Pediatric Trials Network:
Best Pharmaceuticals for Children Act

Long-term Antipsychotic Pediatric Safety Trial (LAPS)

NICHD-2016-LAP01

Phase 4 Trial

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STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Council for Harmonization (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 regulations and ICH guidelines. 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, federal, and international regulatory requirements, and to the principles outlined in ICH guidelines.

Daniel Benjamin, M.D., Ph.D.

Pediatric Trials Network Study Principal Investigator Name (Print)

danny benjamin

Electronically signed by: danny benjamin
Reason: Approved
Date: May 19, 2021 09:29 EDT

Signature

Date

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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
AUCss	area under the curve at steady state
BMI	body mass index
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
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,
CRF	case report form
CRP	C-reactive protein
CSQ	Caregiver Strain Questionnaire
CSR	Clinical study report
DASS	Developmentally Appropriate Suicidality Scale
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
EHR	electronic health record
ePRO	electronic patient-reported outcome
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
FGA	first-generation antipsychotic
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
Hgb A1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
hs-CRP	high-sensitivity C-reactive protein

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent or institutional ethics committee
IND	Investigational New Drug Application
IRB	institutional review board
LAPS	Long-term Antipsychotic Pediatric Safety
LAR	Legally authorized representative
LDL	Low-density lipoprotein
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
RWD	real-world data
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Extrapyramidal Symptom Scale
SGA	second-generation antipsychotic
SMC	study medical clinician (medical doctor, principal investigator, nurse practitioner)
SS	study staff (study coordinator, research assistant)
SWQ	School and Work Questionnaire
$T_{1/2}$	half-life
TD	tardive dyskinesia
Tmax	time of maximum concentration
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	Primary: Longitudinally, evaluate the long term pathologic weight changes associated with multi-year risperidone or aripiprazole therapy over a period of 24 months in children ages 3 - <18 years with varying durations of prior antipsychotic drug exposure at the M0 visit. The primary analysis will focus on changes in the modified Body Mass Index (BMI) z-score in children 6 - <18 years old from M0 visit over 24 months of follow up. Secondary: 1. Evaluate weight change by change in BMI category 2. Evaluate the safety of long-term risperidone or aripiprazole therapy in children by longitudinally, up to 24 months, assessing changes in safety assessments of special interest: • Metabolic measures associated with risk of diabetes and cardiovascular disease • Prolactin related outcomes • Uniformly elicited events of special interest • Adverse events and serious adverse events • Suicidality using DASS -Developmentally Appropriate Suicidality Scale • Adverse neuromotor effects 3. Evaluate the potential long-term quality of life benefits, up to 24 months, of risperidone and aripiprazole by assessing child and parent/guardian/former guardian quality of life 4. Estimate pharmacokinetic (PK) parameters of risperidone and aripiprazole in a subset of normal-weight children aged 6 – <10 years and obese children aged 6 - <18 years. Exploratory: 1. Determine whether baseline characteristics of individual children such as age, gender, or weight might be predictors of AEs. 2. Determine whether exposure to concomitant medications given to reduce weight such as metformin might be associated with development of AEs. 3. Obtain whole blood samples for future genetic analyses that may be used to determine whether there are any genetic factors that might be associated with the development of AEs. 4. To evaluate the impact of a thank you note on enrollment into the LAP01 Registry.
Study Design	Prospective, multi-site, Phase 4, longitudinal observational study designed to systematically collect robust longitudinal post-marketing safety and quality of life data about multiyear pediatric treatment with risperidone or aripiprazole. Screening may occur for up to 37 days prior to enrollment. Assessments will occur at in-person visits planned at months 0, 6, 12, 18 and 24, and at unscheduled, in-person visits that study staff request when the participant switches or stops antipsychotic monotherapy with risperidone or aripiprazole, adds or stops treatment with a weight modifying agent, becomes pregnant, chooses to withdraw from the study prematurely or, has an ongoing Serious Adverse Event (SAE) that requires further assessment. Monthly remote interim

	contacts occurring between in-person visits will monitor for changes (other than dose related) in antipsychotic therapy or weight modifying treatments, potential SAEs, and potential pregnancy. The participant, his/her parent/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 all lab results and changes in the participant's AEs or clinical presentation, which the study medical clinician (SMC) considers medically concerning based on the participant's assessment during in-person visits, with the participant's PPPMP. If an emergency safety concern is evident during an in-person visit, the 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 parent/guardian during remote interim contacts, the participant and/or parent/guardian will be instructed to contact the PPPMP directly. Participation in an optional Registry will also be offered at participating sites to participants who qualify, according to Appendix 4, Section 21.2. Further details regarding the Registry design, objectives, and procedures are detailed in Appendix 4. A Thank You Note sub-study will also occur with all participants age 6 to <18 years old to describe if provision of a Thank You Note (or lack thereof) increase LAPS Registry enrollment.
Outcome Measures	Primary Outcome Measure: Longitudinally, evaluate the long term pathologic weight changes associated with multiyear risperidone or aripiprazole therapy over a period of 24 months in children ages 3 - <18 years with varying durations of prior antipsychotic drug exposure at the M0 visit. The primary analysis will focus on changes in the modified Body Mass Index (BMI) z-score in children 6 - <18 years old from M0 visit, and will include data collected as part of the LAP01 Registry over 24 months of follow up. Secondary Outcome Measures: 1. Change in BMI category 2. Safety Assessments of Special Interest: • Metabolic measures associated with risk of diabetes and cardiovascular disease ○ Clinical laboratory evaluations for high-sensitivity C-reactive protein [hs-CRP]; hemoglobin A1c [Hgb A1c] ○ Presence of acanthosis nigricans or, in females only, hirsutism on physical exam • Prolactin related outcomes ○ Clinical laboratory evaluation of serum prolactin ○ Incidence of gynecomastia in males on physical exam • Uniformly Elicited Events of Special Interest ○ Conditions specified in section 6.10.3.6 • Adverse effects ○ Serious adverse events (SAEs) ○ Adverse events (AEs) of mild (grade 1) severity and related to risperidone or aripiprazole ○ All adverse events of moderate (grade 2) severity or greater regardless of relatedness to risperidone or aripiprazole • Suicidality ○ Assessed using Developmentally Appropriate Suicidality

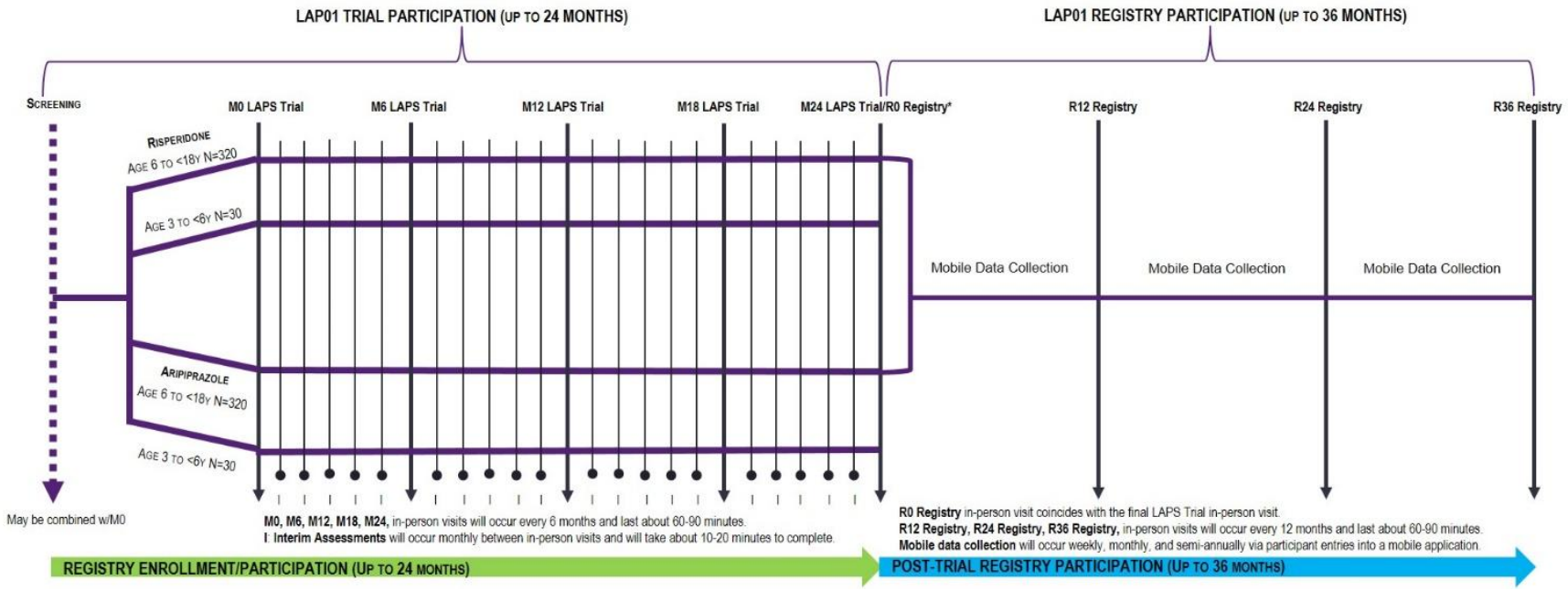
	Scale (DASS) • Neuromotor effects ○ Abnormal Involuntary Movement Scale (AIMS) ○ Simpson Angus Extrapyramidal Symptoms Scale (SAS) 3. Quality of Life • Parent/guardian/former guardian completed Pediatric Quality of Life Inventory (PedsQL, 23 item) • Parent/guardian (participant when they become of legal age, if SMC considers the participant competent and the participant refuses to consent for parent/guardian/former guardian to continue to complete) completed School and Work Questionnaire (SWQ) • Parent/guardian/former guardian completed Caregiver Strain Questionnaire (CSQ) • Participant-completed Delighted-Terrible Faces Scale (DTFS) Data from the LAP01 Trial and LAP01 Registry will be combined for the following outcome measures: • Parent/guardian/former guardian completed Pediatric Quality of Life Inventory (PedsQL, 23 item) 4. Pharmacokinetics in a subset of participants • CL/F, Vss/F, AUCss, Cmax, Tmax, and $T_{1/2}$ at steady state <u>Exploratory Outcome Measures</u>: • Baseline characteristics • Concomitant medications • Genetic factors • Adverse events ○ Serious adverse events (SAEs) ○ Adverse events (AEs) of mild (grade 1) severity and related to risperidone or aripiprazole ○ All adverse events of moderate (grade 2) severity or greater regardless of relatedness to risperidone or aripiprazole • Enrollment to LAP01 Registry ○ Number of participants who enroll in LAP01 Registry

<table>
<tr><td>Study Population</td><td>The study population will consist of two groups of children 3 – <18 years old at the time of the M0 visit:
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.
Participants within each treatment group to be distributed across the age range to permit analyses of age effects with:
~30 being 3 – <6 years
≥35% (n ≥123) being 6 – <12 years
≥35% (n ≥123) being 12 – <18 years
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.</td></tr>
<tr><td>Inclusion Criteria</td><td>1. Parent/guardian has provided informed consent
2. Participant has provided assent if developmentally appropriate and as required by the institutional review board (IRB)
3. 3 – <18 years of age inclusive at time of M0 visit
4. Participant, when developmentally appropriate, and parent/guardian are willing to:
a. Authorize exchange of information between the SS and the PPPMP and/or other significant medical provider
b. Affirm participant's use at M0 visit of either risperidone or aripiprazole mono-antipsychotic therapy 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 specified 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 – <18 years at the doses and for the diagnoses listed below
<table>
<tr><td colspan="2">Drug</td></tr>
<tr><td>Aripiprazole*</td><td>Risperidone*</td></tr>
<tr><td colspan="2">Dose</td></tr>
<tr><td>2 – 30 mg/day</td><td>0.25 – 6 mg/day</td></tr>
<tr><td colspan="2">Indication
<u>Labeled indications (underlined)</u> and Closely Related Disorders (italicized)</td></tr>
<tr><td><u>Irritability associated with autistic disorder</u>
Irritability in autism spectrum disorder</td><td><u>Irritability associated with autistic disorder</u>
Irritability in autism spectrum disorder</td></tr>
<tr><td><u>Treatment of Tourette's disorder</u>
Tourette's disorder, persistent (chronic) motor or vocal tic disorder</td><td>N/A</td></tr>
</table></td></tr>
</table>

