

Pediatric Trials Network

Long-term Antipsychotic Pediatric Safety Trial (LAPS)

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Phase 4 Trial

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STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Council for Harmonisation (ICH) E6(R2) guideline for Good Clinical Practice (GCP), and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including 45 CFR 46 (human subjects protection), 21 CFR 312 (Investigational New Drug), 21 CFR part 50 (informed consent), and 21 CFR part 56 (institutional review board [IRB]) as well as international regulatory requirements, if applicable.

All individuals responsible for the design and/or conduct of this study have completed human subjects protection training and are qualified to be conducting this research.

SITE PRINCIPAL INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the investigator brochure or product label, and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the institutional review board responsible for such matters must approve this protocol in the clinical facility where it will be conducted.

I agree to provide all subjects with informed consent forms, as required by government and ICH regulations. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. CFR, Title 21, part 312.64 as well as international regulatory requirements, if applicable.

Principal Investigator Name (Print)

Signature

Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

The signature below documents the review and approval of this protocol and the attachments (e.g., package inserts), and it provides the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration time curve
AUC _{ss}	area under the curve at steady state
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BSAS	Behavioral Symptom Assessment Scale (modified SLAES)
BUN	blood urea nitrogen
CBC-D	complete blood count with differential
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CL/F	apparent total clearance of the drug from plasma after oral administration
C _{max}	maximum concentration
CO ₂	carbon dioxide, bicarbonate
CRF	case report form
CSQ	Caregiver Strain Questionnaire
DCC	data coordinating center
DCRI	Duke Clinical Research Institute
DCF	data collection form
DMC	data monitoring committee
DMDD	disruptive mood dysregulation disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTFS	Delighted-Terrible Faces Scale
eCRF	electronic case report form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
FGA	first-generation antipsychotic
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HDL-C	high-density lipoprotein cholesterol
Hgb A1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
hs-CRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation

LIST OF ABBREVIATIONS (con't)

Abbreviation	Definition
ICMJE	International Committee of Medical Journal Editors
IEC	independent or institutional ethics committee
IND	Investigational New Drug Application
IRB	institutional review board
LDL-C	low-density lipoprotein cholesterol
MedDRA [®]	Medical Dictionary for Regulatory Activities
MOP	manual of procedures
N	number (typically refers to participants)
NHLBI	National Heart, Lung, and Blood Institute
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
PD	pharmacodynamics
PedsQL	Pediatric Quality of Life Inventory
PHI	protected health information
PK	pharmacokinetics
PPPMP	personal psychotropic-prescribing medical provider
PTN	Pediatric Trials Network
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Extrapyramidal Symptom Scale
SGA	second-generation antipsychotic
SLAES	Systematic Longitudinal Adverse Events Scale
SMC	study medical clinician (medical doctor, principal investigator, nurse practitioner)
SMURF	Safety Monitoring Uniform Reporting Form
SS	study staff (study coordinator, research assistant)
T _{1/2}	half-life
TD	tardive dyskinesia
Tmax	time of maximum concentration
Vineland	Vineland Adaptive Behavior Scales
Vss/F	apparent volume of distribution at steady state after non-intravenous administration
z-score	a numerical measurement of a value's relationship to the mean in a group of values

PROTOCOL SYNOPSIS

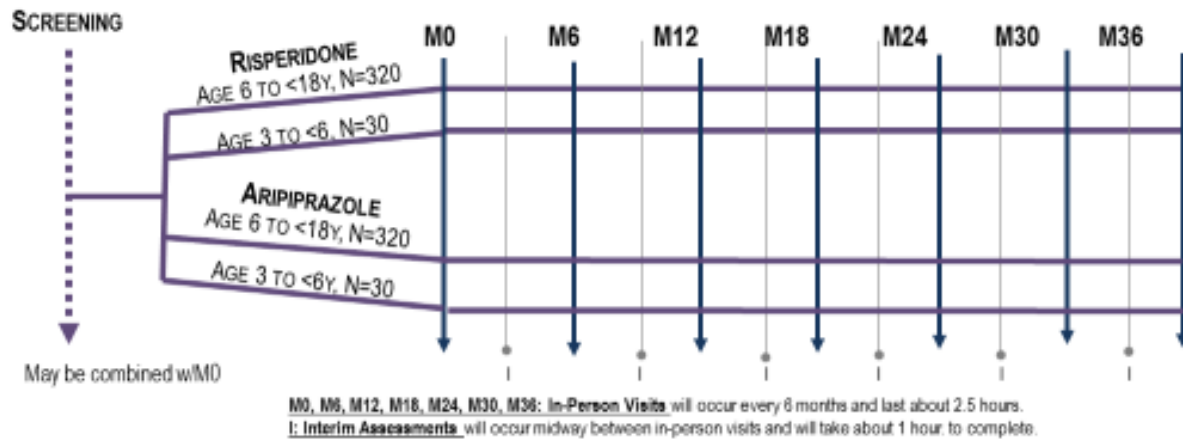
Protocol Title	Long-term Antipsychotic Pediatric Safety Trial (LAPS)
Phase	4
Products	risperidone, aripiprazole
Objectives	<p><u>Primary:</u> Evaluate the long-term pathologic weight changes associated with multi-year risperidone or aripiprazole therapy in 3 – <18-year-old children, who have varying durations of prior antipsychotic drug exposure from the start of study Month 0 (M0). This is critical because children appear to have greater vulnerability to antipsychotic-associated weight gain than adults, and obesity has significant effects on morbidity and mortality. The primary analysis will focus on children 6 – <18 years at M0 visit.</p> <p><u>Secondary:</u></p> <ol style="list-style-type: none"> 1. Evaluate the overall safety of multi-year risperidone and aripiprazole therapy in 3 – <18-year-old children by assessing long-term changes in safety outcomes of special interest: 1) metabolic measures associated with risk of diabetes and cardiovascular disease; 2) serum prolactin; 3) neuromotor effects; 4) rates of adverse effects (AEs) of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater; and 5) suicidality. 2. Evaluate the potential long-term benefits of risperidone and aripiprazole by assessing age-normed adaptive functioning, child and caregiver quality of life, and changes in the intensity and frequency of pre-existing behavioral problems. 3. Estimate pharmacokinetic (PK) parameters of risperidone and aripiprazole in normal-weight children aged 6 – <10 years and obese children aged 6 – <18 years.
Study Design	<p>Prospective, multi-site, Phase 4, observational study designed to systematically collect longitudinal post-marketing safety data. Assessments will occur every 3 months for up to 36 months with in-person, clinic-based assessments at months 0, 6, 12, 18, 24, 30, and 36, alternating with remote interim visits occurring at months 3, 9, 15, 21, 27, and 33. The remote interim assessments may be collected using electronic patient-reported outcome (ePRO) via an electronic device, paper (returned to site), or a phone call with the site staff. Some assessments during the in-person visits may also be completed via ePRO. The participant, his/her guardian, and the participant's personal psychotropic-prescribing medical provider (PPPMP) will make any and all decisions related to antipsychotic medications; any other medications; and the participant's current mental state, developmental/psychiatric condition, and level of risk for potential harm to self or others independent of the study procedures and assessments. Study staff (SS) will share lab results, medically concerning changes in AEs and the participant's clinical presentation as assessed during in-person visits, and positive responses to key safety questions (see the manual of procedures [MOP]) for the remote interim assessments with the participant's PPPMP and guardian (at in-person assessments). If an emergency safety concern is evident during a clinic visit, the study medical clinician (SMC) will immediately assess the participant, following medical standard-of-care procedures, to determine whether the participant is safe to leave the clinic or requires additional emergency care. If new or worsening symptoms are reported by the participant or guardian during remote interim assessments, guardians will be instructed to contact their PPPMP directly.</p>

<p>Outcome Measures</p>	<p>Primary Outcome Measure: Pathologic weight change as reflected by longitudinal assessment of modified body mass index (BMI) z-score from the start of study (M0) as defined in CDC growth charts.</p> <p>Secondary Outcome Measures: Secondary measures of weight change: Change in BMI category Modified BMI z-score increase of ≥ 1.0 unit from M0</p> <p>Safety Outcomes of Special Interest: Metabolic measures associated with risk of diabetes and cardiovascular disease (e.g., fasting glucose and lipid panel; fasting insulin; high-sensitivity C-reactive protein [hs-CRP]; hemoglobin A1c [Hgb A1c]) Hyperprolactinemia - assessed by monitoring serum prolactin levels Neuromotor effects - assessed by physical exam and abnormal movement scale ratings (Abnormal Involuntary Movement Scale [AIMS], Simpson Angus Extrapyramidal Symptoms Scale [SAS], Barnes Akathisia Rating Scale [BARS])</p> <p>AEs - elicited AEs, including AEs of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater and clinically significant changes in suicidality</p> <p>Benefits – relationship of risperidone or aripiprazole therapy to adaptive functioning and quality of life as assessed by the Vineland Adaptive Behavior Scale standard scores, Pediatric Quality of Life Inventory (PedsQL, 23 item), Delighted-Terrible Faces Scale (DTFS), Caregiver Strain Questionnaire (CSQ), and changes in the intensity or frequency of pre-existing behavioral problems indicated at M0 (baseline)</p> <p>Pharmacokinetics - CL/F, Vss/F, AUCss, Cmax, Tmax, and T_{1/2} at steady state</p>
<p>Study Population</p>	<p>The study population will consist of two groups of children 3 – <18 years old at the time of the M0 visit:</p> <ul style="list-style-type: none"> • Risperidone group, n=350, including 30 children 3 – <6 years old and 320 children 6 – <18 years old. Approximately 50% – 80% of the entire group will have ≤ 90 days of prior treatment with any antipsychotic. • Aripiprazole group, n=350, including 30 children 3 – <6 years old and 320 children 6 – <18 years old. Approximately 50% – 80% of the entire group will have ≤ 90 days of prior treatment with any antipsychotic. <p>We will target participants within each treatment group to be distributed across the age range to permit analyses of age effects with:</p> <ul style="list-style-type: none"> • ~30 being 3 – <6 years • $\geq 35\%$ (n ≥ 123) being 6 – <12 years • $\geq 35\%$ (n ≥ 123) being 12 – <18 years <p>A sub-study for centers with PK expertise will collect steady-state PK samples (obtained at up to five time-points relative to taking risperidone or aripiprazole) from ~24 children, 12 in each of the two treatment groups. Within each treatment group, ~6 children who are 6 – <10 years old with normal weight, ~3 who are 6 – <13 years with obesity (BMI ≥ 95th percentile), and ~3 who are 13 – <18 years old with obesity will be studied.</p>

Inclusion Criteria	<ol style="list-style-type: none"> Guardian has provided informed consent Participant has provided assent if developmentally appropriate and as required by the institutional review board (IRB) 3 – <18 years of age inclusive at time of M0 visit Participant, when developmentally appropriate, and guardian are: <ol style="list-style-type: none"> Able to understand and describe key aspects of study procedures and expect to be able to comply with them for the 36-month study period Willing to authorize exchange of information between the SS and the PPPMP and/or other significant medical provider Affirm participant's use at M0 visit of either risperidone or aripiprazole as prescribed by participant's PPPMP Based on their age at the time of M0 visit, participant is receiving aripiprazole or risperidone at the specified dose and for the diagnoses as listed below: <ol style="list-style-type: none"> Participants ages 3 – < 6 years can have any diagnosis and any dose Participants ages ≥ 6 – 17 years (see table below) 	
	Drug	
	Aripiprazole*	Risperidone*
	Dose	
	2 – 30 mg/day	0.25 – 6 mg/day
	Indication	
	<u>Labeled indications (underlined)</u> and <i>Closely Related Disorders (italicized)</i>	
	<u>Irritability associated with autistic disorder</u> <i>Irritability in autism spectrum disorder</i>	<u>Irritability associated with autistic disorder</u> <i>Irritability in autism spectrum disorder</i>
	<u>Treatment of Tourette's disorder</u> <i>Tourette's disorder, persistent (chronic) motor or vocal tic disorder</i>	N/A
	<u>Bipolar mania/acute treatment of manic and mixed episodes associated with Bipolar I disorder</u> <i>Bipolar spectrum disorders including disruptive mood dysregulation disorder</i>	<u>Bipolar Mania</u> <i>Bipolar spectrum disorders including disruptive mood dysregulation disorder</i>
	<u>Schizophrenia</u> <i>Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder</i>	<u>Schizophrenia</u> <i>Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder</i>
	<u>*MYCITE® (aripiprazole) and all forms of injectables are not permitted in this study</u>	
	<ol style="list-style-type: none"> Guardian anticipates risperidone or aripiprazole treatment will continue for ≥6 months 	

Exclusion Criteria	<ol style="list-style-type: none"> 1. History of prior or current diagnosis of an eating disorder or meets diagnostic criteria for an eating disorder as described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and determined by psychiatric exam 2. Pre-existing or suspected major medical, metabolic, or genetic condition that is expected to be associated with weight, cardiovascular, neuromotor, or endocrine problems 3. Known or self-reported pregnancy 4. Taking antipsychotic medication other than either risperidone or aripiprazole at the time of M0 visit 5. Contraindications to participation in the study in the opinion of the SMC 6. Unwilling or unable to provide back-up family contact information
Statistical Approach	<p>The primary endpoint will be modified BMI z-score assessed at each study visit from the M0 visit through the 36-month follow-up period. In the primary analysis, the change in modified BMI z-score over the course of the study will be estimated within each treatment group using a mixed effects model containing treatment and covariates of interest, including estimated duration of prior antipsychotic exposure, as variables in the model. Key demographic and clinical covariates will be identified through variable selection methods. The primary treatment variable will be the treatment received at the time of the M0 visit. All enrolled participants 6 – <18 years old at the M0 visit with at least one follow-up visit will be included in the primary analysis. Sensitivity analyses will evaluate the impact of treatment discontinuation or switching on long-term change in modified BMI z-score. Additional measures of weight change, such as the percentage of all participants with z-score increases of ≥ 1.0 unit(s) from the M0 visit, will be estimated by treatment group as secondary analyses. Secondary safety and benefit outcomes will be summarized by treatment group at the time of the M0 visit and current treatment at the time of the event. Population PK analysis will be performed using samples from a subset of participants in the sub-study.</p>
Number of Participants	Approximately 700 participants
Number of Sites:	Approximately 60 sites
Duration of Participant Participation:	Up to 38 months
Estimated Time to Complete Enrollment:	Up to 18 months

Schematic Description of Study Design



1 KEY ROLES

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2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background Information

Section 409I of the Public Health Service Act, also known as the Best Pharmaceuticals for Children Act (BPCA), mandates the National Institutes of Health (NIH) to prioritize therapeutic areas in critical need for pediatric labeling; to sponsor pediatric clinical trials; and to submit these data to the FDA for consideration for labeling changes. This study will be conducted in accordance with Section 409I of the Public Health Service Act; as such, the results from this research may be submitted to the FDA for review and use in negotiated labeling changes. This research study is contractually supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The NICHD awarded a contract to Duke University (Durham, NC), which established a Pediatric Trials Network (PTN) through its Duke Clinical Research Institute (DCRI) to facilitate trial design for studies supported by the NIH. The NICHD awarded a separate contract to The Emmes Corporation (Rockville, MD) to serve as the BPCA data coordinating center (DCC).

