anxiety, QoL, and drug and nicotine use, into the tablet where it will go directly to the study database. Therefore, there is little information that site staff will collect and most of it is part of a standard clinical visit, so that the risk of loss of confidentiality is minimal.

Subjects will be told that agents of the Academic Health Center's IRB, study monitors, representatives from the USFDA or the study coordinating sites (UC/CCHMC or LIJ/NS), and members of the DSMB will be allowed to inspect sections of their medical and research records related to this study, if requested. Site clinicians are federally mandated to report suspected abuse or neglect. However, we will encourage any such reports to be made with extreme confidentially to the Department of Human Services. Healthy Lifestyle Intervention (LIFE): All patients and families will receive LIFE education from a clinical site staff member. Dr. Seigel will ensure that all clinical site staff are adequately trained prior to initiating LIFE and will be available on an ongoing basis to all site staff that have questions about LIFE. The site staff will suggest that physical activity is spread over the course of 5 days (30 minutes/day) to achieve the recommended 150 hours/week, and not performed all at once to avoid muscle or other discomfort. The information that will be provided to the families outweighs the risks associated with LIFE. MET: Metformin is USFDA approved to treat youth with diabetes type 2, > age 10. Additionally, there are significant safety data for MET down to age 8 years. However, since MET is not approved for the attenuation of weight gain in youth, we will submit a research IND to propose studying MET for this purpose and wait the required 30 days before initiating the study. We will follow all appropriate FDA guidelines for IND submissions. Additionally, Dr. DelBello will be responsible for sending serious adverse events (SAEs) to the FDA, IRBs, and DSMB in a timely fashion in compliance of IND and FDA guidelines.

To further protect against the risks associated with metformin, patient, parent, and endocrinologist research team members will train clinical site staff prior to study initiation regarding the recommended MET dosing for the study, how to discuss MET with patients and families, common and less common side effects, and strategies to mitigate side effects (e.g. decrease dose and how to switch to MET-XR or take it with meals). This training will be taped and available online for any new clinician during the

course of the study. Our study endocrinologists (Drs. Crimmins and Speiser) will also be available throughout the study should any site clinicians have questions regarding MET use. We will also educate site clinicians that it is part of standard of care to obtain labs prior to initiating MET. In particular, since MET is excreted by the kidneys, if a patient has creatinine ≥1.3 mg/dL on 2 occasions, they will be excluded from study participation and referred to their primary care clinician. Since lactic acidosis is a very rare side effect of MET and primarily occurs in elderly diabetic patients with significant renal insufficiency or congestive heart failure,[165] we will inform clinicians of the risk and associated symptoms, but explain that we are excluding those most at risk and to our knowledge, that there have been no reports of lactic acidosis in youth. Additionally, we will encourage site clinicians to inform patients that excessive use of alcohol needs to be avoided as alcohol potentiates the effects of metformin on lactate metabolism (patients may be users of alcohol) and metformin should be discontinued prior to any IV radiocontrast study or surgical procedure. Additionally, to guard against risk, if a patient has two 8-hour fasting glucose levels ≥ 126 mg/dL, they will be referred to their primary care clinician (and if at screening they will not be included in the study), so that they may be evaluated for type II diabetes.

Blood Draws: We will recommend that only trained and certified phlebotomists draw blood at a certified laboratory facility.

Other potential risks: To guard against frustration and fatigue, questions and surveys have been carefully chosen by patients, parents, and stakeholders. However, when necessary, assessments can be divided to decrease the frustration and fatigue. In addition, research staff will be hired based on their research experience and work with children and adolescents. Lastly, patients and their parent(s)/legal guardian(s) will be advised that they do not have to participate in the study and that their participation is voluntary and refusal to participate will not impact their clinical care in any way. Their alternative to study participation is to continue to receive standard clinical care. Additional weight gain or metabolic abnormalities: Patients in the study will be closely monitored for weight gain and metabolic abnormalities. Clinicians, parents, or patients can discontinue assigned study treatment at any point, but will still be monitored for up to 24 month. If a patient continues to have substantial weight gain (> 10%) in the LIFE group, a clinician might decide to add MET to the treatment if clinically indicated. Likewise, if the patient is randomized to the MET + LIFE group and continues to have substantial weight (>10%) they will have the option to continue MET and/or add another treatment or switch the patient's treatment for BSD, whichever is clinically indicated. If a participant's BMI percentile 5% (= underweight) his/her treatment with MET will be discontinued**.**

Although the risk of low vitamin B12 while taking MET is associated with age > 50 years and having type II diabetes, we will encourage clinicians to monitor B12 levels and a CBC throughout study participation.[127] We will educate all study-related clinicians about this potential side effect of metformin and the very rare clinical manifestations of MET-related vitamin B12 deficiency (i.e., peripheral neuropathy and pernicious anemia).