	Bipolar mania/acute treatment of manic and mixed episodes associated with Bipolar I disorder *Bipolar spectrum disorders including disruptive mood dysregulation disorder*	Bipolar Mania *Bipolar spectrum disorders including disruptive mood dysregulation disorder*
	Schizophrenia *Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder*	Schizophrenia *Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder*
	*MYCITE® (aripiprazole) is permitted in this study; all forms of injectable risperidone and aripiprazole are not permitted in this study	
	6. Parent/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 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and determined by psychiatric exam or participant/parent/guardian report. 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 another antipsychotic medication in addition to 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	The primary endpoint will be modified BMI z-score assessed at each in-person study visit from the M0 visit through the 24-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 in-person 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. Secondary safety and Quality of Life outcome changes from the M0 visit through the M24 visit will be summarized by M0 treatment group.	
Number of Participants	Approximately 700 participants	
Number of Sites:	Approximately 60 sites	

Duration of Participant Participation:	Up to 26 months
Estimated Time to Complete Enrollment:	Up to 12 months

SCHEMATIC DESCRIPTION OF STUDY DESIGN



* The first LAP01 Registry in-person visit (R0) may occur at any of the LAPS Trial visits.

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 Company (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.[2,3] Antipsychotics are also frequently used off label to promote weight gain and reduce anxiety in individuals with eating disorders such as anorexia and bulimia.[4] 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] Further, there is 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 appear to increase risk for all adult disorders. Mood and psychotic disorders often persist 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 lower risk for neuromotor side effects, including tardive

dyskinesia (TD), than traditional antipsychotics do, 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.[13-22] 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.[23,24] 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] A recent study demonstrated significantly increased subcutaneous and visceral adiposity with both risperidone and aripiprazole pediatric treatment, with 15% of antipsychotic-naïve participants moving from normal weight status to overweight or obese status in 12 weeks.[25] In this study, age effects contributed significantly to adiposity with younger children having greater and more rapid increases in adiposity. Studies attempting to characterize the long-term effect of antipsychotic drugs on weight gain are limited by lack of generalizability and small sample size.[18,21,26-39]

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 frequently develop during antipsychotic treatment. An early observational study of many different antipsychotics (n=272, 122 on risperidone) found that 17.1% of treated youth developed new-onset dyslipidemia and 8.6% of youth developed insulin resistance over 12 weeks.[14] A more recent randomized trial found that 10% of antipsychotic naïve children treated with risperidone and 2% of those treated with aripiprazole developed impaired fasting glucose levels.[25] The long-term trajectory and consequences of such metabolic changes 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 trajectories. Our knowledge and understanding of the persistence of metabolic abnormalities or weight gain are limited because many participants, who have experienced such adverse events, consequently choose not to continue participation in longer-term continuation studies that typically follow acute trials. 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.[19,40] Risperidone is one of the most commonly prescribed SGAs and is associated with the largest acute increases in serum prolactin.[20,40] However, aripiprazole is associated with a reduction in prolactin levels.[26] There is also evidence that antipsychotic -related increases in prolactin levels are greater and more prevalent in the pediatric population than in adults.[40] There is limited evidence that antipsychotic-induced hyperprolactinemia may normalize over time.[27,28] 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,[32,33,41-44] 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),[29] though maintenance studies of pediatric bipolar patients show low rates of other types of EPS (e.g., dystonia).[26,30]

Risperidone is associated with greater risk of pseudo-parkinsonian symptoms and dystonia.[28,29,32] 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 of risperidone than children with bipolar disorder or schizophrenia.[29,33,36,37] Other antipsychotics such as clozapine and quetiapine are associated with lower rates of EPS.[34,35]

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,[41,42] though rates appear relatively low in a study of up to one year of exposure (0.3% annually for risperidone).[43] 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.[44] 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 of antipsychotics. 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.[14,16,17,25,32,38,39] 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 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.[14] 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. The more recent study by Nicol and colleagues [62] includes 49 children each in the risperidone and the aripiprazole groups, but does not include a control 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 24-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 parent/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 probability that multi-year treatment with each agent will result in increased risk for:

- 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 and prolactin-related events
- Development of neuromotor side effects

In addition, the PK 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 related to weight, elevated Hgb A1c and neuromotor effects after risperidone or aripiprazole is stopped. The trial will also provide information about potential differences in the incidence of adverse health risks and other untoward effects 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 than the 3 – <6-year-olds.

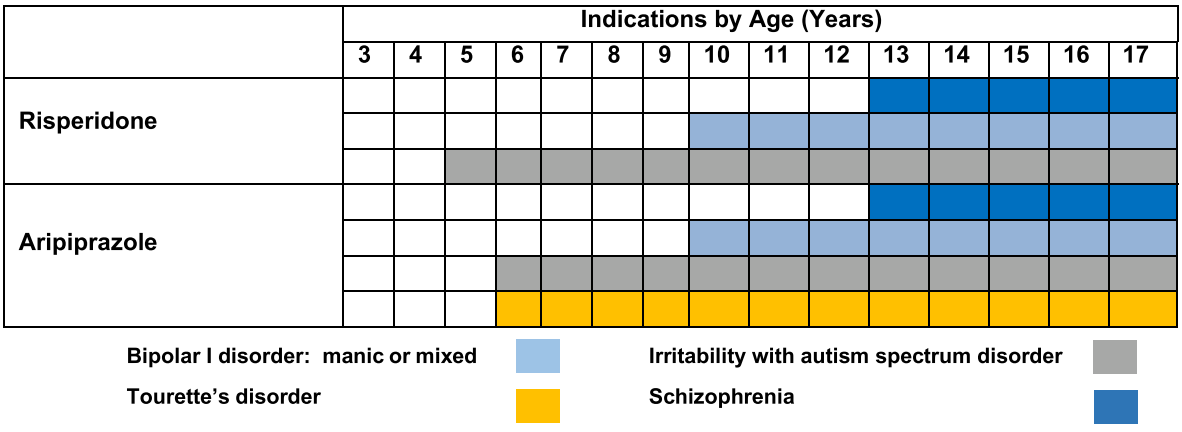
This longitudinal, prospective safety study of community-provided risperidone or aripiprazole fills an urgent public health need given that 1) many children require treatment with risperidone or aripiprazole for many years due to highly significant behavioral benefits from these drugs and 2) there is limited existing data about the long-term safety of these drugs. Thus, this study addresses an essential knowledge gap by systematically assessing both the long-term health risks and quality of life 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; they account for more than two-thirds of the antipsychotic prescriptions in children.[1,45-48] 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).[49] 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 such use in children with diagnoses of attention deficit hyperactivity disorder.[45-48,50,51]

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 and there are likely to be fewer screen failures. Second, the acute side effect profiles of risperidone and aripiprazole differ, with risperidone appearing to have greater weight gain and pseudo-parkinsonian neuromotor risks and aripiprazole having greater neuromotor risk for akathisia. It remains unclear if the two agents have similar metabolic risks and quality of life benefits.

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.[52,53] 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 LAPS Registry

The LAPS Registry (Appendix 4) will extend data collection on participants age 6 to < 18 years-old at the time of the LAPS trial who consent to participate and who meet eligibility criteria. These participants will contribute weight, height, health outcomes and other clinical data via a combination of in-person visits, direct-to-participant mobile application (Pattern Health), and electronic health record (EHR) extraction technologies (Pluto). The goal will be to extend data collection for up to 62 months.

2.2.5 Rationale for Thank You Note Sub-study

A Thank You Note sub-study will randomize potentially eligible LAPS Registry participants to one of the following groups, prior to LAPS Registry consent: Thank You Note or no Thank You Note. The intent of this Sub-study is to describe the effect that a Thank You Note has on continued study participation via the LAPS Registry.

2.2.6 Rationale for Inclusion Criteria

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 for each indication. Similarly, since both drugs are labeled for maintenance treatment in adults and the disorders with pediatric acute indications are chronic and typically require ongoing treatment, it is appropriate to include children receiving maintenance treatment. Further, including children on maintenance treatment will provide information about longer exposures than would be possible if we only included children with no or brief prior antipsychotic exposure. Finally, given the need for rigorously defined populations in clinical licensing trials and the frequent 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 longitudinally, evaluate the long term pathologic weight changes associated with multi-year risperidone or aripiprazole therapy over a period of 24 months in children ages 3 - <18-years, with varying durations of prior antipsychotic drug exposure at the M0 visit. The primary analysis will focus on changes in the modified Body Mass Index (BMI) z-score in children 6 - <18 years old from M0 visit over 24 months of follow up.

3.2 Secondary Objectives

1. Evaluate weight change by change in BMI category
2. Evaluate the safety of long-term risperidone or aripiprazole therapy in children by longitudinally, up to 24 months, assessing changes in safety assessments of special interest:
    - Metabolic measures associated with risk of diabetes and cardiovascular disease
    - Prolactin related events
    - Uniformly elicited events of special interest
    - Adverse events and serious adverse events
    - Suicidality –using DASS
    - Adverse neuromotor effects
3. Evaluate the potential long-term quality of life benefits, up to 24 months, of risperidone and aripiprazole by assessing child and parent/guardian/former guardian quality of life
4. Estimate pharmacokinetic (PK) parameters of risperidone and aripiprazole in a subset of normal-weight children 6 - <10 years and obese children aged 6 - <18 years

3.3 Exploratory Objectives

1. Determine whether baseline characteristics of individual children such as age, gender, or weight might be predictors of AEs.
2. Determine whether exposure to concomitant medications given to reduce weight such as metformin might be associated with development of AEs.
3. Obtain whole blood samples for future genetic analyses that may be used to determine whether there are any genetic factors that might be associated with the development of AEs.
4. To evaluate the impact of a thank you note on enrollment into the LAP01 Registry.

3.4 Study Outcome Measures

3.4.1 Primary Outcome Measure

Longitudinally, evaluate the long term pathologic weight changes associated with multi-year risperidone or aripiprazole therapy over a period of 24 months in children ages 3 - <18 years with varying durations of prior antipsychotic drug exposure at the M0 visit. The primary analysis will focus on changes in the modified Body Mass Index (BMI) z-score in children 6 - <18 years old from the M0 visit, and will include data collected as part of the LAP01 Registry over 24 months of follow up.