Antipsychotic treatment of children and adolescents has greatly increased over the past 20 years. Among nationally representative U.S. households, 0.2% of children and adolescents received antipsychotic drugs in 1996, compared with a rate of 1.2% in 2012 [1]. While specific antipsychotics are FDA-approved for schizophrenia, bipolar disorder, Tourette's disorder, and irritability associated with autism spectrum disorder, off-label use is frequent in other conditions including attention-deficit/hyperactivity disorder (especially if other treatments have failed or there is associated aggression), disruptive behavior disorders (e.g., conduct disorder, oppositional defiant disorder), obsessive-compulsive disorder, and major depression with psychotic features [2-4]. Antipsychotics are also frequently used off label to promote weight gain and reduce anxiety in individuals with eating disorders such as anorexia and bulimia. Because promotion of weight gain is a major focus of treatment in eating disorders, but a primary concern in all other populations, this study will exclude individuals with eating disorders.

Three factors are likely responsible for the increased antipsychotic prescribing in children. First, there has been increased public awareness of mental illnesses in children, with about one in five being diagnosed with a psychiatric disorder prior to age 18 [5], and greater recognition that pediatric mental illness leads to adult mental illness, with >75% of those with adult mental illness having been diagnosed with some mental illness prior to age 18 [6, 7]. Interestingly, childhood disruptive behavior disorders appeared to increase risk for all adult disorders, and mood and psychotic disorders often persisted from childhood into adulthood, with individuals with childhood onset often having worse outcomes [6, 8]. These observations have led to calls for more effective screening for and treatment of mental illness in children, with suggestions that 25–50% of disabling adult mental illness could be prevented by effective treatment during childhood [6, 8-10]. Second, a new class of antipsychotics, referred to as second-generation antipsychotics (SGAs), has been developed. Efficacy of SGA treatment has been demonstrated for several disabling neuropsychiatric disorders in children, including schizophrenia, bipolar disorder, and irritability associated with autism, as well as consistent findings of reduced disruptive behaviors in youth with below-average intellectual functioning. These are the disorders that carry the greatest risk for continued disabling psychiatric problems in adulthood. Third, short-term clinical trials in adults and children with psychiatric conditions have found that SGAs are less sedating and have much lower risk for neuromotor side effects,

including tardive dyskinesia (TD), than traditional antipsychotics, leading to the perception that they are “safer” [11, 12].

However, there are emerging data that link SGAs with important adverse safety events.

Weight Gain during SGA treatment

There is now a growing concern among the medical and scientific community, regulatory agencies, and the general public that the potential benefits of SGAs in children may not outweigh the potential long-term adverse effects, specifically those related to weight gain [13-16]. The FDA specifically noted that the SGA olanzapine should *not* be used as a first-line treatment for schizophrenia or bipolar disorder in children due to weight gain. Among other commonly used antipsychotic drugs, short-term studies show a 10.4% increase in weight from baseline with risperidone, compared with 8.1% with aripiprazole after 12 weeks of exposure in antipsychotic-naïve children and adolescents [14]. In contrast, antipsychotic-naïve adults treated with risperidone for 12 weeks experienced a median weight gain of 8.9% of their baseline weight, and adults treated with aripiprazole for 12 weeks experienced a 6.6% increase in weight. Adults with prior antipsychotic exposure typically show much less weight gain [51, 52]. A six-month study of antipsychotic-naïve pediatric patients suggested that weight gain may occur in phases, with the first three months accounting for the greatest weight increase in youth treated with SGAs, while there was a slowing of weight gain during the subsequent three-month period [17]. Studies attempting to characterize the long-term effect of antipsychotic drugs on weight gain are limited by lack of generalizability and small sample size [1, 18].

Increased Risk of Metabolic Syndrome

Metabolic syndrome includes a constellation of physical (weight, waist circumference, and BP) and laboratory abnormalities (glucose and lipid panel) that are associated with increased risk for diabetes mellitus and cardiovascular disease. Lipid and glucose abnormalities, which frequently develop during antipsychotic treatment—with 17.1% of treated youth developing new-onset dyslipidemia and 8.6% of youth developing insulin resistance over 12 weeks (n=272) [14]—are of great concern and need to be addressed. Lipid and glucose abnormalities appear to follow trends similar to weight gain, with most abnormalities developing in the first three months of treatment. However, long-term studies are needed to determine overall trends. Our knowledge and understanding of the persistence of metabolic abnormalities or weight gain are limited because many participants who have experienced such problems choose not to continue participation in longer-term continuation studies that typically follow acute trials because of these adverse effects. However, because most of the disorders treated with antipsychotics are chronic and persist across the lifespan, many children who stop treatment with an antipsychotic due to adverse effects will resume antipsychotic treatment in the future.

Hyperprolactinemia

SGAs can modify prolactin levels by dopamine D2 receptor antagonism of the tubero-infundibular dopamine pathway. Clinical manifestations of hyperprolactinemia include gynecomastia, galactorrhea, oligomenorrhea or amenorrhea, delayed puberty in children, and reduced libido [19]. Risperidone is one of the most commonly prescribed SGAs and is associated with the largest acute increases in serum prolactin [19, 20]. However, aripiprazole is associated with a reduction in prolactin levels [21]. There is also evidence that antipsychotic-related increases in prolactin levels are greater and more prevalent in the pediatric population than in adults [53]. There is limited evidence that antipsychotic-induced hyperprolactinemia may normalize over time [22, 23]; however, this requires further study in larger samples.

Neuromotor Effects: Extrapyramidal Symptoms and Tardive Dyskinesia

Neuromotor extrapyramidal symptoms (EPS) remain a common side effect of SGAs. EPS caused by antipsychotics include akathisia, pseudoparkinsonism, and dystonia. Compared with adults, children are at increased risk of EPS [24], though they may lack the verbal ability to accurately describe their physical symptoms. As a group, SGAs are associated with lower rates of EPS than high- and mid-potency first-generation antipsychotics (FGAs). However, the risk for EPS varies considerably among the different SGAs. Aripiprazole is associated with greater rates of akathisia (up to 26% in one nonrandomized 12-week study [25]), though maintenance studies of pediatric bipolar patients show low rates of other types of EPS (e.g., dystonia) [21, 26]. Risperidone is associated with greater risk of pseudo-parkinsonian symptoms and dystonia [23, 27, 28]. The incidence of EPS with risperidone appears concentration-dependent, with relatively low rates observed in open-label maintenance studies in children with autism (8% over six months) or disruptive behaviors and sub-average intelligence (2.5% over 12 months), who are typically treated with much lower doses than children with bipolar disorder or schizophrenia [25, 29]. Other antipsychotics such as clozapine and quetiapine are associated with lower rates of EPS [30-33].

Tardive dyskinesia (TD) is a syndrome of repetitive involuntary movements that occur after chronic antipsychotic treatment and may not resolve after antipsychotic discontinuation. Tardive dystonia refers to a similar phenomenon in which dystonia persists long after antipsychotic treatment has been stopped. Typically associated with high-dose FGA use, TD may also occur with SGA use [34, 35], though rates appear relatively low in a study of up to one year of exposure (0.3% annually for risperidone) [36]. Ethnicity may be a risk factor for TD in children, as a greater proportion of African-American children experienced symptoms than European-American children in one clinic sample [37]. However, prolonged exposure over time is the greatest risk factor for TD, which is of particular concern for children with severe mental illness who likely require antipsychotic treatment for many years. Long-term data on rates of SGA-related TD in children are greatly needed.

2.2 Study Scientific Rationale

In 2009, the BPCA Antipsychotic Safety Therapeutics Working Group Evaluation Summary ranked several topics as essential for further evaluation. The highest priority they identified was for the FDA to collate safety data from 6- and 12-month drug trials and to consider requests for long-term studies to examine specific endpoints related to endocrine and metabolic effects. Other top-ranking priorities included 1) “more comparison studies” of different antipsychotics focused on “endocrine/metabolic effects” in children of different ages, races, and genders; 2) “more information on long-term cumulative effects”; and 3) determining “cumulative use/risk over time” and “information about low-frequency adverse events (AEs) from long-term exposures.” There has been little progress in addressing these identified safety needs.

There have been several studies in children evaluating the relationship between atypical antipsychotics and weight gain AEs [14, 16, 17, 28, 39, 40]. However, these studies are limited to a relatively small number of participants (30-300) for relatively short periods of time (3-18 months). The studies that directly compare different antipsychotics to one another have very small samples of individuals on some agents, limiting their ability to detect differences in smaller groups. For instance, the largest of these studies [14] enrolled and collected post-baseline data in 135 patients taking risperidone but only 36–45 in the other antipsychotic groups and only 15 in the control group. Thus, the study’s power to detect within-group differences as

well as between-group differences varies based on the number of participants within each group. Further, there have been very few pediatric studies assessing other types of AEs typically seen with antipsychotic treatment, including hyperprolactinemia and neuromotor adverse effects. See Appendix 1 for a summary of relevant safety studies.

This study has been designed to begin to provide the long-term safety data for multi-year antipsychotic treatment of children, which the BPCA Working Group identified as critical. This study is a 36-month, multi-site, Phase 4, prospective, observational, safety study of children (3 - <18 years) treated with risperidone (n=350) or aripiprazole (n=350). Each participant, his/her guardian, and the participant's PPPMP and other medical providers will make any and all decisions related to antipsychotic medications and any other medications, and the participant's current mental state, developmental/psychiatric condition, and level of risk for potential harm to self or others independent of the study procedures and assessments. A PK sub-study will be conducted in 24 participants to provide needed information about the two medications' steady-state exposure in younger children and obese children.

This Phase 4, observational, longitudinal study will be conducted in accordance with Section 409I of the Public Health Service Act. Its ultimate goal is to provide long-term safety and PK data to the FDA for consideration of potential changes to the risperidone and aripiprazole labels. The information obtained in this study will likely allow amending the two labels to include information about the likelihoods of multi-year treatment with each agent, resulting in the following:

- Clinically significant weight change (significant modified BMI z-score change and switch to different BMI categories)
- Metabolic abnormalities associated with risk of diabetes and cardiovascular disease
- Hyperprolactinemia
- Development of neuromotor side effects

In addition, the sub-study will provide data to amend the labels to discuss changes in PK and dosing in children who are obese and in children 6 – <10 years old. Finally, this study will yield information about persistence of AEs on weight, insulin resistance, elevated Hgb A1c, and neuromotor effects after the medication is stopped. The trial will also provide information about potential differences in the incidence of AEs among children who have ≤90 days of exposure to any antipsychotic at the M0 visit (approximately 50% to 80% per treatment group) and children with longer exposures to antipsychotics. We anticipate that there will be more participants with >90 days of exposure among the 6 – <18-year-olds. The reverse may be true among the 3 – <6-year-olds.

Given the likelihood for increased population exposure to long-term multi-year therapy with risperidone and aripiprazole and the limited existing data about these drugs' long-term safety profiles, this proposed safety study of community-provided risperidone or aripiprazole fills an urgent public health need. Thus, this study addresses an essential knowledge gap by systematically assessing both the long-term risks and functional benefits of antipsychotic treatment initiated during childhood and adolescence.

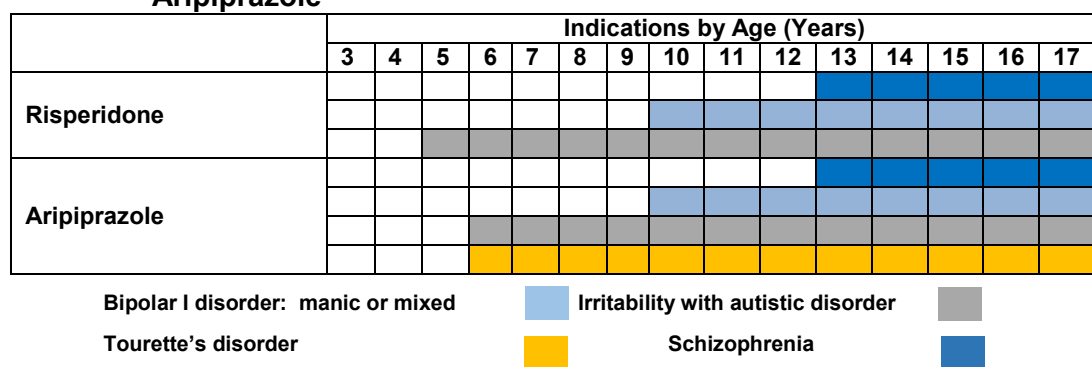
2.2.1 Rationale for Focus on Risperidone and Aripiprazole

Risperidone and aripiprazole are the two most commonly prescribed SGAs, and they account for more than two-thirds of the antipsychotic prescriptions in children [54-57]. Aripiprazole has the most pediatric indications, and risperidone has the second-most pediatric indications of the

antipsychotics. Label indications for both drugs include treatment of schizophrenia, acute manic or mixed episodes associated with bipolar I disorder, and irritability associated with autistic disorder (Figure 1) [38]. Aripiprazole also has a label indication for Tourette's disorder in children. Neither drug has specific indications for maintenance treatment or information about long-term safety. Importantly, off-label use of SGA's in the pediatric population is especially common, with the majority of prescriptions for children with diagnoses of attention deficit hyperactivity disorder [56, 57].

This study utilizes a multidrug protocol (risperidone and aripiprazole) rather than focusing on a single antipsychotic for two reasons. First, a multidrug protocol is highly efficient because the assessments used to evaluate safety are similar across the therapeutic class. Second, the acute side effect profiles of risperidone and aripiprazole differ significantly, with risperidone appearing to have greater metabolic and pseudo-parkinsonian risks and aripiprazole having greater risk for akathisia.

Figure 1: FDA-Approved Pediatric Age Ranges and Indications for Risperidone and Aripiprazole



2.2.2 Rationale for an Observational, Non-randomized Study

This prospective observational design allows us to longitudinally follow a large group of children who are initially treated with risperidone and aripiprazole without risk of censoring children who switch or discontinue antipsychotic treatment, which is a major limitation of current data from acute randomized clinical trials. Further, because clinicians can add other SGAs after the study begins without disqualifying participants from the study, investigators may be able to provide safety information about additional medications within the SGA class.

2.2.3 Rationale for Pharmacokinetic Sub-study

Although PK data for risperidone and aripiprazole are well-described for the labeled indications for normal-weight children ages 10 – <18 years, PK data are lacking in important subpopulations of children: 1) young children 6 – <10 years, and 2) obese children and adolescents (6 – <18 years). PK data are vitally important in determining dose and preventing sub-therapeutic or toxic exposures. PK studies will assess both the parent compounds and their active metabolites. With considerable use of risperidone and aripiprazole in younger children, there is an urgent need to determine the PK parameters in this population. Equally important are the complete lack of PK data in obese children. As noted above, one of the most important side effects of SGAs is pathologic weight gain. Because elevated total body fat and lean body mass in obese children can alter PK and pharmacodynamics (PD) when compared with non-obese

children, childhood obesity may have important implications for drug dosing [41, 42]. It is likely that as weight changes over the course of therapy, antipsychotic dosing will need to be adjusted. PK studies in obese children are needed to determine the extent of dose adjustment.

2.2.4 Rationale for Including Participants Receiving Maintenance Treatment and with Disorders Closely Related to Those with FDA Indications

The studies done to support labeling indications for risperidone and aripiprazole in the pediatric population were all acute treatment studies ranging from 3 weeks (bipolar affective disorder, manic or mixed) to 10 weeks (schizophrenia). For each drug, for one or more indications, the exact ages studied differed. None of the drugs were studied for maintenance treatment in the pediatric population. However, since safety has been established down to age five years for risperidone and down to age six years for aripiprazole, there is sufficient evidence to include children below the labeled age range. Similarly, since both drugs are labeled for maintenance treatment in adults, it is appropriate to include children receiving maintenance rather than acute treatment. Finally, given the need for rigorously defined populations in clinical licensing trials and the use of medications in closely related disorders i.e., schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder; bipolar I disorder mixed or manic vs bipolar spectrum disorders, including disruptive mood dysregulation disorder (DMDD) Tourette's disorder vs Tourette's syndrome or motor tic or vocal tic disorder; irritability associated with autistic disorder vs irritability in autism spectrum disorder, the inclusion criteria include children with the full spectrum of disorders listed above.

