STUDY PROTOCOL AND METHODS ADVANCEMENT

Metformin for Overweight and Obese Children With Bipolar Spectrum Disorders Treated With Second-Generation Antipsychotics (MOBILITY): Protocol and Methodological Considerations for a Large Pragmatic Randomized Clinical Trial

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Objective: Youth with bipolar spectrum disorders may experience improved mood stability when treated with second generation antipsychotics (SGAs); however, SGAs are associated with unhealthy weight gain and adverse metabolic effects. Metformin may mitigate this weight gain but is rarely prescribed by community mental health practitioners. Its long-term efficacy, safety, and acceptability in usual care, and factors that might moderate these effects, are unknown. The Metformin for Overweight and Obese Children and Adolescents with Bipolar Spectrum Disorders Treated with Second Generation Antipsychotics (MOBILITY) trial aims to fill these gaps. We present the design and analytic plan of this multi-site, open-label, randomized trial.

Method: Patients will be randomized to either metformin plus brief healthy diet and exercise education (MET+LIFE) or to LIFE alone. Up to 1637 patients will be followed for up to 2 years at 64 community and academic mental health treatment facilities. Patients may switch between treatment arms during follow-up.

Discussion: Pragmatic trials place few burdens and constraints on participating patients, families, and clinicians. This flexibility will allow MOBILITY to obtain long-term follow-up in a large, diverse sample, but produces analytic challenges. MOBILITY's flexible design has the potential to generate several novel methodological issues that we address. Some patients randomized to LIFE will fail to lose weight, and therefore metformin initiation contrary to the randomization may result from weight gain. Adherence to medications, SGAs, and lifestyle recommendations as well as satiety are potential time-varying mediators, moderators, or confounders of the effect of metformin. Adherence to metformin and SGAs may be positively correlated; therefore, a beneficial effect of metformin on weight could be obscured by the known SGA adverse effect on body weight. However, such correlation could facilitate causal inference by providing indirect information about unknown metformin adherence among patients who did not receive it. A perceived protective effect of metformin could potentially lead to risk compensation, with poorer diet and activity among those receiving metformin. We discuss limitations of traditional statistical approaches and summarize an advanced methodology ("Targeted Learning") that addresses some of these limitations.

Clinical trial registration information: Metformin for Overweight & OBese ChILdren and Adolescents With BDS Treated With SGAs (MOBILITY); https://clinicaltrials.gov/; NCT02515773.

Key words: obesity; bipolar disorders; metformin; antipsychotics; randomized clinical trials

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Bipolar spectrum disorders (BSDs) typically emerge in adolescence or young adulthood and are a leading cause of disability, premature death, and suicide.[1] BSDs are characterized as mood disorders and present with alternating and/or co-occurring symptoms of mania and depression. Second generation antipsychotics (SGAs) are widely used to treat patients with BSDs,[2] but their mood-stabilizing effects are often accompanied by weight gain and other metabolic alterations.[3,4] SGAs include quetiapine, risperidone, aripiprazole, ziprasidone, olanzapine, clozapine, iloperidone, lurasidone, paliperidone, asenapine, brexpiprazole, and cariprazine. There is

considerable variation in how frequently each treatment is prescribed in this population, and although the amount of weight gain produced on average is not clear for some of the less frequently prescribed treatments, all SGAs are associated with weight gain. Substantial weight gain can occur within weeks of initiating treatment and may continue to accumulate with long-term SGA treatment, which is often required to maintain mood stability. SGA-induced weight gain is especially severe in younger patients and is a significant pathway to childhood obesity.[5,6] Adult obesity follows in an estimated 80% of cases,[7] and risks of cardiovascular disease and type 2 diabetes are elevated.[8,9] Despite these risks, cardiometabolic risk monitoring in antipsychotic-treated youth is often inadequate.[10–12]

Strategies to mitigate SGA-induced weight gain are clearly needed. Individualized lifestyle interventions in people with serious mental illnesses, such as psychotic disorders and BSD, have been studied in at least 41 randomized clinical trials. A meta-analysis of these studies concluded that although the average mean difference in change in body mass index [BMI] (a 0.63-kg/m^2 reduction relative to control conditions) was statistically significant, it may not be maintained at follow-up.[13] Moreover, comparable data in youth are limited.[14] Furthermore, some of these trials were judged to be at high risk for bias, and the evidence rests on samples that are motivated and able to consent to and participate in a randomized controlled trial. These factors cast further doubt on the benefit of lifestyle intervention alone in real-world settings.

Among the pharmacological weight loss interventions for adults with severe mental illness to date, metformin is the best studied.[3] A meta-analysis of 21 randomized controlled trials in 1,547 adults found that the addition of metformin to antipsychotic treatment for an average of 3 to 4 months significantly reduced body weight relative to placebo, with an effect size of 0.61 SDs.[15] The mechanism for weight loss induced by metformin is not entirely clear, but data suggest a variety of effects.[16] It has been well documented that metformin decreases hepatic gluconeogenesis and improves insulin sensitivity in the liver and muscle. Because insulin levels are elevated as part of insulin resistance following non-physiologic weight gain, and because insulin increases appetite, improvement of insulin resistance by metformin could reduce appetite and caloric intake. In addition, metformin has been shown to affect hypothalamic signaling, regulating leptin sensitivity, gastrointestinal physiology, and circadian rhythms, which may influence not only food intake but also fat oxidation and fat storage in liver, skeletal muscle, and adipose tissue.[16]