3.4.2 Secondary Outcome Measures

1. Change in BMI category
2. Safety assessments of special interest

- Metabolic measures associated with risk of diabetes and cardiovascular disease
  - Clinical laboratory evaluations for high-sensitivity C-reactive protein [hs-CRP]; hemoglobin A1c [Hgb A1c]
  - Presence of acanthosis nigricans or, in females only, hirsutism on physical exam
- Prolactin related outcomes
  - Clinical laboratory evaluation of serum prolactin
  - Incidence of gynecomastia in males on physical exam
- Uniformly Elicited Events of Special Interest
  - Conditions specified in section 6.10.3.6
- Adverse effects
  - Serious adverse events (SAEs)
  - Adverse events (AEs) of mild (grade 1) severity and related to risperidone or aripiprazole
  - All adverse events of moderate (grade 2) severity or greater regardless of relatedness to risperidone or aripiprazole
- Suicidality
  - Assessed using Developmentally Appropriate Suicidality Scale (DASS)
- Neuromotor effects
  - Abnormal Involuntary Movement Scale (AIMS)
  - Simpson Angus Extrapyramidal Symptoms Scale (SAS)

3. Quality of Life Changes:
   - Parent/guardian/former guardian completed Pediatric Quality of Life Inventory (PedsQL, 23 item)
   - Parent/guardian (participant when they become of legal age, if SMC considers the participant competent and the participant refuses to consent for parent/guardian/former guardian to continue to complete) completed School and Work Questionnaire
   - Parent/guardian/former guardian completed Caregiver Strain Questionnaire (CSQ)
   - Participant-completed Delighted-Terrible Faces Scale (DTFS)

   Data from the LAP01 Trial and LAP01 Registry will be combined for the following outcome measures:
   - Parent/guardian/former guardian completed Pediatric Quality of Life Inventory (PedsQL, 23 item)
4. Pharmacokinetics in a subset of participants:
   - CL/F, Vss/F, AUCss, Cmax, Tmax, and $T_{1/2}$ at steady state

3.4.3 Exploratory Outcome Measures

- Baseline characteristics
- Concomitant medications
- Genetic factors
- Adverse events
  - Serious adverse events (SAEs)
  - Adverse events (AEs) of mild (grade 1) severity and related to risperidone or aripiprazole

  - All adverse events of moderate (grade 2) severity or greater regardless of relatedness to risperidone or aripiprazole

- Enrollment to LAP01 Registry
  - Number of participants who enroll in LAP01 Registry

4 STUDY DESIGN

This study is designed to longitudinally, over 24 months, evaluate long-term pathological weight changes associated with multi-year risperidone and aripiprazole therapy in children ages 3 - <18 years. This study will also provide insights into the overall long-term safety and the quality of life effects of both drugs. The sub-study will estimate PK parameters in subsets of young and obese children. Targeted data collection will extend into the LAP01 Registry, detailed in Appendix 4.

4.1 Study Design

This is a prospective, multi-site, Phase 4, longitudinal observational study designed to systematically collect robust, longitudinal, post-marketing safety and quality of life data about multi-year pediatric treatment with risperidone or aripiprazole. Screening may occur for up to 37 days prior to enrollment. Assessments will occur at in-person visits planned at months 0, 6, 12, 18, and 24, and at unscheduled, in-person visits that study staff request when the participant switches or stops antipsychotic monotherapy with risperidone or aripiprazole, adds or stops treatment with a prescribed weight change medication, becomes pregnant, chooses to withdraw from the study prematurely or, has an ongoing SAE that requires further assessment. Monthly remote interim contacts occurring between in-person visits will monitor for changes (other than dose related) in antipsychotic therapy or prescribed weight change medications, potential SAEs and potential pregnancy.

The study will enroll up to 350 children treated with risperidone mono-antipsychotic therapy at the time of the M0 visit and up to 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 participant, his/her parent/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. The SMCs (unless they are the PPPMP) 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.

Study staff (SS) will share all lab results and changes in the participant’s AEs or clinical presentation, which the study medical clinician (SMC) considers medically concerning based on the participant’s assessment during in-person visits, with the participant’s PPPMP. If new or worsening symptoms are reported by the participant or parent/guardian during remote interim contacts, the participant and/or parent/guardian will be instructed to contact the PPPMP directly.

If an emergency safety concern is evident during an in-person visit, the 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.

4.1.1 LAPS Registry Study Design

The LAPS Registry will extend data collection on participants who are 6 to <18 years old and enrolled in the LAPS Trial. Any weight change data to meet the Primary Objective that is not

collected as part of the LAPS Trial will be collected as part of the LAPS Registry. Refer to Appendix 4 for more details regarding the LAPS Registry study design.

4.2 Study Duration

Each participant enrolled in the study will participate for up to 26 months. Enrollment is expected to be completed within 12 months.

5 STUDY POPULATION

5.1 Selection of the Study Population

The study population will consist of two groups of children 3 – <18 years old at the time of the M0 visit:

- 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.

This will 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.

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

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.[1,45-48]

Siblings will be allowed to participate.

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.

5.2 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Parent/guardian has provided informed consent
2. Participant has provided assent if developmentally appropriate and as required by the institutional review board (IRB)
3. 3 – <18 years of age inclusive at time of the M0 visit
4. Participant, when developmentally appropriate, and parent/guardian are willing to:
    a. Authorize exchange of information between the SS and the participant's PPPMP and/or other significant medical provider
    b. Affirm participant's use at M0 visit of either risperidone or aripiprazole mono-antipsychotic therapy 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 – <18 years at the doses and for the diagnoses listed below

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

6. Parent/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 or participant/parent/guardian report.
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 another antipsychotic medication in addition to either risperidone or aripiprazole at the time of the 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

5.3 Treatment Assignment Procedures

Participants will not be assigned to risperidone or aripiprazole as part of this protocol. Instead, each participant, his/her parent/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. Participants taking MyCite® (aripiprazole) are permitted. Injectable forms of risperidone and aripiprazole are not allowed due to the fact that they are not 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 parent/guardian may choose to discontinue participation in this study at any time. Neither is obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the SMC and reported in EDC.

Participants and parent/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.

The 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)
- The 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 M24) 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 M24 visit.

5.3.4 Termination of Study

This study, including the sub-studies, may be terminated at any time for any reason by the NICHD, Investigational New Drug Application (IND) sponsor, or Data Monitoring Committee

(DMC). A research site's participation in the study may be terminated by the IND sponsor/DCRI study team or NICHD, if the site investigator does not adhere to the protocol.

6 STUDY PROCEDURES

6.1 Summary of Procedures

Table 1: Procedures organized by type of visit.

Study Procedure	Screening/ M0	In Person Visits Months 6 & 18 (+/- 4 weeks)	In Person Visits Months 12 (+/- 4 weeks) & 24 (+ 90 days), unscheduled visits for medication changes[a], pregnancy, premature withdrawal	Unscheduled Visit for unresolved Serious Adverse Event[b]	Monthly Remote Interim Contacts (+/- 14 days from last contact)
Parent/Guardian completes					
Informed consent	X				
Consent to contact PPPMP	X				
Demographics	X				
Contact form	X	X	X		X
ePRO training	X				
Peds Quality of Life [c]	X	X	X		
Caregiver Strain Questionnaire [c]	X		X		
School and Work Questionnaire [c]	X		X		
Respond to monthly contact					X
Participant completes					
Delighted Terrible Faces Scale	X	X	X		
Study staff completes					
Height, weight, vital signs	X	X	X		
Annual Safety labs	X		X		
Optional one-time genetic sample [d]	X[d]	X[d]	X[d]		
Results to guardian, PPPMP [e]	X	X	X		
Initiate & follow-up monthly contacts					X
PK sampling [f]		X[f]	X[f]		
SMC completes					
Antipsychotic and prescribed weight change medications[g]	X	X	X	X	
Medical and Psychiatric History/Evaluation	X				
Uniformly Elicited Events of Special Interest	X	X	X		
Adverse events including SAE review	X	X	X	X	
Developmentally Appropriate Suicidality Scale (DASS)	X	X	X		
Focused physical exam [h]	X	X	X		
Abnormal Involuntary Movements Scale	X	X	X		
Simpson Angus Extrapyramidal Events Scale	X	X	X		
Review of potential SAE				X	X[b]

[a] Unscheduled in-person visits for medication changes are triggered by reports of switching or stopping risperidone or aripiprazole monoantipsychotic therapy or switching or stopping prescribed weight change medication.
[b] Unscheduled in-person visits to assess unresolved SAE reported during remote contact may include any additional clinical measures SMC feels are medically necessary. If there is a positive response to ED/urgent care visit or hospitalization questions during remote interim contact, SMC will review to determine if there has been an SAE and SS will follow-up to get medical records.
[c] Peds QL and CSQ can only be completed by parent/guardian/former guardian. When participant becomes of legal age, SMC will determine if cognitively and developmentally able to complete the SWQ. When participant becomes of legal age, if they consent to continue participation, the former guardian would complete the PedsQL and CSQ.
[d] Optional genetic sample collection, should be completed once during the study, at any in person visit, in participants who consent.
[e] All lab results and any changes in the participant's AEs or clinical presentation, which the study medical clinician (SMC) considers medically concerning based on the participant's assessment during in-person visits will be shared with PPPMP.
[f] For participants in the PK sampling sub-study, PK samples may be obtained at any visit after M0. Participants may only be enrolled in the PK sub-study at selected sites.
[g] Antipsychotic medications and prescribed weight change medications known to be taken prior to study enrollment and any changes to current antipsychotic and prescribed weight change medications over the course of the study will be recorded
[h] Focused physical exam documents whether acanthosis nigricans, hirsutism (in females), or gynecomastia (males only) are present/absent and is the basis of the neuromotor assessments.

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 screening visit is anticipated to last approximately one hour (two hours if combined with M0 visit).

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

Parent/guardian (G):

- Informed consent discussion/process with SS, including consent to exchange information with participant's PPPMP. Re-consent/assent of the participant or parent/guardian may occur as needed, following site-specific policies and procedures.
- Participant demographics
- Contact form, including back-up information for close friends or relatives likely to be able to provide contact information for participant's parent/guardian in case of a move, etc.
- ePRO training

Participant (P) (if developmentally able):

- Informed assent - discussion/process occurs at same time as parent/guardian informed consent process

Study Staff (SS):

- Contact participant's PPPMP and other necessary providers to confirm, if possible, indication for current risperidone or aripiprazole treatment, and collect available information regarding weight and height trajectory, prior antipsychotic exposure, and metformin or prescription weight change medications.

Study Medical Clinician (SMC):

- Complete inclusion and exclusion criteria and confirm eligibility
- Past medical and behavioral history
- Antipsychotic and prescribed weight change medication history
- Medical and psychiatric diagnostic evaluation (see MOP)
- Suicidality Assessment - DASS

6.3 Month 0 (M0)

The M0 visit will occur <37 days after the screening visit, or may occur on the same day as the screening visit if the inclusion and exclusion criteria have been confirmed. The following assessments will be performed and necessary data entered. 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. This visit is expected to last approximately one hour, two hours if combined with screening visit.

Parent/guardian:

- Update information on contact and back-up contact forms, if any changes
- Confirm antipsychotic use and prescribed weight change medications (if any)
- The following questionnaires are completed electronically or via hard copy. It is preferred that they are completed at the visit but all can be completed up to 14 days before or after the visit if necessary.
    - Parent/guardian-completed PedsQL
    - Parent/guardian-completed School and Work Questionnaire
    - Parent/guardian-completed Caregiver Strain Questionnaire

Participant (P) (if developmentally able):

- DTFS

Study Staff (SS):

- Vital signs (standing height, weight, sitting blood pressure, and pulse)
- Clinical laboratory evaluations (See section 6.11): Participant should be fasting with the exception of water or non-caloric beverages for at least six hours prior to blood collection (see section 6.11 and MOP). If this is absolutely impossible, non-fasting labs may be obtained.
- Determine whether parent/guardian/participant is willing to complete optional blood sampling for future unspecified genetic analyses, perform during this visit or future visit if unable to perform at M0 (see section 6.11.2)
- Administer DTFS to participant (see MOP)
- Provide PPPMP with a copy of all lab results (regardless of clinical significance) and any changes in AEs or clinical issues which the SMC considers medically concerning based on his/her in-person assessment of the participant during the visit (see section 8.12).
- May provide a copy of lab results to parent/guardian at parent/guardian's request

Study Medical Clinician (SMC):

- Review for changes in antipsychotic use and prescribed weight change medications
- Update past medical history form as needed
- Focused physical exam, noting whether acanthosis nigricans, hirsutism (in females) or gynecomastia (in males) are present and a neuromotor exam including completion of the AIMS and SAS.
- Uniformly elicited Events of Special Interest (See section 6.10.3.6)
- Suicidality using DASS
- Assess for adverse effects as follows:
    1) AEs with mild (grade 1) severity that SMC considers probably or definitely related to risperidone or aripiprazole
    2) All AEs with moderate (grade 2) or higher severity regardless of relationship to risperidone or aripiprazole
    3) Serious Adverse Events (SAEs)

6.4 Monthly Remote Interim Contacts

In order to assess critical medication and safety changes between in-person visits, remote interim contacts will be completed at approximately monthly intervals between in-person visits, 30 days +/- 14 days from last contact.