3 OBJECTIVES

3.1 Primary Objectives

The primary objective is to evaluate the long-term pathologic weight changes associated with multi-year risperidone or aripiprazole therapy in 3 – <18-year-old children, who have varying durations of prior antipsychotic drug exposure at the M0 visit. This is critical because children appear to have greater vulnerability to antipsychotic-associated weight gain than adults, and childhood obesity has significant effects on morbidity and mortality. The primary analysis will focus on children 6 – <18 years at the M0 visit.

3.2 Secondary Objectives

- Evaluate the overall long-term safety of risperidone and aripiprazole therapy in 3 – <18-year-old children by assessing long-term changes in safety outcomes of special interest: 1) metabolic measures associated with risk of diabetes and cardiovascular disease; 2) serum prolactin; 3) neuromotor effects; 4) rates of adverse effects of mild (grade 1) and related to risperidone or aripiprazole and all AEs of moderate (grade 2) or greater; and 5) suicidality.
- Evaluate the potential long-term benefits of risperidone and aripiprazole by assessing age-normed adaptive functioning, child and caregiver quality of life, and changes in the intensity and frequency of pre-existing behavioral problems.
- Estimate PK parameters of risperidone and aripiprazole and their active metabolites in normal-weight children 6 – <10 years and obese children 6 – <18 years.

3.3 Exploratory Objective

- Determine whether there is any indication of clinical features of individual children such as age, gender, pubertal status, or baseline weight that might be used to personalize AE risk assessments.
- Determine whether there are any features of medication exposure, including drug, concomitant medications, or dose, that might be used to personalize risk assessments.
- Obtain whole blood samples for future genetic analyses that may be used to determine whether there are any genetic factors that might be used to personalize risk assessments.

3.4 Study Outcome Measures

3.4.1 Primary Outcome Measure

Pathologic weight change as reflected by longitudinal assessment of modified BMI z-score from the start of study M0.

3.4.2 Secondary Outcome Measures

1. Secondary measures of weight change:
 - a. Change in BMI category
 - b. Modified BMI z-score increase of ≥ 1.0 unit from M0

-
2. Safety outcomes of special interest:
 - a. Metabolic measures associated with risk of diabetes and cardiovascular disease (e.g., fasting glucose and lipid panel; fasting insulin; hs-CRP; Hgb A1c)
 - b. Hyperprolactinemia - assessed by monitoring serum prolactin levels
 - c. Neuromotor effects - assessed by physical exam and abnormal movement scale ratings (AIMS, SAS, BARS)
 3. AEs - elicited AEs, including AEs of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater, and clinically significant changes in suicidality
 4. Benefits - relationship of risperidone or aripiprazole therapy to adaptive functioning and quality of life as assessed by Vineland standard scores, PedsQL (23 item), Delighted-Terrible Faces Scale (DTFS), CSQ, and changes in the intensity or frequency of pre-existing behavioral problems
 5. PK - CL/F, Vss/F, AUCss, Cmax, Tmax, and $T_{1/2}$ at steady state

4 STUDY DESIGN

This study is designed to evaluate long-term weight changes associated with multi-year risperidone and aripiprazole therapy in children. This study will also provide insights into the overall long-term safety and the effects of both drugs on psychiatric and behavioral symptoms. It will further evaluate long-term development, functioning, and quality of life in children treated with these antipsychotics. Lastly, the sub-study will estimate PK parameters in subsets of young and obese children.

4.1 Study Design

This is a prospective, multi-site, Phase 4, observational study designed to systematically collect robust, longitudinal, post-marketing safety data about multi-year pediatric treatment with risperidone or aripiprazole. Screening may occur for < 37 days prior to enrollment; study assessments will occur every three months for a total of 36 months with in-person, clinic-based assessments at months 0, 6, 12, 18, 24, 30, and 36 alternating with remote interim assessments occurring at months 3, 9, 15, 21, 27, and 33. The remote interim assessments may be collected using ePRO via an electronic device or paper (mailed to site) or phone call with site staff. The study will enroll 350 children treated with risperidone mono-antipsychotic therapy at the time of the M0 visit and 350 children treated with aripiprazole mono-antipsychotic therapy at the time of the M0 visit. Approximately 30 of the participants in each group will be 3 - <6 years old at the M0 assessment, and the remaining 320 will be 6 – <18 years old.

The SMCs will not prescribe nor provide treatment for participants. Each participant's PPPMP will use his/her own best clinical judgment to prescribe the participant's medications over the course of the study. It is anticipated that some participants will remain on the same medication throughout the study, while some will change antipsychotic treatments and/or discontinue antipsychotic treatment at different points in the trial.

4.2 Study Duration

Each participant enrolled in the study will participate for up to 38 months. Enrollment is expected to be completed within 18 months.

5 STUDY POPULATION

5.1 Selection of the Study Population

Eligible participants ages 3 – <18 years will be enrolled in the risperidone and aripiprazole groups. The primary analyses of the study, which are intended to be submitted to the FDA to inform pediatric labeling of risperidone and aripiprazole, will be conducted only in subjects ages 6 – <18 years at the M0 visit (n=320 within each group). A smaller number (n=~30 in each group) of children 3 – <6 years are included because both medications are widely used off label in very young children with autism spectrum disorders and attention deficit hyperactivity disorder [1].

The participants within each treatment group will be distributed across the age range to permit analyses of age effects, with:

- n=~30 being 3 – <6 years
- ≥35% (n≥123) being 6 – <12 years
- ≥35% (n≥123) being 12 – <18 years

To increase feasibility, there are no defined proportions of the study population that are required to be normal weight, overweight, or obese upon entry into the study. However, the distribution of participants within these weight categories will be monitored over time.

Approximately 50% to 80% of the entire risperidone group, and approximately 50% to 80% of the entire aripiprazole group will be required to have ≤90 days exposure to any antipsychotic at the time of the M0 visit to ensure that it is possible to distinguish between type and magnitude of adverse health risks associated with initial risperidone and aripiprazole treatment, vs longer-term risperidone and aripiprazole treatment. This will provide between 175-280 participants per treatment group with minimal prior antipsychotic exposure. We expect more participants <6 years old to be “antipsychotic-naïve” than participants ≥6 years. Siblings will be allowed to participate.

5.2 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Guardian is has provided informed consent
2. Participant has provided assent if developmentally appropriate and as required by the IRB
3. 3 – <18 years of age inclusive at time of the M0 visit
4. Participant, when developmentally appropriate, and guardian are:
 - a. Able to understand and describe key aspects of study procedures and expect to be able to comply with them for the 36-month study period
 - b. Willing to authorize exchange of information between the SS and the participant's PPPMP and/or other significant medical provider
 - c. Affirm participant's use at screening visit of either risperidone or aripiprazole as prescribed by participant's PPPMP

5. Based on their age at the time of M0 visit, participant is receiving aripiprazole or risperidone at the dose and for the diagnoses as listed below:

- a. Participants ages 3 – < 6 years can have any diagnosis and any dose
- b. Participants ages ≥ 6 – 17 years (see table below)

Drug	
Aripiprazole*	Risperidone*
Dose	
2 – 30 mg/day	0.25 – 6 mg/day
Indication <u>Labeled indications (underlined)</u> and <i>Closely Related Disorders (italicized)</i>	
<u>Irritability associated with autistic disorder</u> <i>Irritability in autism spectrum disorder</i>	<u>Irritability associated with autistic disorder</u> <i>Irritability in autism spectrum disorder</i>
<u>Treatment of Tourette's disorder</u> <i>Tourette's disorder, persistent (chronic) motor or vocal tic disorder</i>	N/A
<u>Bipolar mania/acute treatment of manic and mixed episodes associated with Bipolar I disorder</u> <i>Bipolar spectrum disorders including disruptive mood dysregulation disorder</i>	<u>Bipolar Mania</u> <i>Bipolar spectrum disorders including disruptive mood dysregulation disorder</i>
<u>Schizophrenia</u> <i>Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder</i>	<u>Schizophrenia</u> <i>Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder</i>
<u>*MYCITE® (aripiprazole) and all forms of injectables are not permitted in this study</u>	

6. Guardian anticipates risperidone or aripiprazole treatment will continue for ≥6 months

Exclusion Criteria

1. History of prior or current diagnosis of an eating disorder or meets diagnostic criteria for an eating disorder as described in the DSM-5 and determined by psychiatric exam
2. Pre-existing or suspected major medical, metabolic, or genetic condition that is expected to be associated with weight, cardiovascular, neuromotor, or endocrine problems
3. Known or self-reported pregnancy
4. Taking antipsychotic medication other than either risperidone or aripiprazole at the time of the M0 visit
5. Contraindications to participation in the study in the opinion of the SMC or the potential participant's PPPMP
6. Unwilling or unable to provide back-up family contact information

5.3 Treatment Assignment Procedures

Participants will not be assigned to risperidone or aripiprazole as part of this protocol.

Instead, each participant, his/her guardian, and the participant's PPPMP and other medical providers will make any and all decisions related to antipsychotic medications and any other medications. The participant's PPPMP will also assess their current mental state, developmental/psychiatric condition, and level of risk for potential harm to self or others and use his/her own medical judgment to prescribe ongoing treatment independent of the study procedures and assessments. Injections and/or MyCite (aripiprazole) are not allowed due to the fact that neither are indicated in pediatric populations.

5.3.1 Replacement Participants

Participants 3 – <6 years who do not have an in-person follow-up visit at either M6 or M12 will be replaced, provided there is sufficient time remaining to obtain M12 assessments for the replacement participants. No other participants will be replaced.

5.3.2 Reasons for Withdrawal

A participant or his/her guardian may choose to discontinue participation in this study at any time. The participant's guardian is not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the SMC on the completion/withdrawal section of the paper and/or electronic case report form (eCRF).

Participants and guardians who withdraw will be informed that if they would like to resume participation in the study, at any point during the original period of time that they would have had study assessments, they should contact the SS and may be re-consented. Participants who withdraw but later re-consent will continue their participation beginning with the next scheduled assessment on their original timeline.

An SMC may, at his/her discretion, discontinue the participant's participation in this study at any time. Participants may be discontinued from the study for any of the following reasons:

- Requested by the NICHD, FDA, PTN, or the data monitoring committee (DMC)
- SMC feels that it is not in the best interest of the participant to remain in the study

Discontinuation of risperidone or aripiprazole treatments will not result in early termination from the study.

5.3.3 Handling of Withdrawals

All reasonable and non-coercive efforts will be made to complete an end-of-study evaluation (this includes the assessments ordinarily done at M36) prior to withdrawal. In addition, the study team will make all reasonable and non-coercive efforts to encourage participants who have withdrawn from the study prematurely to allow SS to obtain their height and weight and medication history and any other information from their PPPMP and/or other medical provider at the approximate time of the M36 visit.

5.3.4 Termination of Study

This study may be terminated at any time by the NICHD, Investigational New Drug Application (IND) sponsor, or DMC if the investigator does not adhere to the protocol, or if, in the NICHD's judgment, there are no further benefits to be achieved from the study.

6 STUDY PROCEDURES

6.1 Summary of Procedures

Table 1. Procedures organized by type of visit.

Screen Visit (In Clinic)	M0 (In Clinic)
Informed consent/assent (written) - G, P	Informed consent/assent* - G, P
Contact form - G	Contact form* - G
Back-up family contact information - G	Back-up family contact information* - G
Consent to exchange info w/ PPPMP and/or other significant medical provider - G	Height, weight, sitting BP, pulse - SS
Demographics - G	Medical & behavioral follow-up checklist* - G, P (if able), SMC review
Medical & behavior history checklist - G, P (if able), SMC review	Participant-reported changes in medications* - G
Participant-reported current medications - G	Medication log (if changes) - SMC
Medication log - SMC	Past medical history form* - SMC
Prior psychiatric medications - G, SMC review	BSAS* - SMC
Past medical history form - SMC	Physical exam (acanthosis nigricans & [for females] hirsutism) - SMC
Behavioral Symptom Assessment Scale (BSAS) - SMC	PedsQL - G, P (if able)
Physical exam (acanthosis nigricans & [for females] hirsutism) - SMC	Confirm inclusion/exclusion criteria - SMC
Inclusion/exclusion criteria - SMC	Suicidality assessment & acute safety evaluation* - SMC
Suicidality assessment & acute safety evaluation* - SMC	Tanner stage form - G or P, SMC review
ePRO training - G, P, SS review	BARS - SMC
Obtain P medical records from PPPMP and/or other significant medical provider - SS	SAS (parkinsonian) - SMC
	AIMS (TD scale) - SMC
	Vineland Adaptive Behavior Scales 3 - G
	CSQ - G
	School and employment questions - G

Screen Visit (In Clinic)	M0 (In Clinic)
	DTFS - P, SS assist
	Clinical laboratory test - SS
	AE form - SMC
	Notify G about lab results (if requested by G, P) - SS
	Notify PPPMP about labs, clinically significant changes in AEs or behavioral problems, key safety questions - SS

*Not done if combined with the screening visit

Remote interim visits M3, 9, 15, 21, 27, 33 (+/- 4 weeks)	Clinic visits M6, 12, 18, 24, 30, 36 (+/- 4 weeks)
Update contact/back-up family, as needed - G	Update contact/back-up family, as needed - G
Medical & behavioral follow-up checklist - G, P (if able)	Medical & behavioral follow-up checklist - G, P (if able), SMC review
Participant-reported changes in medications - G	Participant-reported changes in medications - G
Medication log (if changes) - SMC	Medication log - SMC
PedsQL - G	PedsQL - G, P (if able), SMC review
Notify SS of certain positive questions - ePRO	Height, weight, sitting BP, pulse - SS
Notify PPPMP of key safety questions - SS	BSAS - SMC
	BARS - SMC
	SAS (parkinsonian) - SMC
	AIMS (TD scale) - SMC
	Tanner stage form - G or P, SMC review
	Vineland Adaptive Behavior Scales 3** - G
	School and employment questions - G, SMC review
	CSQ - G
	DTFS - P, SS assist

	Labs - SS
	Physical exam (acanthosis nigricans & [for females] hirsutism) - SMC
	AE form - SMC
	Suicidality assessment & acute safety evaluation - SMC
	Notify PPPMP about labs, clinically significant changes in AEs or behavioral problems, key safety questions - SS
	Notify G about lab results - SS
	Optional, 1 sample collection for future unspecified genetic analyses - SS
	For PK centers, total of 24 participants will have steady-state PK sampling & CYP2D6 genotyping - SS

Key:

G = guardian

P = participant

SMC = study medical clinician

SS = study staff

ePRO = electronic patient-reported outcomes

******Only performed at the yearly visits (M0, 12, 24, and 36)

6.2 Screening Visit

The screening and M0 visits may be combined and done at the same time; however, for convenience, the screening and M0 visits may also be conducted as separate visits.

After consent/assent have been obtained, the key procedures and assessments needed to confirm participant eligibility will be obtained. Specifically, the following procedures, assessments, and questionnaires will be completed and recorded. The visit is anticipated to last approximately two-and-a-half hours.

For some data, the study will use ePRO, a web-based platform for collecting data. The ePRO system can be used with an electronic device (computer, tablet, phone). Paper completion, as well as telephone communication with site staff, is an option as well. The guardian will choose which format he/she wishes to use. A detailed description of the ePRO system and the forms it will utilize is in the MOP.