Data on pharmacological interventions aimed at weight reduction in youth with antipsychotic-induced overweight/obesity are far more limited than in adults. Three short-term (12-16 weeks) RCTs of metformin in youth with schizophrenia spectrum disorders,[17] mixed psychiatric disorders,[18] or autism,[19] and one 24-week RCT in youth with schizophrenia spectrum or bipolar spectrum disorders, autism with irritability, or depression with psychotic features[20] have been reported. These trials have produced mixed but generally favorable results. Two of these trials reported significant benefits on body weight, although none were able to detect differences on metabolic parameters. In a study of 39 youth with mixed psychiatric disorders, metformin separated from placebo on anthropometric but not metabolic parameters.[18] In a trial of 49 youth with schizophrenia spectrum disorders, differences favoring metformin treatment were not statistically significant for body weight parameters, and no trends toward metabolic benefits were evident.[17] In a study of 60 youth with autism, metformin separated from placebo on anthropometric but not on metabolic measures.[19] In the trial with the largest sample size (n = 127) and longest follow-up (24 weeks), 49 youth treated with open-label metformin plus healthy lifestyle instruction decreased age-and-sex-normalized BMI (BMI *z* score) significantly as compared to those in the control condition (continued use of baseline antipsychotic plus healthy lifestyle instruction) and to a similar degree as switch to a lower weigh-risk antipsychotic.[20] The authors also noted that group differences over 6 months appeared to be grow linearly, suggesting that a plateau in metformin's effect had not yet been reached, and that longer-term studies would be required to determine whether benefits would continue to accrue. Despite these positive findings, data collected from a large national commercial health plan from 2016 to 2017 indicated that metformin is rarely used as a weight-mitigating strategy in youth treated with SGAs.[21] Among 1,502 patients in the 2016 cohort and 1,239 patients in the 2017 cohort, only 2.4% and 2.6% were prescribed metformin.

No controlled studies on treatment with metformin for longer than 6 months in youth with psychiatric disorders exist, but SGA treatment is usually long term. All of the available studies were conducted in highly controlled settings (academic health centers). Therefore, it is unknown how well even the short-term results generalize to typical clinical practice settings and to patients who might not meet the narrow inclusion criteria for the existing studies (eg, exclusionary comorbidities and concomitant treatments). Moreover, relevant moderator and mediator analyses in sufficiently large samples of youth (or adults) treated with SGAs and exposed to metformin or a control condition that would be relevant to inform clinical decision making are missing. For example, there are no data to indicate whether

particular types of patients might respond especially well or poorly to metformin, because small RCTs have virtually no power to detect treatment moderators unless the effects are extremely strong. Furthermore, it is unknown whether metformin is equally effective at preventing SGA-induced weight gain (when initiated at the same time as an SGA) as reversing it when such weight gain has already occurred.[22] Finally, although metformin is believed to have a relatively benign side effect profile, tolerability and safety data in youth are minimal, and is it unknown whether interactions with SGAs that elevate risk for adverse events occur.

To address the limitations of prior studies, we designed the Metformin for Overweight and Obese Children and Adolescents with Bipolar Spectrum Disorders Treated with Second Generation Antipsychotics (MOBILITY) trial. This open-label, multi-site, randomized, pragmatic trial will compare metformin combined with healthy lifestyle instruction (MET+LIFE) to the healthy lifestyle instruction alone (LIFE) over a 2-year period and in a sample large enough to permit assessment of multiple potential treatment moderators and mediators. We conducted pre-study surveys of clinicians and patients as well as caregivers with the assistance of 2 of our partner organizations, the Depression and Bipolar Support Alliance and the National Alliance on Mental Illness. Both patients and families as well as clinicians indicated that weight gain is the most concerning side effect of SGA treatment. Our team of clinical investigators, patient and family representatives, patient advocacy groups members, and other stakeholders including representatives from major insurers and professional organizations determined that change in weight (normalized by height, age and sex [assigned at birth]) was the most appropriate primary patient-oriented endpoint, and that metabolic outcomes should be considered key secondary endpoints.

Our primary goal is to assess the overall and subgroup-specific impact of MET+LIFE vs LIFE alone on short- and long-term changes in weight and metabolic health among overweight and obese youth with BSD. We hypothesize that assignment to treatment with metformin will abrogate more weight gain and lead to fewer adverse metabolic outcomes than healthy lifestyle instruction alone. After considerable discussion with our stakeholder partners and Patient Centered Outcomes Research Institute (PCORI), we included youth with disruptive mood dysregulation disorder (DMDD) and/or mood disorder not otherwise specified (NOS), as these youth have historically been diagnosed with bipolar disorder and are frequently treated with SGAs.

We also hypothesize that metformin's effectiveness at abrogating weight gain and adverse metabolic outcomes will vary with respect to the following factors: (1) prior exposure to and duration of SGA treatment; (2) baseline BMI *z* score; (3) baseline psychotropic weight burden; (4) age; (5) sex; (6) type of insurance (public/private), as a proxy for socioeconomic status; (7) ethnicity; and (8) race.

Secondary aims are to assess the overall and subgroup-specific impact of MET+LIFE vs LIFE alone on SGA adherence and treatment satisfaction, mood and anxiety, psychotropic treatment changes, rates of hospitalization, and overall and weight-related quality of life, and to determine to what degree any effect of metformin on body mass or metabolic outcomes is mediated through decreased appetite and food intake (ie, increased satiety).

In this paper, we discuss specific methodological considerations for the design of MOBILITY, including relevant data analytic strategies that are necessary to allow for causal inferences in a randomized trial that is implemented in real-world settings and that takes real-world populations and clinical decisions into account to maximize external validity. Explanatory clinical trials aim to determine the efficacy of an intervention under tightly controlled circumstances. Alternatively, pragmatic clinical trials, such as MOBILITY, seek to determine effectiveness of an intervention in "real world" settings and bridge the gap from efficacy to effectiveness for clinicians and their patients. The Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool can be used to determine where a study design lies on a continuum from explanatory to pragmatic trials, which can be helpful in assessing whether the design is consistent with the trial's objectives (eg, assessing effectiveness vs efficacy).[23] Nine domains are assessed: Eligibility Criteria, Recruitment Path, Setting, Organization, Flexibility of Delivery of Experimental Intervention, Flexibility of Adherence of Experimental Intervention, Follow-up, Primary Outcome, and Primary Analysis. Each domain is scored on a continuum from very explanatory (1) to very pragmatic (5).