Study Staff (SS) with SMC consultation as needed:

- Initiate remote contact using contact form to ask questions about:
    - Additions, discontinuation or other non-dose related changes to antipsychotic, metformin or prescribed weight change medications
    - Potential serious adverse events through solicitation of information regarding hospitalizations, visits to urgent care or an emergency department,
    - Pregnancy (in female participants with childbearing potential only).
- The responses will be reported in EDC.
- This is expected to take about 5-10 minutes.
- Request an unscheduled visit if participant's antipsychotic medication or prescribed weight change medication has been switched or stopped, an additional antipsychotic or prescribed weight change medication has been added, the participant has become pregnant or a potential SAE, which is unresolved, has been reported.
- No contact between SS and PPPMP is required after a monthly remote interim contact unless the SMC indicates that it is clinically indicated and the participant refuses a requested, related, unscheduled in-person visit

Parent/guardian or Participant if adult and own guardian:
Respond to questions about changes in antipsychotic, metformin or prescribed weight change medications, hospital, emergency department or urgent care visits, and possible pregnancy if applicable (see MOP). This should take no more than 5 to 10 minutes.

6.5 In-person M6, M18 Visits, Unscheduled Visits for Unresolved SAEs

These visits will occur at months 6 and 18, with a +/- 4-week window. The following assessments will be performed and recorded.

Note: Re-consent/assent should occur as needed and following site-specific policies and procedures, e.g., participant becomes a legal adult.

Parent/guardian:

- Update information on contact and back-up contact forms if any changes
- Report changes in antipsychotic medications and prescribed weight change medications
- The following questionnaire is completed electronically or via hard copy. It is preferred that it is completed at the visit but can be completed up to 14 days before or after the visit if necessary.
    - Parent/guardian-completed PedsQL

Participant (if developmentally able):

- DTFS

Study Staff:

- Vital signs (standing height, weight, sitting BP, and pulse)
- Administer DTFS to participant (see MOP)
- Notify PPPMP of any changes in adverse events or clinical issues, which the SMC

considers medically concerning based on his/her in-person assessment of the participant during the visit (see section 8.12).
- Collect optional blood sampling for future unspecified genetic analyses if participant has not yet completed the sampling but has given consent (see section 6.11.2)
- At selected sites and if participant has consented to and is eligible for sub-study of PK sampling (see Table 2, section 6.11.3), provided they have not yet completed the sampling and have not yet taken risperidone or aripiprazole for the day, PK samples can be obtained (see sections 6.6.2)
- Provide PPPMP with a copy of all lab results (regardless of clinical significance)
- If during the M6 or M18 visit the site becomes aware that the participant is considering premature withdrawal, or learns they switched stopped antipsychotic, or prescribed weight change medication or is pregnant, the SS will attempt to obtain all assessments normally obtained during M12 and M24 visits as soon as possible (including at the M6 or M18 visit).

Study Medical Clinician (SMC):

- Review any change in antipsychotic medications, metformin, or prescribed weight change medications
- Review assessments completed by caregiver, participant and SS
- Complete the following assessments
    - Focused physical exam form, noting whether acanthosis nigricans, hirsutism (in females) or gynecomastia (in males) are present/absent
    - AIMS (see section 6.10.3.4)
    - SAS (see section 6.10.3.4)
    - Uniformly elicited events of special interest (see section 6.10.3.6)
    - Suicidality – using DASS
    - Assess for adverse effects as follows:

      1) AEs with mild (grade 1) severity that SMC considers probably or definitely related to risperidone or aripiprazole
      2) All AEs with moderate (grade 2) or higher severity regardless of relationship to risperidone or aripiprazole
      3) SAEs
- Notify SS of any changes in AEs or clinical presentation that they consider medically concerning based on in-visit assessment for reporting to PPPMP

6.6 In-person M12, M24 Visits, Unscheduled Visits for Medication Changes, Pregnancy and Premature Withdrawal

These visits will occur at months 12 (+/- 4-weeks) and 24 (+ 90 days) and at unscheduled visits triggered by non-dose-related adding, switching or stopping of antipsychotic or prescribed weight change medications including metformin, pregnancy or premature withdrawal. The following assessments will be performed and recorded.

Note: Re-consent/assent may occur as needed and following site-specific policies and procedures, e.g., participant becomes a legal adult.

Parent/guardian:

- Update information on contact and back-up contact forms, if any changes
- Report changes in antipsychotic medications and prescribed weight change medications.
- The following questionnaires are completed electronically or via hard copy. It is preferred that they are completed at the visit but most can be completed up to 14 days before or after the visit if necessary.
    - Parent/guardian-completed PedsQL
    - Parent/guardian completed School and Work Questionnaire
    - Caregiver Strain questionnaire

Participant (if developmentally able):

- DTFS

Study Staff (SS):

- Vital signs (standing height, weight, sitting BP, and pulse)
- Administer DTFS to participant (see MOP)
- Safety Laboratory Assessments (see section 6.11.1)
- Notify PPPMP of safety lab results and any changes in adverse events or clinical issues, which the SMC considers medically concerning based on his/her in-person assessment of the participant during the visit (see section 8.13).
- Collect optional blood sampling for future unspecified genetic analyses if participant has not yet completed the sampling but has given consent (see sections 6.6.1 and 6.11.2)
- At selected sites and if participant has consented to and is eligible for sub-study of PK sampling (see Table 2, section 6.11.3, provided they have not yet completed the sampling and have not yet taken risperidone or aripiprazole for the day, PK samples can be obtained (see section 6.6.2 and 6.11.3)

Study Medical Clinician (SMC):

- Review any change in antipsychotic medications, metformin, or prescribed weight change medications
- Review assessments completed by parent/guardian, participant and SS
- Complete the following assessments:
    - Focused physical exam form, noting whether acanthosis nigricans, hirsutism (in females) or gynecomastia (in males) are present/absent
    - AIMS (see section 6.10.3.4)
    - SAS (see section 6.10.3.4)
    - Uniformly elicited events of special interest (See section 6.10.3.6)
    - Suicidality - using DASS
    - Assess for adverse effects as follows:
        1) AEs with mild (grade 1) severity that SMC considers probably or definitely related to risperidone or aripiprazole and
        2) All AEs with moderate (grade 2) or higher severity regardless of relationship to risperidone or aripiprazole
        3) SAEs
- Notify SS of any changes in AEs or clinical presentation that they consider medically concerning on basis of this in-person assessment for reporting to PPPMP
- Review safety lab results when received from lab (see MOP)

6.6.1 Optional Blood Sampling for Future Unspecified Genetic Analyses

If the adult participant/parent/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)

6.6.2 At Selected Centers: Optional Pharmacokinetic Sampling Sub-study

If the parent/guardian consents for the participant to participate in the steady-state PK sampling and the participant meets the criteria for inclusion in the PK study (see Table 2, Section 6.11.3, 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. The PK sampling visit will last approximately 7 to 8 hours.

Study Staff (SS):

- Verify consent/assent for the optional PK study
- Verify participant has:
    - Taken the last 14 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
    - <18 years old at time of PK collection
- 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 sample for *CYP2D6* genotype at time of PK sampling
- Record all medications, including dosing and times for five days prior to PK sampling on the PK medication log
- Record times of all PK blood sampling and ingestion of risperidone or aripiprazole dose

For participants ≥6 years of age to be eligible for the PK sub-study, risperidone and/or aripiprazole must be prescribed for acute or maintenance treatment of a disorder within the FDA-labeled pediatric dose range for the participant's age at the time of the PK sub-study sample collection (See MOP).

6.6.3 At Selected Sites: Thank You Note Sub-study (Participants Eligible for the LAP01 Registry Only, see Section 21 in Appendix 4)

Participants who are enrolled in the LAPS trial and eligible for the LAP01 Registry (see section 21) will be included in the Thank You Note Sub-study. Participants may be randomized to one of the two Thank You Note arms at any time during the LAP01 study, but before offered enrollment

onto the LAP01 Registry. Thank You Notes must be provided prior to participant's LAPS Registry consenting visit or they will not be included in this sub-study. Participants will not be notified of the Thank You Note sub-study, or of their randomized assignment. Participants will be randomized 1:1 to one of the following arms:

1. Thank you note
2. No thank you note

Randomization will be stratified by site. Staff will be notified of randomization assignment for the sub-study for each participant and will distribute study approved Thank You note documents as described in the MOP.

The sub-study serves to address one of the exploratory objectives of the trial, namely, to describe the difference in Registry enrollment between the two groups described above. Additional details regarding the randomization procedure will be provided in the statistical analysis plan.

6.7 Assessments Related to Premature Withdrawal from Study, Change in Medication or Pregnancy

If during a monthly remote interim contact, an unscheduled contact with the parent/guardian and/or participant, or a M6 or M18 scheduled in-person visit, the site becomes aware that the parent/guardian and/or participant is considering premature withdrawal from the study or that the a participant has stopped, added, or switched antipsychotics or prescribed weight change medications, or that the participant is pregnant, the SS should attempt to obtain all the assessments normally obtained at the M12 and M24 visits as soon as possible and ask the parent/guardian to complete all of the questionnaires prior to or during the visit if possible.

If the site staff is informed during the M6 or M12 visit and the participant is not fasting, the SS should determine if the participant is willing to come back within a few days to obtain fasting safety labs. If not, non-fasting labs should be obtained during the visit.

If the information becomes available during a remote contact, the parent/guardian and the participant will be asked to participate in an unscheduled in-person visit as soon as possible. At the unscheduled, in-person visit, all procedures done during a regular in-person annual (M12 or M24) visit (see section 6.6) should be performed, if possible. However, the order of priority for assessments is weight, height, BP, pulse, clinical laboratory evaluations, changes to antipsychotic or prescribed weight change medications DASS, AIMS, SAS, uniformly elicited events of special interest, and AEs. If some of the procedures can't be performed while in the clinic, the SMC should contact the parent/guardian/participant by phone and complete as many of the remaining assessments as possible. If the participant does attend the in-person unscheduled visit, the SS will provide the PPPMP with the laboratory results and any changes in AEs or clinical presentation that the SMC judges to be medically concerning based on his/her in-person assessment of the participant (see section 8.12).

If the participant will not attend an unscheduled in-person visit, the participant and his/her parent/guardian will be asked if they are willing to come in to obtain the participant's weight, height, and/or labs and to speak on the phone with the SMC to complete questions related to the antipsychotic log, uniformly elicited events of special interest, AEs, and DASS.

If the participant won't come in to obtain weight, height and/or labs, study staff will make a reasonable attempt to obtain height and weight records from the PPPMP or other primary care

physician. The SMC will notify the SS about any information that needs to be shared with the PPPMP.