Guardian (G):

- Informed consent - discussion/process with SS
- Contact form, including back-up information for close friends or relatives likely to be able to provide contact information for participant's guardian in case of a move, etc.
- Medical and behavioral history checklist - prior to meeting with SMC
- ePRO training
- Demographics form
- Participant's current and past medications

- Consent to exchange information with participant's PPPMP and any other key medical providers

Participant (P) (if developmentally able):

- Informed assent - discussion/process occurs at same time as guardian informed consent process
- Medical and behavioral history checklist - preferable for participant to complete separate form without assistance from guardian; however, a single form completed together is acceptable if participant prefers
- ePRO training

Study Staff (SS):

- Contact participant's PPPMP and other necessary providers to obtain weight, height, and medical history over past three months (or longer, if available) after obtaining release form

Study Medical Clinician (SMC):

- The following are reviewed via verbal discussion with guardian prior to completing medical or physical exams:
 - Medical and behavioral history checklist
 - Medication log form (see MOP), including section for prior psychiatric medications with approximate doses and dates of use, concomitant medications, and changes over past three months, including alternative and nutritional supplements
- Physical exam, noting whether acanthosis nigricans and hirsutism (for females) is present
- BSAS
- Suicidality assessment and evaluate any acute safety concerns, referring as needed
- Complete inclusion and exclusion criteria form and confirm eligibility
- Past medical history form

6.3 Month 0 (M0)

The M0 visit will most often occur immediately after inclusion and exclusion criteria have been confirmed. However, it must occur <37 days after the screening visit. The following evaluations will be performed and recorded. If the screening and M0 visits occur on the same day, the procedures listed for both visits will only occur once and do not need to be duplicated. The data collected will be used for both the screening and M0 visits. Re-consent/assent of the participant or guardian may occur as needed, following site-specific policies and procedures. This visit is expected to last approximately two hours.

Guardian (G):

- Update information on contact form and back-up contact form, if any changes
- Tanner stage form, if able and form is unable to be completed by participant - prior to meeting with SMC
- Changes in medication
- The following questionnaires are completed electronically or via hard copy. Additionally, most can be completed either at the visit or during the 14-day period following the visit, unless otherwise specified below:
 - Medical & behavioral follow-up checklist - prior to meeting with SMC

- PedsQL
- Vineland Adaptive Behavior Scales 3
- School and employment questions
- CSQ

Participant (P) (if developmentally able):

- The following questionnaires are completed electronically or via hard copy. Additionally, most can be completed either at the visit or during the 14-day period following the visit, unless otherwise specified below:
 - Medical & behavioral follow-up checklist - prior to meeting with SMC
 - PedsQL
 - DTFS
- Tanner stage form - prior to meeting with SMC

Study Staff (SS):

- Vital signs (standing height, weight, sitting BP, and pulse)
- Clinical laboratory evaluations: participant may fast, with the exception of water, for at least six hours prior to blood collection (see section 6.11 and MOP)
- Administer DTFS to participant (see MOP)
- After visit, contact participant's PPPMP if there are concerns about AEs or reports of significant clinical worsening since participant's last contact with PPPMP
- Provide PPPMP with a copy of all lab results (regardless of clinical significance)
- May provide a copy of lab results directly to guardian at guardian's request

Study Medical Clinician (SMC):

- Review/complete, via verbal discussion with the guardian, the following:
 - Medical and behavioral follow-up checklist (guardian- and participant-completed forms)
 - Tanner stage form
- Medication log form (see MOP), including section for prior psychiatric medications with approximate doses and dates of use, concomitant medications, and changes over past 3 months, including alternative medications and nutritional supplements
- Update past medical history form as needed
- BSAS
- Suicidality assessment and evaluation of acute safety concerns, with referral as needed
- Confirm inclusion and exclusion criteria
- Brief physical exam form, noting whether acanthosis nigricans or hirsutism (for females) is present
- BARS
- SAS (parkinsonian)
- AIMS (TD scale)
- AE form

6.4 Remote Interim Assessments

In order to assess changes between in-person visits, assessments will be completed remotely at the three-month time point between in-person visits. The interim visits will occur at months 3, 9, 15, 21, 27, and 33 with a visit window of ± 4 weeks. The assessments will take about one

hour. The guardian and/or participant can complete the assessments electronically with ePRO or on paper.

Guardian (G):

- Update information on contact form and back-up contact form, if any changes
- Medical & behavioral follow-up checklist
- Changes in medication
- PedsQL

Participant (P) (if developmentally able):

- PedsQL
- Medical & behavioral follow-up checklist

ePRO system:

- Reminds guardian to contact participant's PPPMP to report any new or significantly increasing concerns about child's physical or emotional health and to contact the PPPMP or go to the nearest emergency department if concerned about child's safety.
- Notify SS if participant endorses one of the key safety questions (see MOP for complete list)
- Notify SS if participant has stopped prior antipsychotic and/or has begun treatment with a different antipsychotic

Study Staff (SS):

- Notify PPPMP if key safety questions have been endorsed
- Contact guardian if participant's prior antipsychotic medication has been stopped or changed, an additional antipsychotic has been added, or potential SAE has been reported to the site
 - Contact guardian and arrange in-person visit as soon as possible (as applicable)
 - OR
 - Obtains any available additional information about weight, clinical laboratory evaluations, and clinical status (from other medical providers)
 - Updates medication log - SMC

6.5 Clinic Follow-up Visits

These visits will occur at months 6, 12, 18, 24, 30, and 36 with a +/- 4-week window. These procedures may also occur as a part of an unscheduled visit related to antipsychotic changes or SAEs. The following assessments will be performed and recorded. Re-consent/assent may occur as needed and following site-specific policies and procedures. Yearly visits (M12, M24, and M36) are expected to last approximately three hours each. Mid-year visits (M6, M18, and M30) are expected to last approximately two-and-a-half hours.

Guardian (G):

- The following are completed within two days prior to meeting with the SMC:
 - Update information on contact form and back-up contact form, if any changes
 - Medical & behavioral follow-up checklist
 - Tanner stage form, if able and form is unable to be completed by participant
 - Changes in medication
 - PedsQL, if possible
 - School and employment questions

- The following questionnaires are completed electronically or via hard copy. Additionally, they can be completed either at the visit or during the 14-day period following the visit:
 - Vineland Adaptive Behavior Scales 3 (only at M12, M24, and M36)
 - CSQ

Participant (P) (if developmentally able):

- Completes the following within two days prior to meeting with the SMC:
 - Medical & behavioral follow-up checklist, complete separate form from guardian unless participant prefers to do it together
 - PedsQL
 - Tanner scale form
- Completes the DTFS in clinic with assistance from SS as needed

Study Staff (SS):

- Vital signs (standing height, weight, sitting BP, and pulse)
- Collect clinical lab and results for evaluation (see section 6.11 and MOP)
- Administer DTFS to the child, assessing ability to understand faces (see MOP)
- After visit, contact participant's PPPMP if concerned about AEs or reports of significant clinical worsening since participant's last contact with PPPMP
- Provide PPPMP with copy of all lab results (regardless of clinical significance)
- May provide a copy of lab results directly to guardian at guardian's request
- Determine whether participant is willing to complete optional blood sampling for future unspecified genetic analyses during the visit, provided they have not yet completed the sampling but have given consent to collect it (see section 6.5.1)
- Determine whether participant is eligible for sub-study of PK sampling and willing to complete optional PK sampling, provided they have not yet completed the sampling but have given consent for it and have not yet taken risperidone or aripiprazole for the day (see section 6.5.2)

Study Medical Clinician (SMC):

- Review/complete, via verbal discussion with the guardian, the following:
 - Medical & behavioral follow-up checklist
 - Tanner stage form
 - Participant report of current medications and interval changes (completes medication log)
 - PedsQL for guardian and participant, if able to be completed prior to meeting with the SMC
 - School and employment questions, if able to be completed prior to meeting with the SMC
- BSAS
- Suicidality assessment and evaluation of acute safety concerns with referral, if needed
- Brief physical exam form, noting whether acanthosis nigricans or hirsutism (for females) is present
- BARS
- SAS (parkinsonian)
- AIMS (TD scale)
- Elicite AE assessment, any events of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater and record on AE form.

6.5.1 Optional Blood Sampling for Future Unspecified Genetic Analyses

If the guardian consents for the participant to participate in the optional, one-time collection of a whole blood sample for future unspecified genetic analyses, SS will complete the following:

Study Staff (SS):

- Verify consent/assent for future unspecified genetic analyses sample collection
- Collect whole blood sample (see MOP)

6.5.2 At Selected Centers: Optional Pharmacokinetic Sampling Sub-study

If the guardian consents for the participant to participate in the steady-state PK sampling and he/she meets the criteria for inclusion in the PK study, the following procedures will be performed during an in-person visit(s), which may be scheduled for a separate day from the other assessments. All possible efforts will be made to combine PK sampling with sample collection for future unspecified genetic analyses and/ or clinical assessment labs.

Study Staff (SS):

- Verify consent/assent for the optional PK study
- Verify participant has:
 - Taken the last five days of risperidone or aripiprazole as prescribed
 - Not taken the dose prior to the visit
 - Brought the dose that is due to be taken with him/her to the visit
- Confirm time of last meal
- Collect pre-dose PK sample
- Instruct participant to take scheduled dose of risperidone or aripiprazole
- Collect steady-state PK samples at four remaining scheduled time points relative to in-visit dosing of risperidone or aripiprazole (see MOP)
- Collect whole blood samples for *CYP2D6* genotype at time of PK sampling
- Collect all medications, including dosing and times for five days prior to PK sampling (record on the PK medication log)
- Record times of all PK blood sampling and ingestion of risperidone or aripiprazole dose

For participants in the PK sub-study ≥ 6 years of age at the time of PK sub-study collection, risperidone and/or aripiprazole is to be prescribed for acute or maintenance treatment of a disorder within the an FDA-labeled pediatric dose range indication and dose for the participant's age.

6.6 Month 36 Final Study Visit (+/- 4 Weeks or Early Study Withdrawal)

The assessments completed during the M36 or early study withdrawal visits are exactly the same as at other in-person follow-up visits (see section 6.5). However, at the final visit, every attempt should be made to have the participant and guardian complete all rating scales prior to or during the visit itself.

If a guardian or participant contacts SS between visits with thoughts about withdrawing from the study, all reasonable and non-coercive efforts should be made to encourage him/her to remain in the study. If a guardian/participant continues to feel that it is most appropriate to withdraw, SS

should request that they attend an early withdrawal visit and remind him/her that the medical release form will be used to contact the participant's PPPMP or other significant medical provider to obtain the participant's height, weight, and medication history at the approximate time of the M36 visit.

6.7 Unscheduled Assessments Related to Antipsychotic Change

If utilized, the ePRO system will notify the SS if the participant/guardian has reported stopping and/or changing antipsychotic medications. In addition, participants and their guardians will be strongly encouraged to contact the study team as soon as possible if they are planning to discontinue or have discontinued the risperidone or aripiprazole treatment taken at the time of the M0 visit or have started or stopped a subsequent antipsychotic or weight-related medication.

When the site becomes aware that a participant has stopped, added, or switched antipsychotics, the participant will be asked to participate in an in-person visit as soon as possible. At an unscheduled, in-person visit triggered by discontinuation, addition of a second antipsychotic, or switching of antipsychotics, all procedures during a regular in-person visit (see section 6.5) should be conducted, if possible. However, the order of priority for assessments is weight, height, BP, pulse, clinical laboratory evaluations, medication log, AE form, suicidality form, BSAS, and quality-of-life forms.

If the participant will not attend an unscheduled in-person visit, his/her guardian will be asked to complete the current medications and interim changes form and medical and behavioral follow-up checklist as soon as possible. Study staff will contact other medical providers to obtain any available additional information about weight, clinical laboratory evaluations, and clinical status.

If the guardian/participant who attends an unscheduled in-person visit expresses concern about completing their next on-site visit, they may replace it with a web-based visit and resume the standard visit schedule after that one-time change (i.e., their next visit would be a web-based visit).

6.8 Unscheduled Assessments Related to Serious Adverse Event or Pregnancy

At an unscheduled, in-person visit triggered by an SAE or pregnancy, all procedures during a regular in-person visit (see section 6.5) should be conducted, if possible. However, the order of priority for assessments is weight, height, BP, pulse, clinical laboratory evaluations, medication log, AE form, suicidality form, BSAS, and quality-of-life forms.

6.9 Missed Assessments

If a participant and/or his/her guardian are unable or unwilling to complete a scheduled assessment within the visit window, or indicate that the frequency of assessments is too demanding for them at the current time, all reasonable and non-coercive efforts should be made to encourage them to remain in contact with the study team. The participant/guardian should be encouraged to complete as many assessments and/or as many procedures related to a scheduled assessment as possible. Priority should be placed on completing the M36 assessment and notifying the study team when antipsychotic medications are stopped or changed so that they can obtain participant weight and the reason for the antipsychotic change.

Strategies to maintain engagement with participants, particularly those who have missed scheduled assessments, are described in the MOP.

Missed study visits, assessments, or procedures within an assessment will be documented on the eCRF but will not be considered protocol deviations.

6.10 Assessments and Procedures

6.10.1 Diagnostic (to be completed by guardian / participant / study medical clinician)

The SMC will record the PPPMP assigned diagnosis for which the participant was prescribed risperidone or aripiprazole.

Medical and behavioral history checklist: This guardian/participant-completed questionnaire was designed to gather information about a large range of medical and behavioral problems at any point during the participant's life as well as during the two-month period preceding the assessment. The participant is also asked to complete his/her own version of the checklist if cognitively able. It is generally based on the areas of inquiry in the Safety Monitoring Uniform Reporting Form (SMURF) [59] and is designed to facilitate the study clinician's completion of the past medical history form and initial BSAS ratings [Sikich, personal communication].

Medical History form: Before the SMC completes this form, he/she must review the guardian-completed medical and behavioral history checklist, past and current medication forms, interview the guardian and participant, and examine the participant.

6.10.2 Medication Related (to be completed by guardian and/or study medical clinician)

Prior psychiatric medications: The SMC will query the participant's guardian (or participant) asking him/her to list prior medications. This information will be recorded with approximate start and stop dates in the medication log by the SMC.

Current medications and interval medication changes form: At the screening visit, the guardian will be asked to provide information about all medications, including alternative medications and nutritional supplements taken for more than 14 consecutive days during the prior three months. Prior to each subsequent in-person assessment, the participant's guardian will be asked to complete a form with current medications, the doses of antipsychotic medications, and any changes in medication since the last contact.

This form will also be completed by the guardian during the interim web-, phone-, or mail-based assessments.

Medication log: The SMC will record **all** antipsychotic medications with start and stop dates in the medication log, if known. In addition, at the screening visit, the SMC will record concomitant medications, including alternative medications and nutritional supplements taken for more than 14 consecutive days during the three months prior to the screening visit. Subsequently, the SMC will record medications taken for 14 consecutive days, during intervals between study visits, in the medication log. Doses of antipsychotics taken during the trial will be recorded

every six months. If the antipsychotic is discontinued, switched, or if another antipsychotic is added, this information will be recorded in the medication log as soon as possible. Recording the doses of other medications is not required. The approximate dates of starting and stopping medications will be recorded.

6.10.3 Adverse Health Risk or Adverse Event Related to: (to be completed by guardian / participant / study medical clinician)

Weight, height, and vital signs log: This will be maintained for each participant at the site by SS. The information in this log will be reported on the appropriate visit data collection forms (DCF's). This log is used to facilitate rapid, real-time recognition of erroneous measurements (so they can be redone) or significant changes from prior assessments (so they can be assessed by the SMC).