MOBILTY has an overall PRECIS-2 score of 4.2, which confirms the pragmatic nature of the study design. MOBILITY only scored low on 1 domain (Follow-Up), because our protocol does call for regular in-clinic follow-up visits where patient- and caregiver-reported data will be collected. A trial scoring highly on this domain might only collect follow-up data from an electronic health record or would have very limited data collection at follow-up visits. Because our patient/family partners indicated strongly that outcomes other than weight gain (see secondary outcomes below) are also very important to them, a lower score on this domain is consistent with our objectives. Moreover, our primary statistical analyses will follow the intention-to-treat principle by comparing randomized groups regardless of treatment actually received; this is considered a "pragmatic"

analysis in the PRECIS rubric. However, estimating other treatment effects that are useful for decision making (eg, the causal impact of receiving treatment) is an important secondary objective.[24] Whether metformin is effective when taken as directed is perhaps the most important consideration for patients and families, but analyses that accurately address this question are complex and require additional assumptions. We will discuss our approach to answering these questions later in this paper.

METHOD

MOBILITY is a large, multisite, pragmatic trial initiated in October of 2015 and funded by the Patient Centered Outcomes Research Institute (PCORI) (PCS 1406-19276). Sites were approved for eligibility to enroll patients into MOBILITY by a central Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center. Six sites did not use the central IRB and obtained approval from their own IRB. MOBILITY was registered in ClinicalTrials.gov, Identifier NCT02515773. A total of 1,565 youth were enrolled as of December 31, 2022, when recruitment was closed. Follow-up is expected to end in May 2023, with initial results to be presented in the fall.

Patients

Eligible youth will meet the following inclusion criteria: (1) will be aged 8 to 19 years inclusive; (2) will have sex- and age-adjusted body mass index $\geq 85^{th}$ percentile; (3) will have been diagnosed or told by a clinician that they have any of the following bipolar spectrum disorders (BSD) as defined by *DSM-5* or *DSM-IV-TR*[25,26]: bipolar I, bipolar II, unspecified bipolar and related disorders, cyclothymic disorder, other specified bipolar and related disorders; youth previously diagnosed with disruptive mood dysregulation disorder (DMDD) and/or mood disorder not otherwise specified will also be eligible; (4) will receive a new or have an ongoing prescription for an oral regularly dosed SGA (ie, not prescribed only on an as-needed basis). Patients will be excluded if they (1) have been exposed to a total daily dose of 2,000 mg of metformin for at least 2 weeks in the past 3 months; (2) have a major neurological or medical illness that may affect weight gain (eg, unstable thyroid disease), or require a systemic medication that might impact weight or glucose regulation (eg, antidiabetic, cortisol], chronic renal failure; (3) are pregnant or breast feeding; or (4) have fasting serum glucose $\geq$126 mg/dL or serum creatinine $\geq$1.3 mg/dL on 2 occasions during screening or in the prior 6 months, indicating a need for prompt treatment or being a relative contraindication to metformin, respectively.

At baseline, patients must be residing with a caregiver who is able to answer questions (in English or Spanish) about the child's diet, physical activity, behaviors, and mood. After reviewing study procedures, all participants and their legal guardians or representatives from child services will provide written informed assent (if 18-19 years of age, informed consent) or consent, respectively.

Study Sites

Patients will be recruited and followed at 64 clinical locations (39 community-based mental health centers and 24 sites in or affiliated with academic health centers). Sites are located in Ohio, Kentucky, New York, California, Pennsylvania, New Jersey, Texas, Massachusetts, Minnesota, and Maryland. Participating sites are listed in Table 1.

Treatment Groups

Healthy Lifestyle Instruction (LIFE). All patients and their parents/legal guardians will view a brief (5-minute) educational video and receive printed materials about healthy diet and exercise. This healthy lifestyle instruction (LIFE) was developed for MOBILITY by study collaborators from HealthWorks!, a family-based program at the Heart Institute at Cincinnati Children's Hospital Medical Center for overweight youth. The video was produced by members of the Cincinnati Healthworks and MOBILITY teams. The video and written diet/physical activity plan can be accessed at https://med.uc.edu/landing-pages/mobility#metformin. LIFE is based on a "traffic light" model for classifying foods, encouraging "green light" foods that are low-calorie/nutrient-dense and limiting "red light" foods. At least 150 minutes per week of physical activity, spread out over multiple days per week, is recommended. No constraints will be imposed on clinicians' usual approach to counseling patients and families on minimizing risk of weight gain due to SGA.

Metformin (MET+LIFE). Clinicians will receive a suggested titration schedule (Table 2) for patients who will be prescribed metformin.

Treatment Assignment

Randomization will be 1:1 MET+LIFE vs LIFE alone, stratified within each site by obesity status (85^{th}-94.9^{th} percentile vs >/=95^{th} percentile), history of SGA use (any lifetime exposure vs SGA-naive), and sex (assigned at birth). Consecutive assignments within each stratum will be randomly permuted in blocks of 6 to preserve balance within each stratum throughout the study. Site staff will