6.7.1 Procedures Unique to Premature Withdrawal from the Study

If a parent/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 parent/guardian/participant continues to feel that it is most appropriate to withdraw, SS should request that they attend an unscheduled in person 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 M24 visit, unless permission to obtain this information is withdrawn.

6.8 Unscheduled Assessments Related to Serious Adverse Event

If the SS becomes aware of a potential SAE, they will discuss the potential SAE with the SMC. SS will obtain necessary information to complete SAE form and this may include obtaining medical records. The SMC will determine what additional actions are needed and if an unscheduled in-person visit should be scheduled. At an unscheduled, in-person visit triggered by an unresolved SAE, the SMC should determine what assessments are needed for medically appropriate follow-up of the SAE. It is suggested that the Uniformly Elicited Events of Special Interest and AE Form and information about antipsychotics and prescribed weight change medications be collected.

6.9 Missed Assessments

If a participant and/or his/her parent/guardian are unable or unwilling to complete a scheduled procedure, visit or remote contact within the visit window, or indicate that the number or frequency of visits/contacts 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/parent/ guardian should be encouraged to complete as many assessments and/or as many procedures related to a scheduled visit as possible. Priority should be placed on completing the M24 assessment and notifying the study team when antipsychotic medications are stopped or changed so that the SS can obtain participant weight and height 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, contacts or procedures within an assessment will be documented on the Data Collection Forms (DCF) and Electronic Case Report Forms (eCRF) but will not be considered protocol deviations.

6.10 Assessments and Procedures

6.10.1 Diagnostic (to be completed by SMC with input from parent/guardian and participant)

The SMC will record indication for treatment based on parent/guardian report of indication, PPPMP information or record review, and their clinical judgement. The current or past diagnosis of an eating disorder will be determined similarly.

6.10.2 Medication Related (to be recorded by SMC with input from parent/guardian and participant)

The SMC will document medications based on discussions with the participant and participant's parent/guardian during in-person assessments. Changes described in the parent/guardian's response to the monthly remote interim contacts occurring between in-person visits will be reviewed by the SMC during the next in-person visit and recorded accordingly.

The Site Staff will record

- All prior antipsychotic medications with approximate start and stop dates to the extent possible
- Antipsychotic medications, metformin and prescribed weight change medication with doses and approximate stop and start dates throughout the study

6.10.3 Assessments of Potential Adverse Health Risks or Adverse Events (to be completed by study staff and study medical clinician)

6.10.3.1 Height, Weight, Sitting Blood Pressure and Pulse

In order to maintain the most accurate measurements possible a height, weight and vital signs log will be maintained for each participant. These assessments from each in person visit will be reviewed by SS in comparison to prior data 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).

At each in-person visit, the participant will be weighed. His/her height will be measured three times and all three height measurements recorded. Mean height will be derived; BMI and modified BMI z-score will be derived from the height, weight, sex and age based on the 2000 CDC Growth charts, but using the modified z-score, which is more sensitive to changes in obese children.[31,54]

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. Hypertension will be defined using the National Heart, Lung, and Blood Institute (NHLBI) normative data.

Orthostatic vital signs will be obtained only if the participant or parent/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.

6.10.3.2 Clinical Laboratory assessments

Please see section 6.11.1 for details of sample collection. Clinical laboratory results in the ranges identified by the PTN Laboratory Toxicity Table require assessment for clinical significance by the SMC or a delegated licensed clinician. SMC or delegated licensed clinician will acknowledge review of lab results after receipt from lab with signature and date. The PTN Laboratory Toxicity Table is available on the BPCA website.

6.10.3.3 Focused physical examination

The examination will focus on detecting the presence/absence of acanthosis nigricans, hirsutism in females, and gynecomastia in males and a targeted neuromotor exam to complete AIMS and SAS.

6.10.3.4 Neuromotor assessments

Two 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).[55] 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 pseudo-parkinsonism and akathisia. SAS scores can range from 0–40, and each item is assessed on a 5-point scale.[56] 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).[57] There is also a single item to assess akathisia, rated on the same 5-point scale, that will be reported as separate outcome.

6.10.3.5 Suicidality Assessment - DASS

The Developmental Appropriate Suicidality Scale (DASS) will be used to assess suicidality for this study.[58] The SMC makes 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 parent/guardian will be queried at each in-person visit regarding thoughts, 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. If the participant does not understand the concepts of death and suicide in the SMC's clinical judgement, only the parent/guardian questions are asked. If there is any sort of positive response, additional clinical information is obtained and recorded. The SMC will determine the severity and frequency of each event. All significant changes from past medical history in suicidal ideation and non-suicidal self-injury will be reported. All suicide attempts will be reported. Any suicide attempts that are life-threatening and/or result in inpatient hospitalization will also be reported as SAEs.

6.10.3.6 Uniformly Elicited Events of Special Interest

A standardized semi-structured interview will be used by the SMC to assess events of special interest in all participants at every in-person visit.[51] The form queries for potential hospitalizations, emergency department visits, and urgent care visits and for pregnancy. The form also evaluates frequent or especially concerning adverse effects seen with antipsychotics including behavioral events. The SMC will indicate whether the event did not occur, occurred but is not an AE (e.g. fatigue after staying up all night during a sleep over), or occurred and is considered an AE. In the last case, if the AE met the study's guidelines for completing an AE form, it would be entered in the AE report form.

The targeted conditions being solicited include the following:

Sedation	Increased sleep	Problems with attention, thinking or learning
Insomnia	Arrhythmias	Light-headedness (Orthostasis vs Vertigo)
Seizures	Increased appetite	Decreased appetite
Tics	Tremors	Parkinsonian symptoms
Akathisia	Drooling	Dyskinesia
Polydipsia	Polyuria	Enuresis
Galactorrhea	Amenorrhea	Sexual dysfunction/anorgasmia
Diabetes	Fractures	Menorrhagia
Lack of satiety		

6.10.3.7 Adverse Events

At all in-person visits, the SMC will observe the participant, complete the Uniformly Elicited Events of Special Interest interview, and query the participant (if able to understand questions) and parent/guardian regarding new medical or behavioral concerns or problems, and changes in pre-existing medical or behavioral problems since the prior in-person visit. The clinician will then determine the severity/grade of any medical occurrences and, to the extent possible, the relationship between the medical occurrence and risperidone or aripiprazole. Potential AEs related to laboratory collections or physical exam will be reviewed. All medical occurrences of mild (grade 1) severity that are considered by the SMC related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater severity, that are not part of past medical history, regardless of relationship to aripiprazole or risperidone will 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 Quality of Life Outcomes

Specific outcomes are completed as noted until the participant becomes of legal age. When the participant becomes of legal age, the SMC will determine if participant is cognitively and developmentally able to give consent for parent/guardian to complete PedsQL, SWQ and remote interim contacts. If so, able adult participant must provide consent for parent/guardian to complete these, before parent/guardian does so. The able adult participant may consent for the parent/guardian to complete the SWQ and/or remote interim contacts or may do so him/herself. If able adult participant does not consent for parent/guardian to complete the PedsQL, it will not be collected and will be missing. The adult participant will never complete the PedsQL to avoid rater variations between parent/guardian and participant. If the participant is of legal age, but the SMC determines him/her not to be cognitively and developmentally able to give consent, the parent/guardian will continue to complete the PedsQL.

6.10.4.1 Parent Completed 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.[59,60]

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 parent/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 parent/guardian will be asked to complete the parent version for reporting on the participant's quality of life. Quality of life measures have been shown to be important outcome measures in adult schizophrenia health outcomes.[61]

6.10.4.2 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.[62] 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 for at least 3 facial expressions, this measure will be omitted for that participant and considered as missing data. Participants who clearly understand the concepts and faces may subsequently complete the form on their own. Those who have difficulty communicating will continue to complete with SS.

6.10.4.3 Caregiver Strain Questionnaire (CSQ)

This 21-item questionnaire with a categorical scale ranging from 1 (not at all a problem) to 5 (very much a problem) assesses the caregiver's quality of life, and is completed by the guardian. 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 subscales for both objective strain (items 1–10) and a subjective strain (items 11-21).[63]

6.10.4.4 School and Work Questionnaire (SWQ)

This brief questionnaire is completed by the parent/guardian, with age-appropriate skip patterns. It assesses 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 assessment.[64]

6.11 Laboratory Evaluations

6.11.1 Clinical Laboratory Evaluations

The following laboratory evaluations will be conducted at each annual in-clinic visit (M0, M12, and M24) and at unscheduled visits for premature study withdrawal, medication changes and pregnancy. It is very strongly preferred that participants fast (i.e. no food or drink except for water or noncaloric beverages) for at least six hours prior to the blood draw. However, it is recognized that fasting may not be feasible in all situations (e.g., afternoon study visit). If a

participant is absolutely unable to fast prior to laboratory evaluations, this will not be considered a protocol deviation. 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 agents to reduce severe anxiety associated with phlebotomy per their standard of care. A central laboratory will be utilized, see MOP for details. The following labs will be assessed with separate results reported for fasting and non-fasting glucose and lipid panels.

- Glucose, BUN (blood urea nitrogen), creatinine, ALP (alkaline phosphatase), ALT (alanine amino transferase), AST (aspartate amino transferase). These will be drawn as part of a complete metabolic panel.
- Lipid panel that includes total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides
- 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 prescribed weight change medications (e.g., metformin). Outside funding will be sought for these genetic analyses. No analyses will be undertaken prior to obtaining IRB approval.

Parents/guardians of participants will not be informed of genetic results. Detailed information is in the MOP.

Participants/parents/guardians who previously consented to this optional whole blood collection, including those who become legal adults 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/parent/guardian withdrawing consent will not be destroyed.

6.11.3 Whole Blood Samples for Pharmacokinetic Analysis and CYP2D6 Genotyping in the 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. Informed consent for collection of these PK samples will be obtained before participants are enrolled in this sub-study. 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 and inclusion criteria 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
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 confirmed that they have taken the same dose of risperidone or aripiprazole as prescribed by the PPPMP over the 14 days prior to the PK sampling. In addition, the participant/parent/guardian will be instructed to record the date, time, and amount of all drugs 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). As outlined in the consent documents, after PK analyses for this sub-study have been completed, any remaining samples will be transferred to NICHD approved storage facility for unspecified future research, without additional consent from the participants.

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. Parents/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 and laboratory manual.

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 all participants at all in-person visits other than PK visits (described below), the SMC will only monitor current antipsychotic medications, metformin and prescribed weight change medications. No other concomitant medications will be recorded as they would not be analyzed and to reduce burden on participants and sites.

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
- Prolactin related outcomes (serum prolactin levels, gynecomastia in males)
- Neuromotor effects (assessed with quantitatively rated AIMS and SAS Scales)
- Suicidality (DASS)

Suicidal and self-injurious behaviors: Suicidal and self-injurious statements and behaviors will be assessed and documented at each in-person visit with the DASS. 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 that are life threatening or requiring hospitalization will be reported as an SAE.

8.2 Events of Special Interest Elicited via Study Outcome Measures

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, we are only reporting adverse events noted below. Specifically, we will only report outcome measures as AEs not included in section 8.1 above, if they meet one of the following criteria.