Vital signs (pulse and BP) will be measured a minimum of 3–5 minutes prior to phlebotomy using appropriately sized BP cuffs while the participant is sitting, and results will be added to the log.

Orthostatic vital signs will be obtained only if the participant or guardian reveals concerns about dizziness, tachycardia, or fainting during the AE elicitation or if the SMC feels it is medically indicated. An increase in pulse of >30 beats per minute or a decrease in systolic BP of >20 mmHG or in diastolic BP of ≥ 10 mmHG will be considered consistent with orthostatic hypotension and considered an AE, if not part of medical history.

Assessment of BMI: At each in-person visit, the participant will be weighed and his/her height will be measured three times using a calibrated stadiometer.

Laboratory assessments: Please see section 6.11 for details of sample collection. Alert values and values requiring assessment for clinical significance will be defined based using PTN guidelines .

Neuromotor assessments: Three validated, medical, clinician-rated assessments with defined examination procedures will be used in this study and performed by the SMC as listed below.

- **Abnormal Involuntary Movement Scale (AIMS):** The AIMS is composed of 12 items and used to assess TD. Items related to severity of orofacial, extremity, and trunk movements; global judgment about incapacitation; and patient awareness are rated using a 5-point scale (categorical). Overall AIMS scores range from 0–42. Treatment-emergent dyskinesia is often defined as, a score of 3 or more on any of the first seven AIMS items, or a score of 2 or more on any two of the first seven AIMS items. A score of 2 and above (categorical) in the global judgment item (severity of abnormal movement) can indicate a treatment-emergent dyskinesia. In this study, the last approach for identifying treatment-emergent dyskinesia will be utilized.
- **Simpson-Angus Extrapyramidal Rating Scale (SAS):** The SAS is composed of 10 items and used to assess pseudoparkinsonism. SAS scores can range from 0–40, and each item is assessed on a 5-point scale. Signs that are assessed include gait, arm-dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head

dropping, glabella tap, tremor, and salivation. Treatment-emergent parkinsonism can be defined as an SAS score of >3 at any time following a score of ≤ 3 . The scores can also be further categorized into severity groups: total scores from 3-6 (minimum), 7-10 (moderate), and >10 (severe) [43].

- **Barnes Akathisia Rating Scale (BARS):** The BARS scale includes an objective rating of akathisia, a subjective rating of awareness of restlessness and distress, and a global clinical assessment of akathisia. The measure of global clinical assessment (summary score) can be utilized to assess treatment-emergent akathisia. This categorical summary item ranges from 0 (absent) to 5 (severe akathisia). A category 3 (moderate akathisia) or above is generally considered treatment-emergent akathisia [44].

Hypertension assessment: Sitting BP will be obtained at each visit using appropriately sized BP cuffs. Hypertension will be defined using the National Heart, Lung, and Blood Institute (NHLBI) normative data.

Brief physical examination: The examination should include listening to heart and lungs and examining the face, neck, back, extremities, and abdomen for acanthosis nigricans, hirsutism, and signs of self-injury.

Suicidality assessment: The clinician will make a clinical judgment as to whether the participant understands the concepts of death and suicide. If the participant is determined to be able to understand these concepts, both the participant and guardian will be queried at each visit, including screening, regarding the incidence of thoughts or statements or attempts by the participant to hurt or kill him/herself prior to the screening visit or in the interim between the last and current in-person assessments. All suicidal attempts will be reported on the suicidality assessment form.

Any acute concerns related to safety of the participant, including concerns about suicide, identified during in-person assessments will be evaluated by the SMC according to local standard of care and each site's standard procedures. The SMC will determine whether the participant is safe to leave the site or requires ongoing emergency care. In the latter case, the SMC will ensure that the participant receives the needed emergency care. Suicidal events requiring overnight hospitalization will be reported on an AE form as an SAE. Additional information will be provided as updates to the SAE when obtained.

AE Assessment: At clinic follow-up visits, the SMC will review the participant/guardian-completed **medical and behavioral follow-up checklist(s)**, observe the participant, and systematically query the participant (if able to understand questions) and guardian regarding pregnancy (for girls who have experienced menarche), hospitalizations, new medical or behavioral problems, and changes in pre-existing medical or behavioral problems since the prior visit. The clinician will then determine the intensity/grade of any untoward medical occurrences and, to the extent possible, the relationship between the untoward medical occurrence and risperidone or aripiprazole. Potential AEs related to laboratory collections will be reviewed. All untoward medical occurrences of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater, that are not part of past medical history and are not captured on the BSAS (described below) would be recorded on the AE form in Advantage eClinical (the electronic data capture [EDC] system). All events that satisfy SAE criteria or involve pregnancy will be reported in an expedited fashion according to the procedures described in section 8.

6.10.4 Behavioral Symptoms (to be completed by study medical clinician)

Behavioral Symptoms Assessment Scale (BSAS): The intensity of, pattern of, and any changes in pre-existing behavioral symptoms, and any new behavioral symptoms will be systematically tracked throughout the study using the BSAS. This scale is a modification of the SMURF [56] and the Systematic Longitudinal Adverse Events Scale (SLAES) [61], which have been used in prior studies of psychiatric illnesses in children. The study clinician completes this form after reviewing the guardian- and participant-completed medical and behavioral history checklist at screening and the medical and behavioral follow-up checklist at subsequent visits, observing the participant and asking the participant and guardian about significant changes in behavioral symptoms or emergent new behavioral problems. This scale has a listing of generalized prompts for the study clinician on the first page, with more detailed specification of significant behavioral symptoms, including preferred terms for the specific behaviors present, intensity, pattern, and changes since the last visit. If a problem has never been present, this is noted on the first page and the corresponding detailed information entry related to it is left blank. The BSAS will be used to track behavioral symptoms associated with the various psychiatric disorders being treated with antipsychotics in the study.

6.10.5 Developmental Outcomes (to be completed by guardian / participant / study medical clinician)

Developmental questions about school promotion and employment status: This brief questionnaire will be used to assess major milestones in the participants' lives. Specifically, school promotions and graduations, changes in school supports, type of living situations, romantic relationships, arrests, and types and extent of employment during the interval since the prior visit will be assessed. This is typically completed by the guardian, sometimes with the help of the participant.

Vineland Adaptive Behavior Scales 3 (Vineland-3): The Vineland is designed to measure adaptive behavior of individuals from birth to age 90. The Vineland-3 contains five overarching domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional). The domain scores yield an adaptive behavior composite score, which will be the main measure of functional change. Motor skills will not be analyzed since this domain is only valid in young (<5 years) children. Children who are continuing on a normal developmental trajectory would not be expected to show any change in standard scores in each of the domains, whereas those who had developmental delays related to an underlying mental illness may show increased standard scores if treatment allows them to begin to make greater developmental progress than prior to treatment. This is completed by the guardian.

6.10.6 Pediatric Quality of Life Inventory (to be completed by guardian and participant, if able)

Pediatric Quality of Life Inventory v4 (PedsQL): The 23-item PedsQL Generic Core Scales were designed to measure the core dimensions of health as delineated by the World Health Organization in individuals aged 2 years and older [62]. There are separate forms for young adults (age 18–25), teens (age 13–18), children (age 8–12), young children (age 5–7), and toddlers (age 2–4) as well as forms for guardians of individuals at each age group. The main scales include physical functioning, emotional functioning, social functioning, and school functioning. Summary scores can also be utilized to measure change over time. The guardian will be asked to complete the parent version for reporting on their child's quality of life.

In addition, if the participant is developmentally capable of understanding and completing the form, he/she will be asked to separately complete the self-report version. If the guardian and participant both complete reports on the participant's quality of life, both sets of data will be entered and analyzed since there are often discrepancies between guardian and participant reports.

Delighted-Terrible Faces Scale (DTFS) – SS administered, participant completed: The DTFS is a uni-dimensional, single item scale that will be used to assess the participant's perceived life quality. Faces expressing various feelings are depicted, and the participant is asked which face comes closest to expressing how he/she feels about his/her life over the past month. The participant can then select from the range of seven categorical faces depicting delighted to terrible expressions [45]. This scale is included because it can be easily completed by participants with limited verbal and cognitive abilities as well as by very young children.

The first time the scale is completed by young or developmentally disabled participants, the study coordinator will evaluate whether the participant understands the distinction between the various faces and the concept of "how do you feel about your life overall" using standard procedures described in the MOP for individuals with cognitive limitations. If the study coordinator does not feel that the participant understands these concepts or the facial expressions, this measure will be omitted for that participant and considered as missing data.

6.10.7 Caregiver Quality-of-Life Outcomes (to be completed by guardian)

Caregiver Strain Questionnaire (CSQ): This is a 21-item questionnaire with a categorical scale ranging from 1 (not at all a problem) to 5 (very much a problem) that assesses the caregiver's quality of life. It asks specifically about the caregiver's quality of life by assessing the impact of caring for a child with emotional and behavioral problems. The questions include information about disruption of family life and relationships; demands on time; negative, mental, and physical health effects for any family member; financial strain; feelings of sacrifice; disruption of social/community life; worry/guilt; fatigue/strain; and embarrassment. The questionnaire includes both an objective strain (items 1–10) and a subjective strain (items 11–21) [46].

6.11 Laboratory Evaluations

6.11.1 Clinical Laboratory Evaluations

The following laboratory evaluations will be conducted at each in-clinic visit. Participants will be instructed to fast for at least six hours prior to the blood draw, and the time of last caloric intake will be recorded on the sample collection form. Caution should be taken with participants who are treated with beta-blockers to minimize the duration of the fast and ensure that they have been well nourished prior to beginning the fast due to reports of propranolol-related hypoglycemia in young children who have significantly reduced food intake for extended periods. Food and drink should be provided to participants immediately after phlebotomy. The site may use per their standard of care, agents to reduce severe anxiety associated with phlebotomy. A central laboratory will be utilized, see MOP for details.

- Glucose, BUN (blood urea nitrogen), creatinine, ALP (alkaline phosphatase), ALT (alanine amino transferase), AST (aspartate amino transferase), fasting lipid panel: total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides

- Fasting insulin
- hs-CRP
- Prolactin
- Hgb A1c
- Complete blood count with differential (CBC-D)

6.11.2 Whole Blood Samples and Future Unspecified Genetic Analyses (optional)

Participation in whole blood sample collection for future unspecified genetic analyses is optional for all participants. A whole blood sample will be obtained from the participant and uniquely identified with a scannable bar code. The frozen samples will be sent to a central lab until they are sent to an NICHD-approved biorepository.

Future unspecified genetic analyses may focus on the identification of genetic factors that increase or decrease vulnerability to specific antipsychotic-associated adverse effects or likelihood of positive response to antipsychotics or other agents (e.g., metformin). Outside funding will be sought for these genetic analyses. No analyses will be undertaken prior to obtaining IRB approval.

Guardians of participants will not be informed of genetic results. Detailed information is in the MOP.

Participants/guardians who previously consented to this optional whole blood collection, including those who turn 18 years old during the course of the study, may withdraw their consent. His/her genetic sample will be destroyed; however, data resulting from any genetic analyses performed prior to the participant/guardian withdrawing consent will not be destroyed.

6.11.3 Whole Blood Samples for Pharmacokinetic Analysis and *CYP2D6* Genotyping (optional) *Sub-study at Selected Centers*

Intensive steady-state PK studies will be conducted in a subset of 24 children on stable doses of risperidone or aripiprazole). Children enrolled in the PK portion of the study must be prescribed risperidone or aripiprazole for an FDA-labeled indication at time of enrollment as detailed in Table 2.

Table 2. Target enrollment for PK analysis

	Normal weight 6 – <10 years		Obese 6 – <13 years		Obese 13 – <18 years	
	N	Acceptable Indication	N	Acceptable Indication	N	Acceptable Indication
Risperidone	6	Irritability in autism spectrum disorder	3	Irritability in autism spectrum disorder Bipolar Mania	3	Irritability in autism spectrum disorder Bipolar Mania Schizophrenia

	Normal weight 6 – <10 years		Obese 6 – <13 years		Obese 13 – <18 years	
	N	Acceptable Indication	N	Acceptable Indication	N	Acceptable Indication
Aripiprazole	6	Irritability in autism spectrum disorder Tourette's Disorder	3	Irritability in autism spectrum disorder Tourette's Disorder, Bipolar Mania	3	Irritability in autism spectrum disorder Tourette's Disorder Bipolar Mania Schizophrenia

For participants in the PK sub-study: Risperidone and/or aripiprazole is prescribed for acute or maintenance treatment of a disorder within the FDA-labeled pediatric dose range

PK sampling can occur at any visit after M0 as long as the participant is currently on risperidone or aripiprazole and has taken the same dose of risperidone or aripiprazole as prescribed by the PPPMP over the 14 days prior to the PK sampling. The participant/guardian will be instructed to record the date, time, and amount of drug taken during the five days prior to the study visit. The participant will be instructed to refrain from taking that day's dose of study drug and to bring it with him/her to the study visit (see MOP). In addition, the date, time, route, and dose of all concomitant medications of interest (see Appendix 3) administered during the five days prior to administration of the PK dose and until the final PK sample is acquired will be recorded.

Up to five PK samples (approximately 2 ml per sample, or total about 2 teaspoons) per participant will be collected for plasma concentration determinations at specified times relative to in-visit antipsychotic administration (Table 3).

Table 3. Optimal PK sampling collection windows for study drugs

PK Sample #	Sample Collection Window
1	15–45 minutes prior to dose
2	1–2 hrs.
3	2.5–4 hrs.
4	4.5–6 hrs.
5	6.5–8 hrs.

All reasonable and non-coercive efforts possible should be made to collect all five PK samples for each participant enrolled in the PK study. All five samples do not need to be collected after the same dose (see MOP). Collection of PK samples should be timed with collection of other laboratory tests specified in the protocol to minimize blood draws when possible. Parent compound and active metabolite concentrations in plasma will be measured at a bioanalytical laboratory using a validated bioanalytical assay. Participants who have at least one PK sample

will be included in the PK analysis, but participants with <3 evaluable PK samples may be replaced to ensure accurate characterization of drug PK.

***CYP2D6* genotyping (mandatory for PK participants)**

One whole blood sample (~1 ml) for genetic testing of *CYP2D6* will be obtained on all children who participate in the optional PK sub-study. This sample should be collected during the PK procedures (see MOP). Both risperidone and aripiprazole are metabolized by *CYP2D6*. Thus, *CYP2D6* genetic polymorphisms could substantially impact drug clearance. The whole blood sample will be identified by a unique code number, and all other identifying information will be removed. Any leftover sample after genetic analysis will be transferred to the NICHD storage facility. Guardians of participants will not be informed of genetic results.

6.12 Specimen Preparation, Handling, and Shipping

Special instructions for the collection, labeling, preparation, handling, and storage of specimens are clearly detailed in the MOP.

7 STUDY PRODUCT DESCRIPTION

7.1 Other Medications Including Risperidone and Aripiprazole

All drugs will be standard formulations of commercially available products and obtained from commercial pharmacies. All drugs will be obtained outside the study using the participant's insurance or other resources.

7.2 Concomitant Medications/Treatments

There are no prohibited concomitant medications or treatments. For participants enrolled in the optional PK sub-study, the date, time, route, and dose of all concomitant medications of interest (see Appendix 3) administered during the five days prior to administration of the PK dose and until the final PK sample is acquired, will be recorded (see details in MOP).