TABLE 1 Participating Clinical Sites

Site name	Location	Type[a]
Sheppard Pratt Towson Campus (inpatient)	Baltimore, MD	C
Graham Windham	Brooklyn, NY	C
Maimonides Medical Center	Brooklyn, NY	C
New York City Children's Center Brooklyn (outpatient)[a]	Brooklyn, NY	C
New York City Children's Center Brooklyn Day Treatment Program[a]	Brooklyn, NY	C
The Child Center of New York	Flushing, NY	C
Mount Sinai St Luke's (outpatient)	New York, NY	C
Mount Sinai St Luke's Hospital (inpatient units)	New York, NY	C
Mount Sinai St Luke's outpatient Day Treatment Program	New York, NY	C
New York City Children's Center Queens Day Treatment Program[a]	Queens, NY	C
North Shore Child and Family Guidance Center Old Westbury	Roslyn Heights, NY	C
The Child Center of New York	South Jamaica, NY	C
New York City Children's Center Bronx (outpatient)[a]	Bronx, NY	C
Sheppard Pratt (outpatient)	Towson, MD	C
North Shore Child and Family Guidance Center Westbury	Westbury, NY	C
St. Aloysius Butler Campus	Butler, OH	C
St. Joseph's Orphanage Butler Campus	Butler, OH	C
Central Clinic	Cincinnati, OH	C
Child Focus	Cincinnati, OH	C
Lighthouse Youth Services	Cincinnati, OH	C
NECCO	Cincinnati, OH	C
St. Aloysius	Cincinnati, OH	C
St. Joseph's Orphanage Altercrest Campus	Cincinnati, OH	C
St. Joseph's Orphanage Villa Campus	Cincinnati, OH	C
Talbert House Roselawn	Cincinnati, OH	C
Talbert House Walnut Hills	Cincinnati, OH	C
The Children's Home of Cincinnati	Cincinnati, OH	C
Nationwide Children's Hospital (outpatient)	Columbus, OH	C
Children's Home of Northern Kentucky	Covington, KY	C
Samaritan Behavioral Health	Dayton, OH	C
South Community (outpatient)	Dayton, OH	C
South Community Partial Hospitalization Program	Dayton, OH	C
St. Joseph's Orphanage Dayton Campus	Dayton, OH	C
Butler Behavioral Health Services Hamilton	Hamilton, OH	C
Albert J. Solnit Psychiatric Center (outpatient)[a]	Middletown, CT	C
Butler Behavioral Health Services Middletown	Middletown, OH	C
Central Clinic Middletown	Middletown, OH	C
Talbert House Union Day	West Chester, OH	C
TCN Family Solutions	Xenia, OH	C
South Oaks Hospital (inpatient units)	Amityville, NY	A
South Oaks Hospital (outpatient)	Amityville, NY	A
University of Texas, Dell Medical Children's Hospital (outpatient)	Austin, TX	A
Massachusetts General Hospital[a]	Boston, MA	A
State University of New York Downstate (inpatient)[a]	Brooklyn, NY	A
State University of New York Downstate (outpatient)[a]	Brooklyn, NY	A
Cincinnati Children's Hospital Medical Center Base (outpatient)	Cincinnati, OH	A
Cincinnati Children's Hospital Medical Center Base Campus Inpatient Unit	Cincinnati, OH	A
Cincinnati Children's Hospital Medical Center College Hill (outpatient)	Cincinnati, OH	A
Cincinnati Children's Hospital Medical Center College Hill Campus (inpatient units)	Cincinnati, OH	A
University of Cincinnati Resident Mood Clinic	Cincinnati, OH	A
University Hospital (outpatient)	Cleveland, OH	A

(continued)

TABLE 1 Continued

Site name	Location	Type[a]
Ohio State University (outpatient)	Columbus, OH	A
Nassau University Medical Center (outpatient)	East Meadow, NY	A
Zucker Hillside Hospital (inpatient units)	Glen Oaks, NY	A
Zucker Hillside Hospital (outpatient)	Glen Oaks, NY	A
Cincinnati Children's Hospital Medical Center Liberty Campus	Liberty Township, OH	A
University of Minnesota Psychiatry Clinic	Minneapolis, MN	A
Jersey Shore Medical Center[a]	Neptune, NJ	A
New York University Lagone Health (outpatient)	New York, NY	A
Stanford University (outpatient)	Palo Alto, CA	A
Children's Hospital Of Philadelphia (outpatient)	Philadelphia, PA	A
University of Rochester Child and Adolescent Psychiatry (outpatient)[a]	Rochester, NY	A
Stony Brook University (outpatient)	Stonybrook, NY	A
Stony Brook University Hospital (inpatient unit)	Stonybrook, NY	A

Note: *A = academic health center; C = Community-based mental health center.*
[a]*External institutional review board (IRB) rather than central IRB approved the study at this site.*

receive a patient's assignment after entering strata values into a Research Electronic Data Capture (REDCap) database at the baseline visit.[27] REDCap is a secure, Web-based software platform designed to support data capture for research studies, providing the following: (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. Staff will use the Baylor College of Medicine pediatric calculator (https://www.bcm.edu/bodycomplab/BMIapp/BMI-calculator-kids.html) to calculate BMI percentile at baseline. The Centers for Disease Control and Prevention 2000 growth chart data (http://www.cdc.gov/growthcharts/cdc_charts.htm) and the SAS (SAS Institute) programs underlying the calculator will also be used by MOBILITY's statistical team to calculate sex- and age-adjusted BMI and related measures from the measured weights, heights, ages and sex assigned at birth [SaaB]) (these are available at https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas-who.htm).[28]

TABLE 2 Suggested Metformin Titration Schedule

Metformin Titration (by Baseline Weight)		
	<50 kg am/pm	**≥50 kg AM/PM**
Week 1	0/500 mg	0/500 mg
Week 2	0/500 mg	0/500 mg
Week 3	500/500 mg	500/500 mg
Week 4	500/500 mg	500/500 mg
Week 5	500/1,000 mg	500/1,000 mg
Week 6	500/1,000 mg	500/1,000 mg
Week 7	500/1,000 mg	1000/1,000 mg
Week 8	500/1,000 mg	1000/1,000 mg

Primary and Key Secondary Outcomes

The primary outcome is change in age- and sex-normalized body mass index (BMI *z* score) after 6 months. Change after 2 years is a key secondary outcome. We conducted pre-study surveys of clinicians and patients as well as caregivers with the assistance of 2 of our partner organizations, the Depression and Bipolar Support Alliance and the National Alliance on Mental Illness.[29] Both patients and families as well as clinicians indicated that weight gain is the most concerning side effect of SGA treatment. Our team of clinical investigators, patient and family representatives, patient advocacy group members, and other stakeholders including representatives from major insurers and professional organizations determined that change in weight (normalized by height, age and SaaB) was the most appropriate primary endpoint.

Key secondary outcomes include components of metabolic syndrome, mood and anxiety, quality of life, overall functioning, and SGA adherence. Our team selected secondary outcomes to minimize patient and caregiver burden. For example, we chose simple self-report measures from the Patient-Reported Outcomes Measurement Information System (PROMIS) library (https://commonfund.nih.gov/promis/index) to assess multiple domains of interest. Pre-testing indicated that participants would be able to complete assessments within the typical wait time for a clinical appointment. We also sought to minimize burden on clinicians and support staff: to incur only a marginal

increase in the time required to document a clinical encounter, we will request little information not already collected in typical practice.