All changes will be noted, however since this is a pragmatic trial we will not mandate specific study discontinuation criteria, even if data collection is missed at recommended times for study visits. The intervals between study data collection are just guidelines for the most common intervals between clinical visits. However, clinical visits may occur more or less frequently. Regardless, data will be collected from participants at clinical visits, when feasible, at a frequency of no more than recommended in the Schedule of Events (Table 2). We will encourage clinicians to follow recommended guidelines for referrals and treat patients as clinically indicated. We will review guidelines at study initiation. For example, referrals to endocrine will be recommended for fasting glucose ≥126 mg/dL x 2, HbA1C ≥5.7%, or fasting insulin ≥50 mcU/mL. Patients with LDL > 140 or triglycerides > 300 might be referred to a lipid clinic, or those with elevated liver enzymes ALT > 45, for a liver clinic for evaluation of non-alcoholic steatohepatitis (NASH). After a review of the literature and consulting with experts in the NASH field, we selected the

threshold for referral to liver clinic. Abnormal ALT will be defined as approximately 2x the upper limit of normal of the NHANES-derived population-based ULN (>=22.1for girls, >=25.8 for males).[166] Although the cutoff would be higher for boys, for consistency we will use a single cut-off of ALT>=45. Referral for hypertension will be recommended if blood pressure is > 95th % at 3 times or > 130/90. Drs. Crimmins and Speiser will facilitate referrals as clinically necessary to ensure patients safety.

We will monitor all patient records and train all clinicians to ensure that if they note a laboratory value as clinically significant, they will need to specify the recommended follow-up and outcome.

Exacerbation of BSD is also a risk, however patients will be treated for BSD as clinical indicated and there are no restrictions on psychotropic medications use. Patients will be monitored closely by site clinicians who will use the YMRS to systematically assess manic symptoms and the PHQ-9 item #9, to assess current suicidality. Patients will remain in the study even if they require a change in treatment or psychiatric hospitalization. These events will be recorded as psychiatric symptom burden outcomes. Patients who become pregnant during their study participation will continue to be followed. We will encourage treating clinicians to discontinue metformin if it is being prescribed for study participation and to consult with the prescribing clinician prior to discontinuation, if it is prescribed by another clinician and for reasons unrelated to the study.

b. Anticipated Benefit Justifies the Risk - We believe the risks associated with study participation are minimal. Despite patients being randomized to LIFE + MET or LIFE along, this is a pragmatic observational study and there are minimal study specific procedures associated with participation. Additionally, patients will remain in the study and data will be collected regardless of whether they switch treatment arms or miss visits, although all of this information will be recorded. Youth with BSD taking SGAs receive low rates of basic metabolic monitoring and even lower rates of intervention for being overweight or obese, even though weight gain is the side effect of SGAs that causes them the most concern and is a common reason for poor adherence. Participation may increase their likelihood of receiving state-of-the art monitoring and intervention/prevention for weight gain, obesity, and metabolic disorders. Potential benefits also include the chance to contribute to a scientific investigation which may benefit other patients like themselves in the future. The study will benefit society as a whole by potentially providing clinicians with a new means to optimize efficacy, minimize risk for adverse reactions, and ultimately achieve better quality of life for patients treated with SGAs. We may also gain a better understanding of MET's effects on anthropomorphic measurements as well as glucose and lipid metabolism, which may ultimately improve our ability to prevent and/or manage the longer-term effects of SGA. Overall, the risks associated with this study are minimal and subjects may receive direct benefit from participation. Therefore, in the opinion of the research team, including patient, parent, and other stakeholders, the benefits of this study outweigh the risks.

In addition, the benefits of this pragmatic trial to society, as well as to individual patients, such as gaining important information about his/her mental and physical health status and receiving healthy lifestyle intervention and MET, far outweigh its minimal risks involved. This patient-centered study will enhance our understanding of the effectiveness in a community setting of LIFE and MET to abrogate weight gain and its patient-reported complications, such as poor adherence, treatment satisfaction, QoL and psychiatric symptoms burden in obese or overweight youth with BSD who are treated with SGAs. In summary, this study will provide critical information to address an important public health concern in a highly vulnerable population.

c. Anticipated Benefit as Favorable as Alternative Approaches – An alternative to study participation is not participating and receiving standard of care treatment as directed by a physician of that participant's choosing. Participation may increase their likelihood of receiving state-of-the art monitoring and intervention/prevention for weight gain, obesity, and metabolic disorders associated with SGAs.

H. PAYMENT

Patients and their caregiver will each be paid $25 for visits at Screening, month 6, and month 24 for their time and effort. Also, they each will each be paid $10 for visits at month 1, 2, 3, 9, 12, 15, 18, and 21. This totals to $155 for the patient and $155 for the caregiver.

I. SUBJECT COSTS

Patients are expected to provide for the costs of clinical care (e.g., hospitalization costs) through standard health care payment procedures. Subjects will have no costs associated with research participation.

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