8 ASSESSMENT OF SAFETY

8.1 Adverse Health Risks Assessed via Study Outcome Measures

Several adverse health risks comprise specific outcome measures of this study and will not be separately reported as AEs unless they lead to an SAE. These adverse health risks include:

- Weight gain (BMI assessment)
- Metabolic measures associated with risk of diabetes and cardiovascular disease
- Hyperprolactinemia (laboratory assessment of prolactin concentrations)
- Neuromotor effects (assessed via clinical exam, and quantitatively rated using the AIMS, SAS, and BARS)
- Behavioral symptoms captured in the BSAS
- Suicidality

Behavioral symptoms: Pre-existing behavioral problems—including sleep problems, seizures, impulsivity, hyperactivity, poor attention, difficulty following multi-step directions, oppositional behavior, stereotypies, repetitive behaviors, cognitive rigidity, poor frustration tolerance, aggression, tantrums, apathy, anxiety, abnormal mood, disorientation, hallucinations, delusions, or sexual or genital issues—will be carefully characterized with regard to intensity and pattern at M0, recorded on the BSAS form, and followed longitudinally throughout the study. Any changes in intensity, pattern, or subtle worsening or improvement will be noted on this form.

Neuropsychiatric events that are reported on the medical history form and tracked longitudinally throughout the study using the BSAS will not be additionally reported as AEs during the study period unless the neuropsychiatric event meets one of the SAE criteria. If a neuropsychiatric event occurs on study that was not noted at screening or M0, that event will be reported on the BSAS and will not be additionally reported on the AE form as an AE unless the neuropsychiatric event meets one of the SAE criteria.

Suicidal and self-injurious behaviors: Suicidal and self-injurious statements and behaviors will be assessed and documented at each in-person visit. If active acute suicidal ideation is identified during an in-person visit, the participant will be assessed by the SMC to determine whether the participant requires further emergency care or is able to leave the site according to medical and local standards of care. Suicidal events requiring hospitalization will be reported as an SAE.

8.2 Recording of Adverse Events

Because this is an observational study and all drugs are standard formulations of commercially available products administered per standard of care and prescribed by the participant's PPPMP.

AEs will be recorded as follows:

- All adverse events of severity grade 1 or higher that are considered related to aripiprazole or risperidone will be recorded on AE form
- All other AEs severity of grade 2 or higher (regardless of relationship to aripiprazole or risperidone) will be recorded on AE Form:
- Events followed on the BSAS that increase in intensity from screen/M0 and are of severity of grade 2 or higher will be recorded on the AE Form
- Suicidal events requiring hospitalization will be recorded on the AE and SAE Forms.

The following adverse health risks will **not** be recorded on the AE form because they are captured elsewhere in the data.

- Weight gain (BMI assessment)
- Metabolic measures associated with risk of diabetes and cardiovascular disease
- Hyperprolactinemia (laboratory assessment of prolactin concentrations)
- Neuromotor effects (assessed via clinical exam, and quantitatively rated using the AIMS, SAS, and BARS)
- Suicidality that does not result in death/hospitalization (will be recorded on Suicidality Form)

8.3 Reporting of Pregnancy

Although not considered an AE, pregnancy must be reported on the specific pregnancy report form. If a pregnancy occurs during the study, it must be reported immediately by the SMC. The SMC must document that they have informed the PPPMP, advised the participant to obtain appropriate prenatal medical care, and referred the participant for such care. The SMC may be required to inform guardians/parents about pregnancies according to local/state laws.

In addition, per the consent, researchers will follow the participant for the duration of the pregnancy and to obtain information (via direct examination or medical record review) to determine whether the resulting fetus/baby survived delivery or had any congenital abnormalities. If the fetus/newborn does not survive delivery or any congenital abnormalities are present, these must be reported as an SAE following the usual requirements for SAE reporting. Please note that if a pregnancy is reported, the participant's subsequent weight, vital sign, and laboratory data will not be included in analyses for these variables. If the pregnancy is aborted within the first 12 weeks of the pregnancy, inclusion of the participant's subsequent weight/height, vital signs, and laboratory data in the analyses will be determined by the PTN study team.

8.4 Adverse Events Definitions

Taking into account the above reporting exclusions, an AE is any untoward medical occurrence considered clinically significant by the SMC, whether or not considered drug-related, which occurs during the conduct of this clinical trial. Untoward medical occurrences may be detected and reported in multiple ways, including through systematic elicitation of medical problems, abnormal laboratory results, x-rays, neuromotor assessments, BSAS, suicidality assessments, and physical examinations.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study pharmaceutical agent, referred to as the "study drug", was the cause. A "reasonable possibility" implies that there is evidence that the drug caused the event.

An adverse reaction is any AE caused by the study drug.

A serious adverse event (SAE) or serious suspected adverse reaction or serious adverse reaction, as determined by the SMC or the sponsor, is any event that results in any of the following outcomes:

1. Death
2. Life-threatening AE ("life-threatening" means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Congenital anomaly
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Inpatient hospitalization or prolongation of existing hospitalization
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.5 Methods and Timing for Assessing and Recording Adverse Events

AE assessment will begin at the time of the first study procedure conducted during the M0 visit and will continue until the last follow-up visit or resolution of pregnancy or an SAE. Except as described above in "Adverse Health Risks", newly emergent AEs with mild (grade 1) and related to risperidone or aripiprazole and all AEs of moderate (grade 2) or greater and conditions not otherwise reported as part of the BSAS assessment which the SMC determines worsen in a clinically significant way and are (grade 2) moderate or greater severity, must be reported as AEs. New neuropsychiatric events that occur after the study start will be tracked longitudinally throughout the study using the BSAS. These events will not be reported separately as AEs unless they meet the SAE criteria.

8.5.1 Unexpected Adverse Event

This is defined as any AE for which the specificity or severity is not consistent with the package insert, investigational plan, or prior medical history or illness being treated.

8.5.2 Follow-up of Adverse Events

All events (study-related or not) must be followed until resolution or until the last study visit. All serious suspected adverse reactions and serious adverse reactions will be followed until resolution or until the participant is medically stable. All other events that are ongoing at the time of the final study visit will have the status of ongoing event recorded.

8.5.3 Elective Surgery

For the purpose of this protocol, the following conventions will apply for SAE reporting of elective surgery:

A pre-scheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the participant is hospitalized, provided the site stipulates that:

- The condition requiring the pre-scheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the participant's consent to participate in the clinical study and the time of the procedure or treatment
- The pre-scheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention

- Any untoward medical event occurring during the pre-scheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE

8.6 Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an AE:

- Mild (grade 1):** Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required; hospitalization usually not required.
- Moderate (grade 2):** Participant experiences enough symptoms or findings that a medical intervention would be appropriate and functioning is somewhat impaired; hospitalization occasionally may be required.
- Severe (grade 3):** Participant experiences symptoms or findings that require significant medical intervention; hospitalization usually required.

8.7 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an AE to risperidone or aripiprazole: “Is there a reasonable possibility that the study drug caused the event?” “Reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the AE. An affirmative answer designates the event as a suspected adverse reaction.

8.8 Discontinuation Due to Adverse Events

Due to the nature of the study, no participants will be discontinued from the study due to an AE, pregnancy, or change in treatment, including change in the dosing or indication for use of risperidone or aripiprazole, addition of a different antipsychotic medication or other concomitant medication, and/or discontinuation of risperidone or aripiprazole. The goal of the study is to continue to follow participants throughout the 36-month study period in order to comprehensively assess the long-term safety outcomes of treatment with risperidone or aripiprazole. Establishing the persistence and sequelae of AEs after the participant stops risperidone or aripiprazole is part of this goal.

8.9 Adverse Event Reporting Procedures

All reportable safety events that are mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater will be entered into the safety data system within seven days of identification. SAEs will be entered into the data system within 24 hours of identification. If there are any technical difficulties, the SAE will be reported by fax communication.

8.9.1 Serious Adverse Events

Any SAE entered in the safety database will generate an automatic email notification to the IND sponsor, study protocol principal investigator, funding sponsor, and the DCC designated staff. The BPCA medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB.

8.9.2 Regulatory Reporting

The Medical Monitor will notify the IND sponsor of any event that requires expedited reporting based on federal regulations. In accordance with the study Transfer of Regulatory Obligations (TORO), the IND sponsor will submit expedited safety reports (e.g., IND safety reports) to regulatory agencies as necessary and also will inform all investigators of such regulatory reports. Site investigators must submit safety reports as required by their IRB. Documentation of the submission and receipt by each IRB, which requires such reporting, must be retained for each expedited safety report.

All serious events, irrespective of their designation as “related” or “not related” to study product(s), will be reported to the FDA at least annually in a summary format within the annual report.

8.10 Type and Duration of Follow-up of Participants after Adverse Events

SAEs will be followed by the SMC in-person, by phone or email, by medical record review, and/or by contact with the participant’s PPPMP until the event is resolved or the participant is medically stable. If the participant/guardian provides consent for SS to collect information about pregnancy outcome, pregnancies will be followed using the same approaches until the pregnancy resolves and the fetus/newborn is delivered and its survival and the presence of congenital abnormalities has been assessed. All other AEs that have not resolved, except those identified at the M36 visit, will be followed-up at the next scheduled in-person visit (i.e., in ~6 months). Any AEs present at the M36 visit that are not SAEs or pregnancies will not be followed-up and will have the status of “ongoing event” recorded at that time.

8.11 Halting Rules

As this is an observational study and no treatments are being prescribed or discontinued as part of the study, there are no safety-based halting rules.

8.12 Safety Oversight

The study will be monitored by the BPCA DMC on a regular basis. The DMC is well established and aware of the mission of the BPCA and PTN. Specifically, the DMC will review data on changes in modified BMI z-score, secondary measures of pathological weight gain, laboratory assessments, neuromotor assessments, suicidality, AEs of mild (grade 1) and related to risperidone or aripiprazole and all AEs of moderate (grade 2) or greater and SAEs.

In addition, the study has a designated BPCA DCC medical monitor, who is otherwise independent of the study, and will review all SAEs at the time they are reported and/or updated. The BPCA DCC medical monitor will be available to study sites as needed. The study protocol chair will also review all SAEs and be available to study sites as needed.

On a monthly basis, the DMC will review a listing of SAEs, including the associated clinical narratives. DMC will also receive narratives for SAEs that are assessed by the BPCA DCC medical monitor related to risperidone or aripiprazole.

If safety concerns are identified, the medical monitor may request a meeting of the DMC to review safety data. At a minimum, the medical monitor will comment on the outcomes of the SAE and causal relationship of the SAE to the study drug. The medical monitor will also indicate whether he/she concurs with the details of the report provided by the study investigator. If no SAEs prompt review at an earlier time point, the DMC will review AEs and SAEs at the next regularly scheduled meeting.

8.13 Reporting Adverse Events to the Participant's Personal Provider

The study site will share the participant's study laboratory results and medically concerning changes in AEs and in the participant's clinical presentation detected during an in-person assessment with the participant's PPPMP. If the SMC feels that a new or worsening AE or behavioral symptoms might be related to the antipsychotic dose, he/she will share this information with the participant's PPPMP.

In addition, if the guardian positively endorses any key safety questions on the interim web-, phone-, or mail-based assessments, the site will notify the PPPMP.

Finally, the guardian and participant will be encouraged to discuss any physical, behavioral, or safety concerns that they have with the participant's PPPMP as soon as possible.

8.14 Reporting Concerns or Abnormal Clinical Laboratory Results to the Guardian

Although all clinical laboratory results will be directly transferred to the database from the central laboratory, a copy of laboratory results will also be provided to the site after each in-person visit. If requested, the SS will provide the participant's guardian with a copy of clinical laboratory test results and the vital signs log.

If the SMC has medical concerns about laboratory tests, neuromotor assessments, AEs, dosing of the antipsychotic or another medication, or has general information about potential treatment strategies, the SMC will share these with the guardian during or after the study visit and encourage the guardian to discuss any concerns or alternatives with the participant's PPPMP.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human participant protection, study procedures, laboratory procedures, and data-collection processes are of high quality and meet GCP/ICH and regulatory guidelines. Site monitoring will also ensure that the study is conducted in accordance with the protocol and Emmes and DCRI standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations (TORO), the BPCA DCC, NIH/NICHD, or its designee will conduct site-monitoring visits as detailed in the monitoring plan or MOP.

Site visits will be made at standard intervals as defined by the site monitoring plan and may be made more frequently as directed by the IND sponsor and NICHD/NIH. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, DCFs, informed consent forms (ICFs), medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

9.1 Site Monitoring Plan

A site monitoring plan will be designed for each study to supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

10 STATISTICAL CONSIDERATIONS

The general statistical analysis approach is outlined below. A more detailed description of the statistical methods will be provided in the separate statistical analysis plan (SAP), which will be finalized before database lock.

10.1 Statistical Endpoints

10.1.1 Primary Endpoint:

The primary endpoint is pathological weight change as reflected by longitudinal change in the modified BMI z-score from M0. BMI will be calculated within the database using the formula: weight in kg / (height in cm)². The modified BMI z-scores are calculated by adjusting for the appropriate population, age- and sex-specific levels for the normal population provided by 2000 CDC growth charts. The primary analysis will estimate change over the 36-month study period within each treatment group. Change from M0 to M36 will be estimated using 95% confidence intervals. No formal hypotheses will be tested. The primary analysis for the clinical study report will focus on children 6 – <18 years old at the M0 visit with at least one follow-up visit. BMI data obtained after a participant becomes pregnant will be eliminated from this analysis.

Exploratory analyses will include all age groups in the entire study sample. Change in participants who stay on the treatment from M0 to the end of study will be compared to change in participants who switch to another SGA treatment, who discontinue SGA treatment, and who are taking specific concomitant medications (e.g., metformin or multiple SGAs simultaneously) as part of the exploratory analyses.

10.1.2 Secondary Endpoints:

All secondary endpoints, other than the PK endpoints, are primarily descriptive or exploratory in nature. Event rates and longitudinal change will be evaluated within and between groups using 95% confidence intervals. No formal hypotheses will be tested. PK endpoints will be evaluated using population PK methods as described in section 10.1.2.4. Key secondary endpoints are listed below.

10.1.2.1 Additional Weight Change Endpoints

Other measures of pathological weight change will also be analyzed to complement the primary outcome measure: 1) change in BMI category (underweight, normal, overweight, obese, severely obese [$\geq 99^{\text{th}}$ percentile]) over specific time intervals; and 2) modified BMI z-score increase of ≥ 1.0 unit from M0. Data obtained after a participant becomes pregnant will not be included in these analyses.

10.1.2.2 Additional Safety Endpoints

Secondary safety endpoints of special interest are 1) metabolic measures associated with risk of diabetes and cardiovascular disease, 2) hyperprolactinemia, and 3) neuromotor effects. Metabolic risks will be assessed by measuring laboratory values such as fasting insulin, fasting lipid profile, and Hgb A1c at each study visit. Additional laboratory values of interest, including

hs-CRP and prolactin, will also be measured. Data obtained after a participant becomes pregnant will not be included in these analyses.

Changes in neuromotor symptoms will be assessed at each study visit by physical exam and quantified using the AIMS, BARS, and SAS rating scales. Changes in suicidality over time will be examined. The study will also record the incidence of all SAEs, serious adverse reactions, and AEs mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater adverse reactions and/or AEs over the course of the study. Data for these analyses will include those obtained after a participant has become pregnant.

10.1.2.3 Developmental, Functioning, and Quality-of-Life Endpoints

Potential benefits or function adverse effects of multi-year risperidone or aripiprazole treatment will be assessed by examining change over time in key outcomes. These outcomes include: adaptive behavior (Vineland), behavioral problems (BSAS), and quality-of-life scales (PedsQL-G and PedsQL-C), reflecting the participant's quality of life and completed by the guardian and participant respectively; the DTFS, reflecting the participant's overall happiness; and the CSQ, reflecting the guardian's quality of life. Data for these analyses will include those obtained after a participant has become pregnant.