Assessments and Follow-up Schedule

Follow-up visits are recommended monthly for the first 3 months of participation, and every 3 months thereafter for up to 2 years. However, consistent with the pragmatic study design, visit frequency will be dictated by usual clinical practice. Figure 1 contains a schedule of study events. The schedule of events is an approximation for when routine clinic visits might occur. To adhere to the pragmatic nature of the study, data will be collected only during the patient's regularly scheduled clinical visits, and visits will not be scheduled exclusively to conduct study-specific assessments. No specific study laboratory procedures will be mandated for study participation, with the exception noted above (ie, pregnancy test) The laboratory tests noted in the table of events are suggested in accordance with clinical practice guidelines for patients receiving SGAs.[30] Although an SGA must be prescribed at baseline, participants whose SGA prescription is subsequently discontinued remain eligible to continue in the study.

Use of BMI *z* scores in overweight/obese children has been criticized. These critiques first appeared before our protocol was established and have been amplified since.[31–33]

FIGURE 1 Schedule of Events

Measures	Visit (Approximate Months)										
	SCREEN / BASELINE	1	2	3	6	9	12	15	18	21	24
Demographics & Clinical Characteristics	X										
Structured Diagnostic Assessment (K-SADS)	X										
Medication List	X	X	X	X	X	X	X	X	X	X	X
Body Mass Index	X	X	X	X	X	X	X	X	X	X	X
Recommended Metabolic Labs [insulin, lipid profile, glucose, hemoglobin A1C]	X				X		X		X		X
Treatment Satisfaction	X	X	X	X	X	X	X	X	X	X	X
Adherence	X	X	X	X	X	X	X	X	X	X	X
Mood / Anxiety	X	X	X	X	X	X	X	X	X	X	X
Quality of Life	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [blood pressure, heart rate]	X	X	X	X	X	X	X	X	X	X	X
Other recommended laboratory measures: Thyroid, renal and liver panels, pregnancy test, CBC, and Vitamin B12	X				X						X
Modified Treatment Emergent Symptoms Scale	X				X						X
Suicidality, Patient Health Questionnaire (PHQ)-Item 9	X	X	X	X	X	X	X	X	X	X	X
Total Time/Visit for Youth Questions (minutes)	15-20	5	5	5	15-20	5	7	5	7	5	15-20
Total Time/Visit for Caregiver Questions (minutes)	15-20	5	5	5	15-20	5	7	5	7	5	15-20

There now appears to be consensus that the methods used to derive z scores are problematic at very high percentiles and can underestimate degree of change because the calculation has an upper bound, leading to compression of z scores among youth with very high BMI. Consequently, we now consider alternative BMI metrics that do not share this limitation to be more informative than unadjusted BMI z scores, especially when assessing the role of baseline obesity itself as a potential effect moderator. These include BMI as a percentage of the 95th percentile for age and sex, and a modified z score that expresses BMI relative to the median BMI for age and sex while adjusting for the dispersion in the BMI distribution for that age and sex.[34]

Weight and height will be measured by study staff at each visit using standardized stadiometers and scales provided by MOBILITY. Staff will be instructed to record height to the nearest 0.1 cm, and weight to the nearest 0.1 kg. Stadiometers and scales will be calibrated annually. In response to the COVID-19 pandemic and the global transition of clinical visits to telehealth, we made modifications to allow for data to be collected remotely. In these cases, height and weight will be measured by the family at home using standardized scales and tape measures that are sent to each family. Although enrollment was substantially reduced during the initial phase of the pandemic, the introduction of remote visits appears to have been very successful, as the rate of follow-up visits did not differ from that of the pre-pandemic period. We will compare the variance of height and weight measures collected via remote visits to measures collected from clinic visits to determine whether remote visits incur a detectable increase in measurement error.

Patient- and caregiver-reported variables will be completed on tablet computers, using the REDCap mobile application. Site staff will upload tablet data to the main study database (in REDCap, hosted at Cincinnati Children's Hospital Medical Center). At every visit, clinicians will record any new or ongoing adverse events elicited from the patient, and will rate severity and potential relation to treatments. These events will be coded into a standard format (Medical Dictionary for Regulatory Activities [MedDRA]) that enables analysis at varying levels of hierarchical abstraction (ie, by body system, organ, or etiology). MedDRA terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Occurrence and severity of specific gastrointestinal adverse events known to be associated with metformin (ie, nausea, diarrhea, stomach cramps, flatulence, and vomiting) will be assessed at every visit. At months 6 and 24, clinicians will complete a 49-item inventory of common SGA-related adverse events, modified from the Treatment Emergent Symptoms Scale (TESS).[35]

An independent Data Safety and Monitoring Board (DSMB), comprising experts in pediatric psychopharmacology, endocrinology, and biostatistics, as well as a patient representative, will review all safety data at least every 6 months. The DSMB will also monitor the rate at which study data are monitored, transferred from the sites to central staff, and entered into the study database.

Adherence to Metformin and SGAs

In accordance with the pragmatic nature of this trial, we carefully assess all aspects of adherence, but do not make any special attempt to encourage or enforce adherence to metformin, SGAs, or the lifestyle recommendations. At each study visit, clinicians will complete a medication log listing dosage and start/stop dates for all medications prescribed (or will indicate no changes since the preceding visit, if applicable). As part of the tablet assessments, patients and caregivers will report the name and daily frequency of SGAs and metformin (if prescribed), as well as adherence to these treatments over the previous week. We will measure adherence to each medication prescribed as the reported number of doses taken over the past week divided by the reported number of doses prescribed. We will use the patient/caregiver-reported doses prescribed to measure adherence, as the informants understand it, but will also use the frequency recorded by the clinician to compute rates of adherence to the actual regimens prescribed. Consistent with prior literature, $\geq$80% of doses taken will be defined as good adherence.[36] Twenty percent or less of doses taken will be defined as nonadherence, and >20% but <80% of doses taken will be defined as partial adherence.

Self-reports have been observed to overstate adherence; electronic adherence monitoring using medication bottle caps or pill boxes has been considered more reliable.[37,38] We will obtain electronic adherence measures from a quasi-randomly selected subset of patients and will compare these to self-report data. Our target subsample sizes are n = 150 per group (for SGA monitoring) and n = 100 from the MET+LIFE group for metformin monitoring.