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:
- Suicidal events that are life-threatening or require hospitalization will be recorded as SAEs

The Uniformly Elicited Events of Special Interest semi-structured interview will determine if key events of special interest are absent, present but not determined to be an adverse event, or present and determined to be an adverse event. Those events of special interest that are determined to be adverse events will be reported if either 1) of mild (grade 1) severity and probably or definitely related to risperidone or aripiprazole or 2) of moderate (grade 2) or greater severity regardless of relatedness to risperidone or aripiprazole.[51]

8.3 Reporting of Pregnancy

Although not considered an AE, pregnancy must be reported on the specific pregnancy report form and 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 (section 8.1), 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 the uniformly elicited events of special interest, AEs, and abnormal laboratory results. Symptomatology related to the underlying diagnosis being treated is not considered an AE, unless it worsens significantly (compared to its severity and/or frequency as in past medical history) during the study. As noted in section 8.1 there are many potential AEs that are specific outcomes in this trial, which will not be separately reported as AEs.

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/stabilization of pregnancy or resolution/stabilization of 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 which the SMC determines worsen in a clinically significant way and are moderate (grade 2) or greater severity, will be reported as AEs.

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 or end of the study of the LAPS Trial, whichever comes first. Safety follow-up will not occur on the LAPS Registry. 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
- Routine hospitalization for labor and delivery are not reportable as SAEs.

8.6 Guidelines for Assessing Severity of an Adverse Event

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

1. **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.
2. **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.
3. **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 antipsychotic drugs being administered 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 24-month study follow-up 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 adverse 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 data system within 7 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

In accordance with the study Transfer of Regulatory Obligations (TORO), the Medical Monitor will assess each reported SAE and make recommendations to the IND Sponsor and study leadership on whether the SAE meets expedited reporting criteria in 21 CFR 312.32. The IND sponsor is responsible for making the final determination regarding the need for expedited reporting, and the IND Sponsor and DCRI are responsible for approving the final submission. The DCC 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.

8.9.3 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. 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, unless the participant or parent/guardian withdraws consent to follow the outcome. All other AEs that have not resolved, except those identified at the M24 visit, will be followed-up at the next scheduled in-person visit (i.e., in ~6 months). Any AEs present (not simply identified, but resolved) at the M24 visit that are not SAEs will not be followed-up and will have the status of “ongoing event” recorded at that time.

All pregnancies are followed until an outcome is known. Any pregnancy ongoing at the time of data lock will have the status of “ongoing event” recorded in the database, however the outcome is captured outside the database for supplemental reporting.

8.10 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.

8.11 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.

8.12 Reporting Adverse Events to the Participant’s Personal Provider

The study site will share all of the participant’s study laboratory results and those changes in AEs and in the participant’s clinical presentation that the SMC feels are medically concerning based on his/her in-person assessment of the participant with the participant’s PPPMP. If the SMC feels that a new or worsening condition, which he/she feels is medically concerning, might be related to the antipsychotic dose, he/she will share the FDA indicated dosing information with the participant’s PPPMP.

Finally, the parent/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.

8.13 Reporting Concerns or Abnormal Clinical Laboratory Results to the Parent/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 parent/guardian (and participant if appropriate) 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 parent/guardian during or after the study visit and encourage the parent/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, source documentation, 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. A separate monitoring plan will be established for the LAP01 Registry.

9.2 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.

9.3 Statistical Endpoints

9.3.1 Primary Endpoint:

The primary endpoint is pathological weight change as reflected by longitudinal change in the modified BMI z-score from baseline over 24 months. 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 24-month study period within each treatment group. Change from baseline to month 24 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 baseline visit with at least one follow-up visit and will combine data from participants in both the main trial, as well as the registry. The primary endpoint analysis will only use data from in person visits and not remote assessments. 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 baseline 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.

9.3.2 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.

9.3.2.1 Additional Weight Change Endpoints

Change in BMI category (underweight, normal, overweight, obese, severely obese [≥99th percentile]) over specific time intervals will also be analyzed to complement the primary outcome measure. Data obtained after a participant becomes pregnant will not be included in these analyses.

9.3.2.2 Additional Safety Endpoints

Secondary safety endpoints of special interest are

- Metabolic measures associated with risk of diabetes and cardiovascular disease
  - Clinical laboratory evaluations for high-sensitivity C-reactive protein (hs-CRP); hemoglobin A1c (Hgb A1c)
  - Presence of acanthosis nigricans or, in females only, hirsutism on physical exam
- Prolactin related outcomes
  - Clinical laboratory change of serum prolactin
  - Incidence of gynecomastia in males on physical exam
- Uniformly Elicited Events of Special Interest
  - Conditions specified in section 6.10.3.6
- Adverse effects
  - Serious adverse events (SAEs)
  - Adverse events (AEs) of mild (grade 1) severity and related to risperidone or aripiprazole
  - All AEs of moderate (grade 2) severity or greater regardless of relatedness to risperidone or aripiprazole
- Suicidality
  - Assessed using DASS
- Neuromotor effects
  - Abnormal Involuntary Movement Scale (AIMS)
  - Simpson Angus Extrapyramidal Symptoms Scale (SAS)

Changes in metabolic measures, prolactin outcomes, suicidality and neuromotor symptoms will be examined over time. Data for neuromotor symptoms will include those obtained after a participant has become pregnant.

9.3.2.3 Quality-of-Life Endpoints

Potential quality of life benefits of multi-year risperidone or aripiprazole treatment will be assessed by examining change over time in key outcomes. These outcomes include: quality-of-life scales (PedsQL-G, SWQ and DTFS), reflecting the participant's quality of life and completed by the parent/guardian and participant respectively; and the CSQ, reflecting the parent/guardian's quality of life. Analysis for PedsQL outcome will combine data from participants in the main trial, as well as registry. Data for these analyses will include those obtained after a participant has become pregnant.

9.3.2.4 Pharmacokinetic Endpoints:

Clearance (CL), volume of distribution (V), area under the curve (AUC), elimination half-life ($T_{1/2}$), maximum concentration (Cmax), and time of maximum concentration (Tmax) 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.

9.3.3 Exploratory Endpoints:

9.3.3.1 Thank You Note Sub-Study

The exploratory outcome of the randomized Thank You Note Sub-Study is the estimation of the proportion of participants enrolling in the registry among the two randomized groups. The proportion of participants enrolling in registry from each group is calculated by dividing the number of participants who enroll in the registry by the total number of participants at participating sites which take part in registry study.

9.4 Populations for Analysis

Primary analysis population will be defined as all enrolled participants in the age group of 6-<18 years old, from both the main trial and registry, 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.

The analysis population for the exploratory aim of Thank You Note Sub-study will include all eligible LAPS Registry participants (see Appendix 4) enrolled at the sites participating in the registry.

9.5 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, metabolic lab, prolactin related outcomes or suicidality 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, and changes in key safety outcome measures including labs.

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.

9.5.1 Baseline Descriptive Statistics and Participant Disposition

Descriptive statistics will be calculated to summarize demographic and other variables from the initial baseline 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 baseline and month 24 assessments, but do not complete all interim assessments, and the number who do not complete the month 24 assessment will be reported. The number of participants who discontinue the baseline antipsychotic treatment prior to the month 24 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 parent/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.

9.5.2 Primary Analysis

The primary analysis will combine data obtained from participants in the main study and registry from baseline through 24 months of follow-up and will estimate long-term weight change evaluated through changes in modified BMI z-score measured longitudinally from baseline to 24 months. Modified BMI z-score will be derived 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 24-month study period will be evaluated, although the change from

baseline to month 24 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 baseline visit, gender, and estimated duration of exposure to any antipsychotic drugs and to risperidone or aripiprazole prior to the baseline 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.

9.5.3 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 baseline to occurrence of the event.

Clinical laboratory values and neuromotor assessments will be summarized using changes in quantitative values from baseline and proportion of subjects with changes to value that is clinically concerning. 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.

Uniformly elicited events of special interest will be summarized. The number or events at each visit and number of new events that were not reported at baseline visit will be summarized.

Rates of suicidality, significant changes in severity or frequency of suicidal ideation and non-suicidal self-injury will also 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”).

9.5.4 Exploratory Analyses

The objective of the exploratory analysis is to explore how various factors, such as age, gender, baseline weight, concomitant medications, genetic factors might be associated with the development of adverse events.

The objective of the Thank You Note Sub-study is to determine whether the use of thank you notes impacts enrollment in the registry portion of the study. The outcome for the sub-study is summarized in Section 10.1.3.1. A Chi-Square test will be used to determine if there are any significant differences in the proportion of enrollment between any of the 2 groups.

9.6 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.

9.7 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 24 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 month 24 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.[16,49] 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 baseline to month 24 or from month 12 to month 24 were evaluated with 95% confidence intervals. Bias was small in the one-year to two-year comparison, and the precision of estimates is thought to be adequate to identify large average increases in BMI through two 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 2-year visit by treatment group (1=higher BMI change, 2=smaller BMI change) under two different assumptions of variances (high or low) and N = 320 per group.

	Low Variance		High Variance	
Group (years)	Estimate	CI Width	Estimate	CI Width
1 (2 vs 0)	1 (0.97, 1.04)	0.08	1 (0.93, 1.08)	0.14
2 (2 vs 0)	0.61 (0.58, 0.65)	0.08	0.62 (0.54, 0.69)	0.14
1 (2 vs 1)	0.31 (0.29, 0.34)	0.08	0.31 (0.25, 0.37)	0.14
2 (2 vs 1)	0.11 (0.09, 0.13)	0.08	0.11 (0.05, 0.17)	0.14

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

10 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.

This study has received a Certificate of Confidentiality from the NIH. 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.

IRB-approved HIPAA Authorization language is combined in the consent/parental permission templates provided to study sites. Study sites may substitute their own institutionally-approved Authorization forms, according to site policy.

Study results will be shared publicly in accordance with NIH policies for the dissemination of clinical trial information for NIH-funded studies. In addition, statutory language in the Best Pharmaceuticals for Children Act requires the NIH to make redacted clinical study reports available publicly after completion of a BPCA study. In compliance with the BPCA regulations and NIH policies, de-identified data, redacted CSRs, and study results will be made available on the appropriate NIH websites, including the NICHD Data and Specimens HUB (DASH). The intention to disseminate study results, and the steps the study team will take to protect patient privacy in those public reports, are outlined in the IRB-approved consent documents.

11FUTURE 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. In accordance with the Federal Policy for the Protection of Human Subjects (the "Common Rule"), the plan to store and make these samples available for future research (without further consent from the participants), and the steps the study team will take to protect patient privacy, have been outlined in the IRB-approved consent documents.

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 but will be able to link to clinical information from the study.

Parents/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' parents/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.

12 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.

13 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.

14 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

14.1 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 regulations. So that bias is prevented, the investigator will choose participants in accordance with the eligibility criteria detailed in this protocol, and will not exercise selectivity.

14.2 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.

14.3 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.

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. However, although not part of the study, 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.

The IND sponsor or designee will provide the site 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 site investigator to the participants' parent/guardian. The informed consent document will be updated, and the participants' parent/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 parent/guardian or participant completed scales may be embarrassing or make the participant uncomfortable. All participants and parents/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 parent/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.

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 parent/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.

14.4 Potential Benefits

Physical benefits
Participants will receive laboratory assessments at no cost, which may provide important information about the participant's health. Proactive longitudinal assessment of weight, height, vital signs, and assessment scales for movement disorders will identify concerns in these areas and provide an opportunity for the participant's PPPMP to try to change the medication regimen to reduce such adverse effects. To facilitate these potential benefits, clinical laboratory evaluations, and changes in AEs and in the participant's clinical presentation that SMC considers medically concerning on the basis of his/her in-person assessment of the participant will be shared with the participant's PPPMP and, if requested, the participant's parent/guardian to facilitate treatment decisions. In addition, during interim monthly remote interim contacts, the participant and parent/guardian will be encouraged to contact the participant's PPPMP if they have any new concerns.