10.1.2.4 Pharmacokinetic Endpoints:

Clearance (CL), volume of distribution (V), area under the curve (AUC), elimination half-life ($T_{1/2}$), maximum concentration (C_{max}), and time of maximum concentration (T_{max}) for each drug and its metabolites within each PK sub-population within each treatment group will be estimated in the population PK analysis. Estimated parameters will be compared to those already available in the medications' labels.

10.2 Populations for Analysis

Primary analysis population will be defined as all enrolled participants in the age group of 6-18 years old with at least one follow-up visit and who are not pregnant (pre-pregnancy data for females who become pregnant will be included). Participants with doses that are changed to be outside the FDA-labeled dose range will be included in the primary analysis as part of the treatment group.

All enrolled participants with at least one follow-up visit after M0 will be included in the safety population.

The PK population will include only the subset of ~24 participants who have been consented into the PK portion of the study and who have at least one PK sample.

Planned populations for exploratory sub-analyses to better understand factors associated with individualized risk include: 1) "quasi-naïve" participants who have ≤90 days exposure to any antipsychotic at the M0 visit, and 2) those with exposure only to the antipsychotic taken at the time of the M0 visit.

10.3 Analysis Plan

In this prospective, multi-site, Phase 4, observational study, participants who switch treatment from what they were receiving at enrollment will remain in the study. Separate analyses will be performed using the treatment group at enrollment and the treatment group at the time of the specific outcome event. Participants who have switched off risperidone or aripiprazole to another SGA or who have discontinued SGA treatment or have taken multiple SGAs will be summarized separately. Data from participants after they have become pregnant will not be included in the primary weight, vital sign, and metabolic lab analyses. Only the PK sub-study population will be included in the PK analyses.

Event rates and longitudinal changes will be analyzed using both descriptive summaries and modeling approaches. Descriptive statistics will be calculated by treatment and age groups (3 - <6 and 6 – 18 years). Statistics such as number of observations, mean, median, standard deviation, minimum, and maximum will be calculated for continuous variables. Counts and proportions or percentages will be calculated for summaries of discrete variables. Confidence intervals will be calculated using the 95% confidence level.

No interim analysis is planned other than the DMC's monthly review of related and unexpected SAEs and the DMC's regularly scheduled reviews of AEs, all SAEs, the proportion of participants with clinically meaningful weight change (defined as modified BMI z-score ≥ 1.0 unit from M0), and changes in key safety outcome measures including labs, neuromotor assessments, and suicidality.

Descriptive summaries and the primary analysis will be performed using SAS software version 9.4 or later. The PK analysis will be performed using NONMEM software.

10.3.1 Baseline Descriptive Statistics and Participant Disposition

Descriptive statistics will be calculated to summarize demographic and other variables from the initial M0 visit by treatment group. Baseline weight and height measured before antipsychotic and risperidone/aripiprazole initiation as well as duration of any prior antipsychotic treatment and duration of current risperidone/aripiprazole treatment will be summarized when possible. Pre-treatment baseline data is unlikely to be available from a large minority of participants.

Participant disposition will be summarized. The number of participants who complete all scheduled study assessments, the number who complete the M0 and M36 assessments, but do not complete all interim assessments, and the number who do not complete the M36 assessment will be reported. The number of participants who discontinue the M0 antipsychotic treatment prior to the M36 visit and their reasons for discontinuation will be tabulated. Treated participants who switch to the other study treatment (aripiprazole or risperidone) or alternative therapies (SGA or non-SGA) will be summarized. The duration of each participant's treatment on each antipsychotic medication during the study period, as well as the total duration of any antipsychotic treatment during the study period, will be summarized based on the participant/guardian reporting of current medications and interval changes. If information about duration and/or type of prior antipsychotic treatment is available for at least one-third of participants within a treatment group, that information will be consolidated with their on-study antipsychotic treatment information and analyzed in an exploratory fashion. The proportion of participants who are antipsychotic-naïve (≤ 90 days of prior treatment with any antipsychotic)

and those who have had more extended use at baseline will be tabulated and considered as a potential analytic subpopulation.

10.3.2 Primary Analysis

The primary analysis will estimate long-term weight change evaluated through changes in modified BMI z-score measured longitudinally from M0 to M36. Modified BMI z-score will be evaluated using height and weight data collected at each in-person visit. Only pre-pregnancy data for females who become pregnant during the study will be included in the analysis. Participants with doses that are changed to be outside the FDA-labeled dose range will be included in the primary analysis as part of the risperidone or aripiprazole treatment group. Due to varying treatment exposure duration prior to study enrollment and potential missing data, the primary analysis will use mixed effects modeling for repeated measures. Longitudinal changes in BMI over the entire 36-month study period will be evaluated, although the change from M0 to M36 will be estimated as the primary analysis using adjusted mean change with 95% confidence intervals.

Key demographic and clinical covariates will be identified through variable selection methods. Covariates of interest include age at M0 visit, Tanner stage at M0 visit, gender, and estimated duration of exposure to any antipsychotic drugs and to risperidone or aripiprazole prior to the M0 visit. Only covariates that are measured at the baseline visit will be included in the variable selection model. The primary model will include treatment group, time or exposure duration effects, interactions between treatment and time, and covariates of interest. Treatment group will be a time-varying covariate in which participants will be classified as belonging to a treatment group if they received treatment within a month prior to the visit. Otherwise, they will be classified as having switched treatments. Non-linear and categorical time effects will be considered. The correlation structure will be selected using goodness-of-fit criteria. This model will allow estimation of change in modified BMI z-score within treatment groups.

Sensitivity analyses will be performed to evaluate the effect of treatment switching, the potential impact of missing data and effect of concomitant medications of interest. Multiple imputation methods will be considered to assess the robustness of the parameter estimates from the model.

10.3.3 Secondary Analyses

Secondary analyses will include both summaries of descriptive statistics and model-based analyses. Binary safety endpoints of special interest and secondary endpoints assessing abnormal weight change will be summarized using both the proportion of participants with the event and the time from M0 to occurrence of the event. Survival models such as the Cox proportional hazards model will be used to analyze time-to-failure in participants who are “quasi-naïve” to treatment.

Clinical laboratory values and neuromotor assessments will be summarized using both changes in quantitative values from M0 and event rates for abnormal laboratory values or categorical movement ratings. SAEs, adverse reactions/serious adverse reactions, and AEs mild (grade 1) and related to risperidone or aripiprazole and all AEs of moderate (grade 2) or greater will be summarized overall, by severity, by relationship, and by each Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Both the number of events and the

number of participants with each type of event will be summarized. The number of participants with events leading to risperidone or aripiprazole discontinuation will be summarized.

To evaluate the impact of doses that are changed to be outside the FDA-labeled dose range, additional secondary analysis by adding dose received as a covariate to the primary outcome model and a sub-analysis on the children who only received a labeled dose during the follow-up period will be conducted.

Additional secondary analysis will be performed on a sub-population that only includes children who receive treatment for FDA-approved indications (excludes those treated for “closely related disorders”).

10.3.4 Pharmacokinetic Analysis Plan

Population PK analysis using non-linear mixed effects modeling in NONMEM software will be used to estimate population PK parameters and their variance. The influence of covariates on PK parameters will be explored. The plasma concentrations-time profiles of each study drug and its key metabolites will be presented in figure form by participant and cohort. PK parameters will be summarized by age cohort, obesity status, and treatment group. Results from the PK analysis will be combined with data from other PK trials (e.g., Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care [NCT01431326]) to determine the impact of age and obesity on drug disposition in children and adolescents.

10.4 Sample-Size Considerations

The sample size was calculated to be sufficient to estimate change in BMI z-score within treatment group and event rates for key safety events with adequate precision.

Simulations were performed to assess the bias and precision of within-group estimates of BMI z-score change. BMI z-score growth curves were generated from a biphasic linear model with a 0.2 z-score/year difference in the growth rate between treatment groups and between-subject variability in growth curve parameters. Population parameters were selected so that the initial peak increase of 0.75 SD was reached at nine months, with an increase to 0.775 SD at 12 months and 0.975 SD at 36 months after treatment initiation. The time between treatment initiation and enrollment into the study (M0) was assumed to be log-normally distributed. Expected dropout was assumed to be 20% and uniformly distributed. The estimate of 20% participant dropout is realistic given that 1) participants who discontinue risperidone or aripiprazole will not be withdrawn, and 2) participants will be encouraged to return for the M36 assessment even if they have missed prior assessments. Based on previous studies, expected switching to other SGA treatments was assumed to be 15% and 25% were expected to discontinue SGA treatment after baseline visit [16, 64]. Reversible switching and additional covariate effects were not considered in these simulations.

Simulated data were analyzed using a mixed effects model, with visit treated as a categorical factor, a visit-by-treatment-group interaction, and whether treatment-naïve at baseline was added as a covariate. Treatment group was a time-varying covariate in which participants were classified as belonging to a treatment group if they received treatment within a month prior to the visit. Otherwise, they were classified as having switched treatments. Estimated changes in BMI z-score from screening or at one year to the three-year visit were evaluated with 95% confidence intervals. Bias was small in the one-year to three-year comparison, and the precision

of estimates is thought to be adequate to identify large average increases in BMI through three years of follow-up (Table 4).

Table 4. Median (5th, 95th percentiles) for estimated differences in BMI z-score and median widths of 95% confidence intervals between the screening or 1-year visits and the 3-year visit by treatment group (1=higher BMI change, 2=smaller BMI change) under two different assumptions of variances (high or low).

Group (years)	Low Variance		High Variance	
	Estimate	CI Width	Estimate	CI Width
1 (3 vs 0)	1.29 (1.25, 1.33)	0.08	1.3 (1.2, 1.41)	0.16
2 (3 vs 0)	0.71 (0.66, 0.75)	0.08	0.71 (0.61, 0.81)	0.16
1 (3 vs 1)	0.61 (0.58, 0.64)	0.08	0.61 (0.53, 0.7)	0.16
2 (3 vs 1)	0.21 (0.18, 0.24)	0.08	0.21 (0.12, 0.29)	0.16

The ability to evaluate key secondary safety endpoints given the study sample size was also assessed. After accounting for up to 20% of participants having unevaluable endpoints due to dropout, a total sample size of 350 enrolled per treatment group will provide sufficient precision to estimate the incidence of key secondary safety events in the 3 – <6 (n=24 after dropout) and 6 – <18 (n=256 after dropout) age groups (Table 5). The same sample size will also provide a probability of >0.9 to detect a rare AE occurring with a probability of 0.01 in a specific treatment group. The upper bound of a two-sided 95% Wilson score confidence interval for the event rate is 0.031 if the event is observed in 0.01 of participants, and 0.015 if the event is observed in no participants, with n=320 per group. In the youngest age group, the upper bound of a two-sided 95% Wilson score confidence interval is 0.14 if the event is observed in no participants, with n=30 per group.

Table 5: Widths of 95% confidence intervals of incidence rates of key secondary safety endpoints within a treatment group as a function of observed event rates at n=320 enrolled older patients per treatment and n=30 enrolled younger patients per treatment with 20% dropout.

Observed Event Rate	Width of 95% CI	
	n=320	n=30
0.05	0.06	0.20
0.1	0.07	0.25
0.15	0.09	0.28
0.2	0.10	0.31
0.25	0.11	0.33

11 PARTICIPANT CONFIDENTIALITY

Participant confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor, and their agents. This confidentiality extends to genetic and biological sample tests, in addition to the clinical information relating to participating participants. Participants will be assigned unique code numbers and will not be identified by name, birth date, or any other personally identifying characteristic in the database. All records obtained from the PPPMP or other agencies will be maintained in a secure manner within the participant's records. The principal investigator will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the HIPAA Privacy Rule.

A certificate of confidentiality will be obtained. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The principal investigator will ensure that the use and disclosure of PHI obtained during this research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of PHI by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials.

"Authorization" is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's PHI). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

12 FUTURE USE OF STORED SPECIMENS

The only two specimen types that will be stored are blood samples used in PK analyses, which includes the *CYP2D6* genotyping and whole blood samples for future unspecified genetic analyses. After all study-specific PK analyses have been completed, remaining PK samples including the *CYP2D6* genetic sample will be transferred to a storage facility selected by the NICHD.

The whole blood samples collected for future unspecified genetic analyses will be labeled at the site upon collection with a study-provided barcode label. The barcode will only contain a unique code number without PHI or any other information that could identify the study participant. This sample will be stored frozen at the site and will be shipped to a storage facility selected by the NICHD for possible future genetic testing prior to study and site closure. These samples may be stored at the storage facility indefinitely. The NICHD repository will never have access to any personally identifying information of the participant.

Guardians/participants will not be informed of any genetic results. Detailed information is included in the study MOP.

Procedures for withdrawing consent for stored samples

Participants' guardians or participants who become adults who wish to withdraw consent for future unspecified genetic analyses will be requested to do so in writing according to the procedures provided in the ICF and in the study MOP.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2), Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. DCFs will be derived from the eCRFs and provided by the DCC.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The investigator will provide direct access to all trial-related sites, source data/documents, DCFs, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities. The principal investigator will ensure that all SS are appropriately trained and applicable documentations are maintained on site.

DCC-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the principal investigator, PTN, and NIH/NICHD.

The DCC will implement quality-control procedures beginning with the data entry system and generate data quality-control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

15 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

15.1 Ethical Standard

The investigator will ensure that the study will be conducted in accordance with the protocol, the ethical principles of GCP (ICH E6[R2]) that have their origin in the Declaration of Helsinki, and all applicable local regulations. The investigator will ensure the study is conducted in accordance with the provisions as stated and will comply with the prevailing local laws and customs. The investigator will choose participants in accordance with the eligibility criteria detailed previously. So that bias is prevented, the investigator will not exercise selectivity.

15.2 Institutional Review Board

Prior to enrollment of participants into this trial, the protocol, the ICF(s), and any materials or advertisements presented to participants will be reviewed and approved by the appropriate IRB.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB's composition and the institution's Federalwide Assurance (FWA) number will be provided to the DCC.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB.

15.3 Potential Risks

Risks specific to this study are limited to phlebotomy, embarrassment or psychological distress related to study assessments, and breach of confidentiality as a result of compromised data. However, participants are also subject to the risks inherent in their psychiatric and developmental disorders and any medications their personal psychotropic prescribing and other medical providers prescribe for them. As a consequence of the participant's psychiatric or developmental disorders and being evaluated as part of the study, there is a risk that the SMC may determine that a participant is not safe to leave a study visit and require that he/she be hospitalized.

The IND sponsor or designee will provide the investigator in writing with any new information that bears significantly on the participants' risk to receive risperidone or aripiprazole. This new information will be communicated by the investigator to the participants' guardian. The informed consent document will be updated, and the participants' guardian will be re-consented, if necessary.

Blood draw risks

There are small risks to blood sampling, including some pain/discomfort with the blood draw, bruising, and minor blood loss. Every effort will be made to minimize the number of needle sticks for this study. Additionally, finger pricks will be used whenever possible to minimize the risk of discomfort.

Embarrassment or psychological discomfort

Some of the questions asked during the clinical interview and in the participant/guardian-completed scales may be embarrassing or make the participant uncomfortable. All participants and guardians will be informed that they can decline to answer any question that makes them uncomfortable without consequence. They will also be reminded that all of their responses are confidential. Participants will be reminded that their responses will not be shared with their guardians or PPPMP unless the participant wishes to do so or unless there is a serious, immediate concern about the participant's current safety or the safety of those around them.