Delayed Initiation of Metformin

Our original protocol recommended obtaining glucose and creatinine serum levels prior to starting metformin (although clinicians could disregard this recommendation based on their clinical judgment). This was a conservative recommendation as compared to usual practice, and it soon became apparent that because of missing laboratory test results,

metformin initiation was frequently delayed. In September 2016 (10 months into enrollment), we amended the protocol so that metformin could be started without prior bloodwork based on clinician choice. We expect some clinicians to elect on their own to delay initiation until laboratory values are obtained, and some clinicians/families may choose to do so because they want to try lifestyle modification before starting a new medication. These delays may be relevant to estimating the causal effect of receiving metformin, particularly in the case in which metformin is only added per the randomization once lifestyle modification has been tried and judged to be insufficient. Methods to account for delayed initiations are discussed below.

Adherence to LIFE

We expect adherence to LIFE to be quite variable among patients and over time. LIFE adherence is very likely to affect outcomes and could possibly moderate the effects of metformin, but accurate measurement of relevant behaviors (eg, by collecting daily diet and activity diaries) is difficult and would present an unacceptable burden in a large pragmatic long-term study. Instead, patients and caregivers will respond to a small, carefully selected set of questions concerning changes in diet (eg, frequency of consuming fast food and soft drinks, snacking between meals or near bedtime) and activity (eg, frequency of activities leading to heavy breathing or perspiration), as well as perceived barriers to making these changes.

Potential Effect Moderators

A principal goal of MOBILITY is to determine whether metformin is especially effective/efficacious in particular subpopulations. Potential moderators that are stable patient characteristics include age (at baseline), sex assigned at birth (SaaB), race, and Hispanic ethnicity. Characteristics that are modifiable in principle include prior SGA exposure, baseline BMI measures, highest level of education among household members, and insurance type (coded as either public or private). We determined that detailed ascertainment of socioeconomic status would be overly burdensome, so we will collect insurance status and parent/guardian education level as convenient proxies for socioeconomic status. Potential mediators or moderators that can vary over time and will be repeatedly measured to capture this variation include SGA regimen, SGA adherence, and LIFE adherence. Metformin adherence is a partially observed mediator (ie, effects of metformin assigned and prescribed are realized through the proximal effect of actually taking metformin, but metformin adherence is directly observed only in patients who are prescribed metformin). Observed SGA adherence may carry some information about unobserved (counterfactual) metformin adherence, and we will detail our strategy for using these data in an upcoming report.

Statistical Analysis

For the intention-to-treat (ITT) analysis of the primary endpoint (change in BMI z score at 6 months), we will fit mixed-effects analyses of covariance with fixed terms for treatment assignment and baseline BMI z score, and with random effects for site and site-by-treatment interaction. Where more than 1 clinical visit falls within the window, the measurement closest to the target time will be used. For patients without a measurement in the target window, the final BMI measured will be their endpoint. Patients with no post-baseline visits will be excluded. Because the Centers for Disease Control and Prevention reference tables for computing z scores end at age 20 years, and because patients could be as old as 22 years at their final visit, z scores for such visits will be computed fixing age at 20 years. As a sensitivity analysis, we will omit patients with endpoint visits at age >20 years. Because the protocol calls for visits intermediate to the 6-month and 24-month windows, we will also analyze the full longitudinal series to determine in detail the time course of effects (eg, effects might become detectable at some intermediate duration, might weaken or strengthen over time, etc).

Analyses of absolute BMI change at the same times will have fixed terms for treatment assignment, BMI at baseline, age, SaaB, and interaction between age and SaaB. The latter 3 terms adjust for the expected relationships that are already incorporated in the z scores. To avoid over- or under-fitting age effects (which are expected to be nonlinear and vary by SaaB), we will choose the number and width of age categories prior to fitting models with a treatment effect by comparing bin widths of 1 to 4 years (ie, fitting alternative specifications for the age and age-by-SaaB terms, with a main effect of SaaB and a linear effect of baseline BMI included, but no metformin effect). The best specification will be chosen as the one that minimizes the Akaike information criterion (AIC).[39] It should be noted that the issue of visits at ages >20 years does not apply to these analyses.

Moderator effects at each primary time point will be estimated in 2 stages. The first, pre-specified analyses will fit a separate model for each moderator, expanding the models above by adding a main effect of the moderator and an interaction with treatment (capturing the effect of interest). The issues with using z scores noted above are directly related to degree of obesity. Therefore, we expect that obesity as a moderator may be particularly sensitive to the choice of BMI metric. Because we expect moderators to be

correlated, in the second stage we will fit a model with all moderator main and first-order interaction effects included simultaneously.

ITT analyses of other outcomes will follow the approach described above, with appropriate modifications based on the distribution of each outcome (ie, mixed-effects logistic/cumulative-logit regression for binary/ordinal categorical outcomes, Poisson regression (possibly zero-inflated) for count outcomes, etc).

In addition to the ITT analyses, we will fit similar models for analytic sets based on whether and when metformin was prescribed (rather than randomized assignment). These will include as-treated [AT] analyses and per-protocol [PP] analyses. Although the ITT analyses are listed as primary, these alternate analyses address additional questions of direct clinical relevance and may be of greater practical importance to some stakeholders. All post-switch data from patients who switched from their assigned group will be included in the AT analyses. Data collected up to the point of switching will be included in the PP analyses. Delays <90 days in initiating assigned metformin will not exclude patients from the PP analyses. We will also take an alternate approach to delayed initiation of metformin by redefining the baseline for these patients as the last visit before metformin was started. This way of defining the PP set will result in a larger group of patients whose observation period consists entirely of metformin exposure, unless and until they discontinue. This PP model does have the limitation that patients with delayed starts will not have received both interventions at the same time (their redefined baselines may be weeks or months after the "true" baseline when they were randomized and presented with the LIFE instruction video and materials).