Psychological benefits
Participants and their parents/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 parent/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 monthly remote interim contacts, the participant/parent/guardian will be prompted to contact the PPPMP as soon as possible if there are concerns about side effects or behavioral/psychiatric problems. The prompts to contact the PPPMP with concerns are expected to increase the parent/guardian's ability to advocate for the participant and increase the participant's psychiatric and developmental well-being.

14.5 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 parents/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 or the participant's parent/guardian to read and note any questions after phone screening. SS will meet with the participant, if developmentally appropriate, and his/her parents/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 re -consenting 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 (of legal age) while participating in the study and who are capable of providing consent (as determined by the SMC) 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 participant and/or the participant's parent/legal guardian (as appropriate) for their records.

The rights and welfare of the participants will be protected by emphasizing to participants and parents/guardians that the quality of medical care the participant receives from his/her PPPMP or the site institution will not be adversely affected if they decline to participate in this study.

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

This study includes minor participants who may be enrolled in the study only with the consent of their parent/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 reaches the age of majority 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 permission form signed by the participant's parent/guardian. Sites should consult with their institution's policies regarding enrollment of participants who are unable to provide informed consent.

14.7 Informed Consent Documents

The informed consent documents 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, that participation is voluntary and can be withdrawn at any time, and contact information for the principal investigator and the ethical review board. In addition, all consent documents and privacy Authorizations 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 HIPPA 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 24 months and access to medical records at 24 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 withdrawing consent for future unspecified genetic analyses if participants' parents/guardians or participants, who become adults, wish to do so. The information will include the requirement that these requests should be in writing. Further information is in the MOP and the confidentiality section of this protocol.

15 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.

15.1 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. Sites should 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.

15.2 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 rated for severity, assessed for severity and causality, and reviewed by the site investigator or designee. Data collection is the responsibility of the SS and the SMC at the site under the supervision of the Site Investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

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

15.3 Data Capture Methods

Clinical data (including AEs and specified concomitant medications) will be entered into a 21 CFR Part 11-compliant internet data entry system provided by Emmes. 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.

15.4 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 and semi-structured interviews to elicit medication history, psychiatric and developmental diagnoses, events of Special Interest and suicidality, participant- and parent/guardian-completed rating scales, PK data).

15.5 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.

15.6 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.

15.7 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 including entire in-person visits due to participant or parent/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.

16 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.

17 APPENDICES

Appendix 1: Safety Studies of Antipsychotic Drugs

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

Study	Design	Duration	Weight Gain Related Findings
Gencer et al, 2008[32]	(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[38]	(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[39]	(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 months	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[36]	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[37]	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.
Pandina et al 2012[65]	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).
Calarge et al, 2014[16]	Open label FU of children initially treated with risperidone over 18 months (2 assessments)	18 months	BMI z-score decreased in the 18% who discontinued any antipsychotic, but increased in those who switched to another antipsychotic (%), and remained stable in those who continued risperidone. Mean prior exposure was 2.5 years.
Findling et al., 2012[39]	Randomized, double-blind trial lasting one year with subjects randomized to risperidone, olanzapine, and molindone.	12 months	Risperidone group gained a total of 11.0 kg over the course of 52 weeks, with ~ 50 % of the weight gain occurring during the first 8 weeks of treatment.

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).

Table 8: Drug of Interest and PK Relevant Concomitant Medications

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

Appendix 4: Long-term Antipsychotic Pediatric Safety (LAPS) Registry

18 REGISTRY BACKGROUND AND RATIONALE

18.1 Background Information

The long-term trajectory and consequences of weight gain and metabolic changes in children and adolescents are of significant concern given the increase in pediatric obesity and related health disorders.[66] Given the substantial increase in antipsychotic medication use in this population over the last two decades and the concern that exposure to antipsychotics can lead to weight gain, there is significant public health interest to characterize the long-term metabolic effect of antipsychotics in children and adolescents.[1,13-22] However, studies attempting to do this have been limited by a lack of generalizability, small sample size, and a relatively short period of follow-up.[14,16-18,21,25-33,35-39,67]

Given the deficiency of these studies and the critical need to examine specific endpoints related to endocrine and metabolic effects of antipsychotics, the Pediatric Trials Network (PTN) Long-term Antipsychotic Pediatric Safety (LAPS) Trial is enrolling children and adolescents (6 – < 18 years) treated with risperidone or aripiprazole in a 24-month, multi-site, Phase 4, prospective, observational safety study. The primary outcome is to evaluate the long-term pathologic weight changes associated with multi-year treatment of these antipsychotic drugs and secondary outcome is to evaluate select safety assessments of special interest including quality of life measures.

Because most of the disorders treated with antipsychotics are chronic and persist over time, many children will have prolonged exposure to antipsychotics into adolescence and adulthood. Therefore, continued tracking of metabolic, endocrine, cardiovascular, and quality of life outcomes beyond the currently enrolling LAPS Trial would be useful to assess the long-term health risks of early antipsychotic exposure. The use of real-world data (RWD) from electronic health records (EHRs), mobile platforms and applications, and digital devices may allow for this longitudinal tracking of pragmatic patient-related data. Combined with rigorous clinical trial data, the information extracted from RWD sources would help in understanding the long-term health outcomes of children and adolescents exposed to antipsychotics.

The development and implementation of a long-term longitudinal registry of real-world clinical data, quality of life outcome data, and traditional clinical trial processes from patients in the currently enrolling LAPS Trial would support this need.

18.2 Registry Rationale

The purpose of the LAPS Registry is to:

1. Extend collection of weight and height measurements from the LAPS Trial via traditional in-person site visits in order to evaluate long-term pathologic weight changes of antipsychotics and update product labeling by regulatory agencies.
2. Extend collection of pediatric quality of life data from the LAPS Trial via mobile surveys in order to evaluate potential long-term quality of life benefits of antipsychotics.
3. Collect real-world metabolic data from children and adolescents exposed to antipsychotics using mobile technology, digital devices, and EHR data.
4. Validate weight and height data collected via these RWD sources with traditional in-person site visits in order to evaluate the utility of RWD to generate regulatory-compliant data.

5. Develop a longitudinal data registry through an innovative and integrated approach of traditional clinical trial data with RWD sources to help collect long-term health outcomes of early antipsychotic use in children and adolescents.

19 OBJECTIVES

Objective	Outcome Measure(s)	Endpoint(s)
Primary: Evaluate the long-term pathologic weight changes associated with multi-year risperidone or aripiprazole therapy over a period of 36 to 62 months in children who were 6 to <18 years of age at the time of LAPS Trial enrollment	Modified Body Mass Index (BMI) z-score	Change in the modified BMI z-score over time in children 6 to < 18 years of age from M0 LAPS Trial in-person visit to R36 LAPS Registry in-person visit
Secondary: Evaluate the potential long-term quality of life benefits of multi-year risperidone and aripiprazole therapy in children who were 6 to <18 years of age at the time of LAPS Trial enrollment	Parent/guardian/former guardian/LAR completed Pediatric Quality of Life Inventory (PedsQL, 23 item) survey	Change in PedsQL outcomes over time from M0 LAPS Trial in-person visit to R36 LAPS Registry mobile data collection
Exploratory 1: Validate weight and height data collected from RWD sources with traditional in-person site visits in children on multi-year risperidone and aripiprazole therapy who were 6 to <18 years of age at the time of LAPS Trial enrollment	Weight and height	Concordance between weight and height collected over time from R0 LAPS Registry to R36 LAPS Registry in-person visits and mobile data
Exploratory 2: The feasibility of using EHR data collected via a mobile application for collecting long-term health outcomes.	• Demographics • Measurements and vital signs • Lab measurements • Clinical data	• Describe extraction and transfer completeness of proposed data elements (e.g. blank fields versus error fields). • Describe if extracted measurements, vital signs, and lab values are within the expected biological range. • Describe concordance of extracted height and weight values with height and weight values obtained from in-person study visits. • Describe the format and usability of extracted data.

20 STUDY DESIGN

This registry is designed to: (1) extend in-person data collection for weight, height, and blood pressure measurements for 36 months from the time of LAPS Registry enrollment, which could represent participation for up to 62 months after initial LAPS Trial enrollment; and (2) collect weight and height measurements, quality of life, laboratory, and clinical data from RWD sources such as mobile technology, digital devices, and EHRs for 36 months from the time of LAPS Registry enrollment. LAPS Trial participants who choose to enroll in the LAPS Registry will provide their consent.

Study Design

The LAPS Registry is a multi-center initiative that will longitudinally track in-person weight and height measurements and incentivized mobile application acquired weight and height measurements, metabolic, clinical, and participant-reported quality of life data in children who were 6 to <18 years of age at the time of LAPS Trial enrollment. The operationalization of the LAPS Registry will occur as outlined in the steps below:

1. Participants who enroll in the LAPS Registry by signing the registry consent will be provided with the following at the Month 0 (R0) visit that will coincide with the participant's last LAPS Trial visit:
    - Bluetooth digital scale for monthly weight checks.
    - Tape measure for obtaining monthly self-height measurements.
    - Access to a custom-built Pattern Health mobile application that:
        - Interfaces passively with the digital scale via Bluetooth.
        - Allows for participant-reported data input of monthly self-height measurements and semi-annual parent/guardian/former guardian/LAR completed PedsQL questionnaires.
        - Digitally tracks progress of required items through an incentivized virtual bank embedded into the mobile application.
        - Provides video and/or on-screen tutorials within the mobile application for participant activities.
2. Access to the Pluto mobile application will be provided at the R0 visit or at a subsequent in-person visit, as appropriate once the application is ready for deployment. This application will merge participant's EHRs and:
    - Provide participants with a centralized location for their medical records.
    - Allow for the extraction of the following elements from a participant's EHRs: (1) longitudinal real-world metabolic measures such as weight, height, blood pressure, HgbA1c, fasting and non-fasting glucose, total cholesterol, HDL, LDL, triglycerides, CRP, hs-CRP, serum creatinine, AST, ALT, ALP, total bilirubin, direct bilirubin, and GGT; and (2) clinical EHR data such as diagnoses, medications, and hospitalizations.
3. Data from both mobile applications will be transferred directly to a secure data warehouse managed by the Duke Clinical Research Institute (DCRI) on a monthly basis.
4. Weight, height, vital signs, and medication history data collected via electronic case report

forms (eCRFs) from annual traditional in-person site visits will be entered into the electronic data capture (EDC) system and transferred directly to the data coordinating center (DCC).

5. Weight, height, and parent/guardian/former guardian/LAR completed PedsQL data obtained from the Pattern Health mobile application and transferred into the secure data warehouse managed by DCRI will be sent to the DCC monthly for validation and/or clinical study report (CSR) submission to regulatory agencies.
6. Participant EHR data obtained via the Pluto mobile application and transferred into the secure data warehouse managed by DCRI will be sent to the DCC at the end of the LAPS Registry study for validation, submission to NIH Data Repository, and/or clinical study report (CSR) submission to regulatory agencies.
7. Select data elements from the LAPS Trial (demographics, weight, height, vital signs, PedsQL, metabolic labs, and medication history) plus weight, height, vital signs, and medication history data collected via eCRFs from annual in-person site visits from the LAPS Registry will be transferred from the DCC to the secure data warehouse managed by DCRI at the end of the LAPS Registry study.
8. Data that has been transferred to the secure data warehouse managed by DCRI will be cleaned and collated into a final functional data registry.

20.1 Study Duration

Each participant enrolled in the LAPS Registry will participate for 36 months. This could represent a total combined time of up to 62 months in the LAPS Registry and LAPS Trial.

21 STUDY POPULATION

21.1 Selection of the Study Population

Registry participants will be selected exclusively from the population that has enrolled onto the LAPS Trial.