Breach of confidentiality

All data will be collected with close attention to the need for confidentiality. All study data will be identified only by study number and maintained in a secure password-protected database, which can be accessed only by SS and data monitors. However, it is always possible that a password-protected database may be compromised. If there is a known data breach, participants will be notified and told what information was compromised.

Risks inherent to psychiatric and/or developmental disorder

All individuals with psychiatric disorders and/or developmental disorders are at risk for worsening of their neuropsychiatric symptoms. These symptoms may interfere with the individuals' happiness; academic, vocational, and interpersonal achievement; or personal safety and the safety of others. Some individuals with psychiatric or developmental disorders may be at risk of being bullied or traumatized, harming or killing himself/ herself, or harming others. In addition, some developmental disorders may be associated with other sorts of medical problems that may emerge over time such as seizures in autism spectrum disorders. Finally, participants in this study will be on medications (antipsychotics and others) that are associated with risk for specific adverse effects. None of these inherent risks are increased by participation in the study.

Risk of abuse reporting and involuntary hospital evaluation

As part of this study, participants will be seen by the investigator who is legally and morally obligated to assess individuals who appear to be at imminent risk of being seriously harmed, seriously harming themselves, or seriously harming others. Furthermore, some study assessments ask specifically about these types of behaviors. If a member of the study team becomes concerned about the imminent safety of a participant during an in-person visit, the SMC will immediately evaluate the participant following medical standard-of-care procedures and determine whether the participant is safe to leave the study site or requires additional emergency care. If the SMC determines that the participant requires additional emergency care, the participant may be legally obligated to go to an emergency department or hospital even if he/she and/or his/her guardian does not want to do so. In addition, the participant's insurer or family would be financially responsible for paying for any emergency assessment. In addition, the SMC may determine that it is necessary to notify child protective services if he/she determines that the participant may be at serious risk of being harmed by others. Participation in the study does not inherently increase these risks; however, if the child were not participating in the study, he/she might not be seen by a medical professional who felt such actions were necessary.

15.4 Potential Benefits

Physical benefits

Participants will receive laboratory assessments at no cost, which may provide important information about individual health. Proactive longitudinal assessment of weight, height, vital signs, and assessment scales for movement disorders will identify any concerns and provide an opportunity for the participant's PPPMP to try to change the medication regimen to reduce such adverse effects. Ongoing assessment of the participant's behavioral symptoms may also identify concerns that require additional or different treatment by the PPPMP. To facilitate these potential benefits, clinical laboratory evaluations, and medically concerning changes in AEs and in the participant's clinical presentation that are evident at the in-person assessments will be shared with the participant's PPPMP and the participant's guardian to facilitate treatment decisions. In addition, during interim assessments, the participant and guardian will be encouraged to contact the participant's PPPMP if they have any new concerns.

Psychological benefits

Participants and their guardians will know that the participant's health status is being monitored on a regular basis and will have frequent opportunities to share concerns about potential AEs or behavioral changes. This often reduces anxiety and provides support to both the participant and guardian.

If there is a concern about the participant's immediate safety during an in-person visit, the participant will be assessed by the SMC at no charge following medical standard-of-care procedures to determine whether the participant is safe to leave the clinic or requires additional emergency care. Additional emergency care might include further professional assessment and monitoring and/or participant hospitalization for either somatic or psychiatric problems. The SMC will do everything in his/her power to ensure that the participant receives medically necessary additional emergency care in accordance with the site's local laws and medical standard of care. See the MOP for further details. These procedures are expected to increase the safety of the participants.

During the interim assessments, the participant/guardian will be prompted to contact the PPPMP as soon as possible if there are concerns about side effects or behavioral/psychiatric problems. In addition, if the participant/guardian reports the symptoms described by specific key questions on the medical and behavioral problem form, the site's SS and the site will notify the PPPMP. The prompts to contact the PPPMP with concerns are expected to increase the guardian's ability to advocate for the participant and increase the participant's psychiatric and developmental well-being. In addition, notifying the PPPMP if there are positive responses to key safety questions as defined in the MOP is expected to increase the likelihood and rapidity of response to worsening of the participant's mental state and thus increase the overall safety of the participant.

15.5 Informed Consent Process

Site staff may employ IRB-approved recruitment efforts prior to the participant consenting. The site staff may utilize IRB-approved phone screening procedures, including elicitation of verbal consent, for phone screening.

Informed consent and assent procedures are initiated prior to the individual agreeing to participate in the study and continuing throughout the individual's study participation. Extensive

discussion of risks and possible benefits of participation in this study will be provided to the participants and their guardians prior to signing consents.

Consent forms with detailed descriptions of the study procedures, risks, and potential benefits will be approved by the IRB. Consent forms (and assent forms if appropriate) will be given to the participant's guardian to read and note any questions after phone screening. SS will meet with the participant, if developmentally appropriate, and his/her guardians to further review the consent/assent forms, encourage them to ask any questions they may have, and answer those questions. Written documentation of informed consent is required prior to performing any study assessments unless documentation of written consent is waived by the local IRB.

If information about new potential risks related to participating in the study emerges or study procedures are modified, the consent/assent forms will be updated to reflect those potential risks, and the participants currently active in the study will be re-consented with the updated consents. If the consent forms are changed for any other reason and the local IRB requires reconsenting of active participants, the participant will be asked to review, discuss, and sign the new consent forms at the next in-person visit.

Participants who become an adult while participating in the study and who do not have a legal guardian will also be re-consented prior to continuing participation in the study. Participants who become an adult while participating in the study who are incapable of providing consent may continue to participate if they have a legally authorized representative (LAR) who consents on their behalf.

A copy of the executed informed consent/assent documents will be given to the participants' legal guardians for their records. The rights and welfare of the participants will be protected by emphasizing to guardians that the quality of their child's medical care will not be adversely affected if they decline to allow their child to participate in this study.

15.6 Informed Assent Process (e.g., minor)

This study includes minor participants who may be enrolled in the study only with the consent of their guardian. The minor participant should be informed about the study to the extent compatible with his/her neurodevelopmental abilities. Participants who are nonverbal or minimally verbal, have significant intellectual disability, are younger than seven years old, or have marked thought disorganization or positive psychotic symptoms are very unlikely to be considered developmentally able to provide assent. If the SMC judges the participant to be developmentally able to understand the concepts of voluntary participation in research, the participant will be given a simplified, developmentally appropriate assent form to review, will be asked to share any questions they may have, and then will be asked to sign and personally date the assent form. If a participant turns 18 during the course of participation in the study, and is developmentally capable of giving consent and does not have a legal guardian, he/she will be asked to sign an IRB-approved consent form prior to participating in any additional study procedures.

Assent does not substitute for the consent form signed by the participant's guardian. Sites should consult with their institution's policies regarding enrollment of participants who are unable to provide informed consent for themselves.

15.7 Informed Consent Documents

The informed consent documents will specify the investigators conducting the study, the purpose of the study, the procedures involved in participation in the study, the potential risks of participation in the study, whether there are any benefits potentially associated with the study, any costs that the participant will incur as a result of study participation, reassurance that participation is voluntary and can be withdrawn at any time, and contact information for the principal investigator and the ethical review board if concerns emerge. In addition, the ICF must comply with the requirements of both 21 CFR Part 50 and HIPAA. A consent form that complies with the requirements of 21 CFR Part 50 and a separate HIPAA-compliant authorization form for the use and disclosure of the participant's PHI may be used instead, per institutional standard operating procedures. The HIPAA Privacy Rule provides U.S. federal protection for the privacy of PHI by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's PHI). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule.

Additionally, the consent form for this study will seek specific consent for the following procedures: 1) PK sampling including *CYP2D6* genotyping, 2) whole blood sampling for future unspecified genetic analyses, and 3) re-contact at 36 months and access to medical records at 36 months if participants withdraw from the study prematurely, and 4) follow-up in the event of pregnancy.

It will also include information describing procedures for participants' guardians or participants who become adults who wish to withdraw consent for future unspecified genetic analyses to do so, including that these requests should be in writing. Further information is in the MOP and the confidentiality section of this protocol.

16 DATA HANDLING AND RECORD KEEPING

The investigator will conduct this study in accordance with the protocol, applicable state laws, and the ICH GCP Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of SAEs, as required by their local IRB.

16.1 Data Handling

The investigator will ensure the accuracy, completeness, legibility, and timeliness of the data reported. DCFs will be derived from the eCRFs and provided by the DCC to the sites to record and maintain data for each participant enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent blue or black ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the database should be consistent with the DCF/source documents or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the DCFs.

16.2 Data Management Responsibilities

All CRFs and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. AEs must be graded, assessed for severity and causality, and reviewed by the site investigator or designee. Data collection is the responsibility of the SS at the site under the supervision of the Investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

The Emmes Corporation will serve as the DCC for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

16.3 Data Capture Methods

Clinical data (including AEs and concomitant medications) will be entered into a 21 CFR Part 11-compliant internet data entry system provided by The Emmes Corporation. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the DCF/source documents.

16.4 Types of Data

Data for this study will include physical measurements, vital signs, elicited safety concerns (AEs), laboratory values, and outcome measures (e.g., SMC-assessed ratings based on physical exam, participant- and guardian-completed rating scales, PK data).

16.5 Timing/Reports

The DMC will convene and make recommendations on study continuation based on the safety data collected at the interval they specify or annually, whichever is shorter.

16.6 Study Records Retention

Study records will be kept for a minimum of 2 years after study has ended and any study submissions to the FDA by the sponsor have been decided. The research data collected in this study will be kept indefinitely.

16.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be on the part of the participant, investigator, or SS. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. For this study, missed assessments due to participant/guardian request will not be considered protocol deviations in order to facilitate retention of participants for later study assessments, but will be tracked and reported to the sponsor.

These practices are consistent with GCP:

- 4.5. Compliance with protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1. Quality assurance and quality control, section 5.1.1
- 5.2. Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor via the data system.

All deviations from the protocol must be addressed in study DCFs. A completed copy of each protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB or independent/institutional ethics committee (IEC) per their guidelines. The site investigator and SS are responsible for knowing and adhering to their IRB requirements.

17 PUBLICATION POLICY

Following completion of the study, the investigator may publish the results of this research in a scientific journal under the oversight by the Publication Committee of the PTN. The PTN Publication Committee comprises representatives of the network cores, thought leaders, DCC, and PTN and is responsible for generation and coordination of the publications that report scientific findings of the network. All public presentations (abstracts, manuscripts, slides, text of oral or other presentations, and text of any transmission through any electronic media) by participating investigators, participating institutions, the DCC, and the PTN that use PTN data, are intended to represent the PTN, or are supported by the PTN will be reviewed by the Publication Committee per the Publication Committee charter.

The Publication Committee guarantees that the study results are presented by experts in the field that have working knowledge of the study design, implementation, data synthesis/analysis, and interpretation. The committee goals are to ensure that any confidential or proprietary information is protected and that all appropriate statistical analyses have been included.

The PTN Publication Committee will adhere to the trials registration policy adopted by International Committee of Medical Journal Editors (ICMJE) member journals. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this in an acceptable registry.

The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study PK or major toxicity (e.g., Phase 1 trials), would be exempt from this policy.

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to: <http://publicaccess.nih.gov/> and <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html>.

18 APPENDICES

Appendix 1: Safety Studies of Antipsychotic Drugs

Table 6 Summary of SGA Weight Gain Side Effects in Children from Published Studies

Study	Design	Duration	Weight gain -Related Findings
Gencer et al, 2008[28]	(n=28) open-label continuation study of youth with autistic disorder (ages 8-18 yrs.). Subjects completed a 12 week RCT comparing risperidone and haloperidol.	24 weeks	Risperidone was better tolerated overall. Neither drug resulted in significant weight gain. No clinical finding of hyperprolactinemia in either group.
Fleischhaker et al, 2008[39]	(n=33) nonrandomized prospective trial of weight gain in clozapine, olanzapine and risperidone (ages 9-21 yrs.).	45 weeks	All groups experienced significant weight gain, though average weight gain significantly higher for olanzapine. Weight gain plateaued with risperidone only.
Correll et al, 2009[14]	(n=272) nonrandomized, prospective study of cardiometabolic risk of olanzapine, quetiapine, risperidone and aripiprazole in treatment-naïve youth (ages 4-19 yrs.).	12 weeks	Significant weight gain, increased fat mass, and waist circumference occurred in all groups though metabolic parameters varied.
Findling et al, 2010[40]	(n=54), double-blind, randomized maintenance study of safety and efficacy of risperidone, olanzapine, and molindone in early-onset schizophrenia (ages 8-19 yrs.).	48 weeks	All treatment groups showed significant weight gain and BMI increases. Random assignment to olanzapine discontinued. No body mass changes in molindone initially but did emerge later. Molindone also had more akathisia.
Arango et al, 2014[17]	(n=279) nonrandomized, naturalistic, multicenter, cohort study of naïve/quasi-naïve youth (ages 4-17 yrs.) on risperidone, olanzapine and quetiapine. 15 age matched healthy controls.	24 weeks	Marked weight increase in the first 3 months in all groups. Fasting metabolic parameters increased for risperidone and olanzapine but not quetiapine. Healthy controls showed no weight change.
Calarge, et al., 2014[16]	101 youth previously treated with risperidone (mean 2.5 yrs.) were assess at baseline and 18 mths	72 weeks	18 youth DC'd all SGA and showed weight loss and metabolic improvement. 9 switched to different SGA and show increased weight. 74 continued treatment and showed no change.

Appendix 2: Longer Term Studies of Risperidone Treatment

Table 7 Selected Published Studies Assessing Longer-Term Risperidone Treatment in Children

Study	Design and Indication	Duration	Reported weight changes and extrapyramidal
Aman et al, 2005	a 16-week extension on open label risperidone for all risperidone responders in Autism	total exposure to risperidone = 2 months + 4 months, or 6 months total)	Weight and body mass index (BMI) statistically increased with risperidone during the open-label extension (0.19 and 0.16 SDs, respectively). SARS and AIMS showed no group differences
Haas et al 2008	Treating disruptive behavior disorders with risperidone: open label extension study: 26 weeks	12 months	Weight gain and EPS were each reported as AEs by 10 subjects (4.3%). Mean weight z-scores decreased for RIS/RIS subjects (-0.04 ± 0.28) and increased for PLA/RIS subjects (0.11 ± 0.43). No subject developed TD.
Correll et al, 2009	Non-randomized Multisite controlled trial of cardiometabolic risk of olanzapine, quetiapine, risperidone and aripiprazole in treatment-naïve youth (ages 4-19 yrs.). (SATIEITY)	3 months	Significant weight gain, increased fat mass, and waist circumference occurred in all groups though metabolic parameters varied
Pandina et al 2012	Open label extension study: up to 12 months for Schizophrenia	Up to 12 months	Weight increase was reported as a treatment-emergent AE for 60 (15%) subjects. In all but three subjects, weight increase was rated as mild or moderate in severity. One subject in discontinued treatment due to weight increase of moderate severity (19.6 kg at day 134 of the study).

Appendix 3: Concomitant Medications of PK Interest

For participants enrolled in the PK portion of the study, the date, time, route, and dose of all Concomitant medications of interest administered in the 5 days prior to administration of the PK Dose until the final PK sample, will be recorded (see MOP).

Drug of Interest	PK relevant Concomitant Medications
Risperidone	Carbamazepine Fluoxetine Paroxetine Amiodarone Citalopram Clarithromycin Erythromycin Fluconazole Gemifloxacin Hydromorphone Linezolid Metoclopramide Telithromycin
Aripiprazole	Carbamazepine Famotidine Ketoconazole Quinidine Ranitidine Rifampin Citalopram Clarithromycin Fluoxetine Hydromorphone Metoclopramide

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