Targeted Minimum-Loss Estimation (TMLE) was developed to consistently and efficiently estimate a key feature of a distribution of interest, such as the Average Treatment Effect (ATE) with minimal reliance on parametric assumptions.[40] Causal assumptions are encoded in a directed acyclic graph, which can be expressed as a set of nonparametric structural equations.[41] In this very general framework, treatments received can be a function of baseline or of time-varying confounders, including intermediate values of the outcome measure. As described above, MOBILITY's design will give rise to data with these types of dynamic relationships among treatment, outcomes, and other time-varying factors, such as SGA regimens and adherence to the metformin and LIFE interventions. Therefore, TMLE (also known as Targeted Learning) is an appealing analytic framework. Properties of TMLE include the following:

1) Double robustness: If either the portion of the model describing the relationship of measured confounders to treatment received or the portion describing the data-generating mechanism of the outcome model are correctly specified, the method is consistent (ie, estimates will converge to the true value with increasing sample size). If both of these components are correctly specified, the procedure is also efficient.
2) Flexible and data adaptive: TMLE is usually performed using an ensemble of models, which can range from purely parametric models such as the traditional general linear model to semi-parametric and completely nonparametric models (eg, neural nets, support vector machines, and regression trees). Cross-validation performance is used to weight each model's estimate of the target parameter to form an ensemble estimate, a procedure known as Super Learning; theoretical and empirical results show that the ensemble estimate performs at least as well as the best single model in the set, and this makes the double robustness property mentioned above more likely to hold.[42] This machine-learning approach allows researchers to make few assumptions about the data-generating mechanism beyond what is specified in the causal equations (ie, the directed graph), because the ensemble will discover relationships between parent nodes in the graph (causes) and their descendent nodes (effects) empirically while avoiding overfitting.

We are preparing a separate report that discusses in detail the workflow to apply TMLE to the MOBILITY data. The overall advantage of supplementing traditional approaches to causal inference based on parametric analysis of different analytic sets with TMLE is that the target quantity is the distribution of outcomes that would be observed if all patients received metformin vs the distribution that would be observed if all patients received LIFE only.

Power and Sample Size

The target sample size (N = 1,637) was selected based on power to detect moderators of the metformin effect. We calculated power to detect interaction effects of $d = 0.40$ SD (eg, a null metformin effect in the subpopulation having 1 value of a binary moderator and $d = 0.40$ at the other level). Because the relative sizes of the subgroups affect power (with maximum power when sample sizes are equal), we conservatively assumed subgroup imbalance as large as 3:1, but equal proportions assigned to metformin within each subgroup. For potential moderators used to stratify randomization, close balance is ensured by design and holds in expectation for other moderators. We assumed a 25% missing data rate for the 6-month outcome, a 50% rate for

the 24-month outcome, and 2-sided hypothesis tests with a maximum type I error rate of 5% ($\alpha = .05$). This sample size yields very high power to detect an overall metformin effect (80% power to detect an effect as small as 0.16 SD). A recently reported randomized trial led by one of our team members observed a metformin effect of 0.68 SD.[20] From these data, we estimated the standard deviation of absolute BMI change after 6 months to be about 2 points. Thus, differences as small as 0.33 points are likely to be detectable at that time (patient characteristics and treatment regimens are more heterogeneous than in the IMPACT trial, so variation in BMI change may be greater).

As interactions are estimated with much less precision than main effects, substantial sample size is required to reliably detect modest effects. Without any adjustment for multiple testing, per-test power to detect moderators at month 6 will be 85%. Although we will present unadjusted 95% confidence intervals for all interaction effect sizes, in determining an appropriate sample size, we were aware that our goal of assessing multiple moderators obliges us to consider the issue of multiplicity. We seek to strike a reasonable balance between the multiplicity-adjusted per-test type I error rate (controlling false discovery) and the per-test type II error rate (controlling missed discovery of effects of a given minimum size). There is no obvious way to precisely balance these risks, but we assume that the cost of failing to identify populations that would especially benefit from metformin is not dramatically greater than the cost of reporting unnecessarily specific estimates that would overstate expected benefit for some patients and understate it for others. Scientific convention is to avoid type I errors at the cost of type II errors (eg, by choosing sample size to yield a ratio of $[1-0.80]/0.05 = 4$). We believe that this preference is appropriate but prefer to keep the ratio of per-test type II error to type I error less than 10. Because, in most cases, we expect the unadjusted per-test power to detect moderation to be approximately 85%, this ratio is $[1-0.85]/0.05 = 3$ without multiplicity adjustment. We cannot allow either the per-test or cumulative error rates to be too high in absolute value. We propose to use per-test $\alpha = .025$, yielding per-test power = 77% and a type II/type I ratio of 9.2. If none of the up to 10 variables that we will assess actually moderate the effect of metformin, then by the Bonferroni inequality we can expect the chance of identifying at least 1 false moderator to be at most $1-(1-0.025)^{10} = 22.4\%$.

Missing Data

Not all patients will have a visit in the window for the primary endpoint measurement, and we expect as many as 50% of patients to be lost to follow-up by 2 years. We expect that the data will be missing at random with respect to weight gain; we have no reason to think that patients will miss appointments or drop out of the study because of their weight. When we analyze, for example, mood or quality of life outcomes, the missing at random assumption may not hold. We will assess these assumptions about missing data by examining associations between attrition and variables measured at baseline or follow-up visits prior to dropout. Variables that significantly predict dropout will be considered for inclusion as covariates. Some special treatment of missing data will be required to apply Targeted Learning; we will discuss this problem and our solution in a separate report.

DISCUSSION

The numerous benefits of MOBILITY's flexible and pragmatic design that enhances external validity and reduces barriers to recruitment and follow-up produce some significant potential challenges that must be adequately addressed in the statistical analyses.

Outcome-Driven Switching Between Treatment Groups

Because MOBILITY is randomized but open label, clinicians, participants and caregivers will know whether or not the patient is receiving metformin. Participants will be allowed to switch between treatment arms and could even do so repeatedly. This flexibility might make the study more appealing to a broad range of participants, caregivers, and clinicians than a double-blind randomized controlled trial (RCT) in which the investigational agent is not easily accessible to patients who are not randomized to receive it. Although this design feature will aid enrollment and potentially increase external validity, it may also be problematic, because LIFE-only patients may switch to MET+LIFE specifically because of perceived inadequate response to LIFE alone. Receiving treatment on the basis of intermediate results on the primary outcome can produce potentially serious confounding when 1 of the principal goals is to estimate the causal effect of treatment received. For example, if the efficacy of metformin is moderated by body mass itself (either absolute levels or rate of recent change), the distribution of this moderator will become unequal between groups over time and could distort the treatment effect. The intention-to-treat effect still estimates the causal effect of assignment, but from a patient perspective this is less relevant than the effect of taking the treatment. Per-protocol analysis can somewhat mitigate this issue, but the extent of PP follow-up will vary systematically based on intermediate outcomes, which might also distort the analysis. As-treated analysis would yield an accurate

causal estimate only if moderation by factors dictating the treatment effect or treatment received does not exist, a condition that must be demonstrated rather than assumed. Discontinuation of metformin could also be related to perceived inefficacy, although we expect these switches to more often be in response to adverse events rather than insufficient weight change (and to occur earlier than switches from LIFE to MET+LIFE). If the reasons for treatment crossover in each direction differ, our analyses should reflect this.

Potential for Correlated Adherence

Adherence to metformin is logically distinct from adherence to other medications, such as SGAs. However, these adherence behaviors may be correlated, either because the SGA stabilizes dysfunctional psychiatric symptoms that could interfere with metformin adherence,[43] or because adherence to metformin mitigates the adverse cardiometabolic effects of the SGA and the increased tolerability makes adherence to the SGA more likely. Although medications may be differentially acceptable to a patient, we hypothesize that rates of adherence to multiple treatments will show at least moderate positive correlation. Adequate SGA adherence is desirable to manage psychiatric symptoms despite potential for weight gain. Importantly, however, if metformin mitigates weight gain as hypothesized, then a positive correlation between adherences could potentially produce offsetting effects. To isolate the causal effect of metformin, we seek to vary metformin exposure while keeping SGA exposure fixed to a constant level. Although this potential correlation is a complication, it could also prove useful. Because SGA adherence is measured in all patients but metformin adherence can only be observed in the subgroup prescribed metformin, SGA adherence might serve as a proxy for potential metformin adherence among those who are not prescribed metformin.

Potential for Risk Compensation

Changes in weight will also depend on adherence to the diet and exercise recommendations that all patients receive. This type of adherence may differ as a direct consequence of being prescribed metformin. Risk compensation (also known as behavioral disinhibition) refers to situations in which the perception that a treatment reduces risk causes those receiving it to alter their behavior in ways that offset the benefits of treatment by increasing risk.[44] For example, in an HIV prevention trial of vaginal microbicides, those women who were aware that they were not receiving an active treatment reported higher rates of condom use than those who were blinded to whether they were receiving an active treatment or placebo.[45] Indeed, it has been suggested that risk compensation may be an "Achilles' heel" in HIV prevention research.[44] As an open-label trial in which all families are asked to make behavioral changes that are challenging to initiate and sustain, MOBILITY may be subject to a similar phenomenon: awareness that metformin potentially mitigates weight gain may lower motivation to embrace sustained healthy lifestyle modifications among those receiving metformin. Alternatively, addition of a potentially beneficial weight treatment might make patients more hopeful that they can successfully address weight gain and thereby improve their diet and physical activity. It is also possible that perceived protection from weight gain will improve adherence to SGAs. In any case, these interactions would be relevant to the real-world implementation of metformin and LIFE; therefore, we wish to learn whether treatment-specific behavioral effects add to or detract from whatever biological effects metformin might cause.

A "patient-centered" estimate of treatment effect should be one that reflects the decision actually facing the patient, conditional on relevant patient-specific factors that might include prior outcomes. Because the ITT estimate averages over variable adherence, it may provide useful information to clinicians who must decide whether to prescribe a treatment to their patients without knowing which of them will be able to tolerate it or how well they will adhere to the treatment. An individual patient faces a different decision: if a treatment is prescribed, the most relevant questions are whether it will be tolerable, and if so, what benefit can be expected if they adhere closely to the prescribed regimen.[46,47] Therefore, a key causal estimand is the effect of treatment under perfect adherence among those who can tolerate the treatment. We wish to estimate the efficacy of metformin among patients who would adhere to whichever treatment they were assigned, with adherence to metformin set to 100% and adherence to LIFE held constant at 1 or more meaningful values (eg, average adherence).

Summary

We have described the protocol for a large, pragmatic, randomized clinical trial comparing the effectiveness of metformin plus brief diet and exercise education (MET + LIFE) with diet and exercise education (LIFE) alone for control of weight gain in a sample of up to 1,637 overweight and obese children and adolescents, aged 8 to 19 years, with bipolar spectrum and related mood disorders who will receive treatment with second generation antipsychotics (SGA). The primary outcome selected through consultation with stakeholders was change in BMI z score after 6 months. Follow-up is ongoing, but the final sample recruited was N = 1,565 youth recruited from community and academic settings and

followed for up to 2 years. We have discussed a number of novel challenges posed by the pragmatic design.

To our knowledge, MOBILITY will be largest randomized, prospective treatment trial conducted in youth with bipolar spectrum disorders. The treatment and measurement protocol were designed to maximize acceptability to all parties in terms of incremental time and effort above usual practice and do not unduly constrain treatment options. Continual input from a range of stakeholders in every phase of the study will be critical to achieving these goals. MOBILITY is well positioned to generate large-scale evidence with an excellent balance of internal and external validity. Although several of the inevitable hurdles that such a complex trial entails have been outlined, we expect MOBILITY not only to produce a robust conclusion regarding the effectiveness/efficacy, tolerability, and safety of metformin in a large and highly vulnerable population, but to support numerous additional lines of investigation that will improve the physical and mental health of these youth.

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Author Contributions
MPD, JAW, CUC conceived of the study. MPD, JAW, CUC, CCK, and TJB initiated the study design. MS and VMF helped with implementation. MPD is the grant holder. JAW, BH, and AC provided statistical expertise in clinical trial design and JAW will conduct the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

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