21.2 Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Enrolled in LAPS Trial
2. Access to a personal mobile device (with Bluetooth capability and data or internet access) and willing to use it for the purposes of this study
3. Parent/guardian/LAR/participant has provided informed consent
4. Participant has provided assent/consent if developmentally appropriate and as required by the institutional review board (IRB)
5. Participant was part of the 6 to <18 year-old group in the LAPS Trial

Exclusion Criteria:

1. Participant has completed the M24 LAPS Trial Visit

22 STUDY PROCEDURES

Summary of Procedures

Table 9: Schedule of Registry Study Procedures Organized by Type of Visit

Study Procedure	R0 Registry In-Person Visit[1]	Mobile Data	R12 Registry In-Person Visit	Mobile Data	R24 Registry In-Person Visit	Mobile Data	R36 Registry In-Person Visit
	Month 0	Months 0-12 (±1 Week)	Month 12 (±4 weeks)	Months 12-24 (±1 Week)	Month 24 (±4 weeks)	Months 24-36 (±1 Week)	Month 36 (±4 weeks)
Registry informed consent	X						
Contact information	X						
Mobile application training	X						
Monthly digital weight	X[2]	X		X		X	
Self-reported pregnancy	X		X		X		X
Monthly self-height	X[2]	X		X		X	
In-person weight & height	X		X		X		X
Semi-Annual PedsQL	X[3]	X[3]		X		X	
Virtual bank	X	X		X		X	
In-person blood pressure	X		X		X		X
Medication history[4]	X		X		X		X
EHR data[5]		X		X		X	

[1] Will coincide with final LAPS Trial in-person visit
[2] Initial digital weight and self-height measurements to be obtained at first in-person visit for validation with in-person measurements, if possible.
[3] The first PedsQL at month 0 (R0) will be completed as part of the last in-person LAPS Trial visit and will be completed electronically in the custom built Pattern Health application.
[4] Antipsychotic medications and prescribed weight change medications known to be taken over the course of the study will be recorded.
[5] Includes measurements (weight, height, blood pressure); labs (HgA1c, fasting and non-fasting glucose, total cholesterol, HDL, LDL, triglycerides, CRP, hs-CRP, serum creatinine, AST, ALT, ALP, total bilirubin, direct bilirubin, GGT); and clinical data (diagnoses, medications, and hospitalizations)

22.1 R0 Registry In-Person Visit (Month 0)

The R0 LAPS Registry in-person visit will coincide with the last LAPS Trial in-person visit.

The following procedures will occur at the R0 LAPS Registry in-person visit (in addition to the procedures completed as part of the LAPs Trial) and will be recorded in the eCRF or collected virtually via mobile applications, whichever is appropriate:

- Registry informed consent/assent
- Contact information
- Pattern Health mobile application download, sign-up, and training
- Pluto mobile application download may occur at the R0 visit or at a subsequent in-person visit, as appropriate once the application is ready for deployment.
- Initial digital weight. Obtained at first in-person visit via Bluetooth digital scale.
- Self-reported pregnancy (in female participants with childbearing potential only). Initial self-height. Obtained at first in-person visit to validate self-measurement technique and manually entered into the Pattern Health mobile application.
- In-person weight and height. These measurements may coincide with the final LAPS Trial in-person visit. Record date and time of collection.
- Virtual bank. Point values will be assigned for each required action performed via the Pattern Health mobile application.
- In-person sitting blood pressure. Record date and time of collection.
- Medication history. Antipsychotic and prescribed weight change medication history will be recorded.

22.2 Mobile Data (Months 0-36)

The following procedures will be performed or collected virtually via mobile applications:

- Monthly digital weight. Obtained at home and passively transferred into the Pattern Health mobile application via Bluetooth.
- Monthly self-height. Obtained at home and manually entered into the Pattern Health mobile application.
- Semi-annual parent/guardian/former guardian/LAR completed PedsQL. Recorded at home and manually entered into the mobile application beginning at R6. The R0 PedsQL assessment will occur at the last LAPS Trial in-person visit.
- Virtual bank. Point values will be assigned for each required action performed via the Pattern Health mobile application.
- Electronic health record (EHR) data. Demographics, measurements and vital signs (e.g. weight, height, blood pressure), laboratory measurements (e.g. HgA1c, fasting and non-fasting glucose, total cholesterol, HDL, LDL, triglycerides, serum creatinine, CRP, hs-CRP, AST, ALT, ALP, total bilirubin, direct bilirubin, GGT), and clinical data (e.g. diagnoses, medications, and hospitalizations) will be extracted from an EHR-based mobile application called Pluto and transferred directly to the secure data warehouse managed by DCRI.

22.3 R12, R24, R36 Registry In-Person Visits (Month 12, 24, and 36)

The following procedures will occur at the R12, R24, and R36 LAPS Registry in-person visits and will be recorded in the eCRF:

- In-person weight and height. Record date and time of collection.
- In-person sitting blood pressure. Record date and time of collection.
- Medication history. Antipsychotic and prescribed weight change medication history will be recorded.
- Self-reported pregnancy (in female participants with childbearing potential only).
- Pluto mobile application download may occur at the R0 visit or at a subsequent in-person visit, as appropriate once the app is ready for deployment.

22.4 Missed Assessments

Missed in-person study visits, assessments or procedures will be documented on the eCRF, but will not be considered protocol deviations. Missed remote assessments, procedures, or other participant reported data elements will not be documented and will not be considered protocol deviations.

22.5 Assessments and Procedures

22.5.1 Weight, Height, and Sitting Blood Pressure

Weight measurements for the registry will occur at home by the participant or their parent/legal guardian/LAR and passively transferred via a Bluetooth digital scale to the Pattern Health mobile application in the participant's electronic mobile device. The mobile application will prompt participants to weigh themselves monthly via this method and instructions will be provided within the application using video and/or on-screen tutorials.

Height measurements for the registry will be collected at home by the participant or their parent/legal guardian/LAR and recorded manually in the Pattern Health mobile application on the participant's electronic mobile device. The mobile application will prompt participants every month to measure themselves via this method and instructions will be provided within the application using video and/or on-screen tutorials.

At each in-person visit, the participant will be weighed. In addition, his/her height will be measured three times and all three height measurements recorded. Mean height will be derived; BMI and modified BMI z-score will be derived from the height, weight, sex and age based on the 2000 CDC Growth charts, but using the modified z-score, which is more sensitive to changes in obese children.

At each in-person visit, blood pressure will be measured using appropriately sized BP cuffs while the participant is sitting. Hypertension will be defined using the National Heart, Lung, and Blood Institute (NHLBI) normative data.

22.5.2 Pediatric Quality of Life (PedsQL) Generic Core Scales

The Pattern Health mobile application will prompt participants every 6 months to have the parent/guardian/LAR complete the parent version of the PedsQL within the mobile application. Instructions will be provided within the Pattern Health mobile application using video and/or on-screen tutorials.

When the participant becomes of legal age, the SMC will determine if the participant is cognitively and developmentally able to give consent to continue participation in the study. If so, the able adult participant will be asked to provide consent to continue study participation, which will include the continuation of his/her parent/guardian/LAR completing the PedsQL. The able adult participant must provide consent before the parent/guardian/LAR can complete the PedsQL. The adult participant will never complete the PedsQL to avoid rater variations between parent/guardian/LAR and participant. If the participant is of legal age, but the SMC determines him/her not to be cognitively and developmentally able to give consent, the parent/guardian/LAR will also continue to complete the PedsQL.

22.5.3 Data Collection for Registry

This study develops a registry from data collection in children on multi-year risperidone and aripiprazole therapy who were 6 to <18 years of age at the time of LAPS Trial enrollment using data from traditional in-person sites visits and RWD from mobile applications, a digital weighing scale, and/or EHR data. The following data will be collected for the registry from traditional in-person visits or the Pattern Health mobile application:

- Demographics
- Weight and height
- Blood pressure
- PedsQL survey data

A subset of the registry data will also be collected directly from the participant's EHR via the Pluto mobile application. Data transfer will include data elements such as:

- Demographics
- Weight and height
- Blood pressure
- Hemoglobin A1c (HgbA1c)
- Fasting and non-fasting glucose
- Total cholesterol
- High-density lipoprotein (HDL)
- Low-density lipoprotein (LDL)
- Triglycerides
- C-reactive protein (CRP)
- High-sensitivity CRP (hs-CRP)
- Serum creatinine
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Total bilirubin
- Direct bilirubin
- Gamma-glutamyl transferase (GGT)
- Diagnoses
- Medications
- Hospitalizations

23 ASSESSMENT OF SAFETY

Safety will not be assessed or reported as part of the LAPS Registry. All use of anti-psychotics will be managed per standard of care.

Pregnancy is not exclusionary in the Registry protocol; pregnancy will be recorded but not followed within the context of this sub-study.

24 CLINICAL MONITORING

The BPCA-DCC will monitor data collected at the in-person LAPS Registry visits.

25 STATISTICAL CONSIDERATIONS

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

25.1 Statistical Endpoints

25.1.1 Primary Endpoint

The primary endpoint included in statistical analysis is pathological weight change as reflected by longitudinal change in the modified BMI z-score from M0 LAPS Trial in-person visit to R36 LAPS Registry in-person visit. This will include up to 62 months of data over the duration of the LAPS Trial and LAPS Registry. BMI will be calculated 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 analysis will estimate change over the study period within each treatment group (aripiprazole and risperidone). This change will be estimated using 95% confidence intervals. No formal hypotheses will be tested.

25.1.2 Secondary Endpoint

The secondary endpoint included in statistical analysis is change over time in PedsQL scale and is 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.

25.1.3 Exploratory Endpoints

The exploratory endpoints included in statistical analysis include validation of digital height and weight data (Section 25.1.3.1). Additional endpoints as described in Exploratory Objective #2 (Section 20) related to the registry, including feasibility of EHR data transfer via the Pluto mobile application, will also be analyzed, as determined appropriate, and are exploratory in nature.

25.1.3.1 Validation of Digital Height and Weight Data

The first exploratory objective is to validate weight and height data collected from RWD sources with traditional in-person site visits in children on multi-year risperidone and aripiprazole therapy who were 6 to <18 years of age at the time of LAPS Trial enrollment. The corresponding exploratory endpoint is the concordance between weight and height collected over time from R0 to R36 LAPS Registry in-person visits and weight and height from Pattern Health mobile data. The exploratory endpoint is primarily descriptive/exploratory in nature.

25.2 Populations for Analysis

Primary analysis population will be defined as all participants enrolled in the LAPS Registry in the age group of 6 to <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.

25.3 Analysis Plan

Event rates and longitudinal changes will be analyzed using both descriptive summaries and modeling approaches. Descriptive statistics will be calculated by treatment groups. 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. Descriptive summaries and the primary analysis will be performed using SAS software version 9.4 or later.

25.3.1 Baseline Descriptive Statistics and Participant Disposition

Participant disposition will be summarized. The number of participants who complete all scheduled study assessments; the number who complete the M0 LAPS Trial in-person visit, R36 LAPS Registry in-person visit, but do not complete all interim in-person visits; and the number who do not complete the R36 LAPS Registry in-person visit will be reported. The duration of each participant's treatment on each antipsychotic medication during the study period (M0 LAPS Trial in-person visit to R36 LAPS Registry in-person visit), as well as the total duration of any antipsychotic treatment during the study period, will be summarized based on the parent/guardian/LAR reporting of current medications and interval changes.

25.3.2 Primary Analysis

The primary analysis will estimate long-term weight change evaluated through changes in modified BMI z-score measured longitudinally from M0 LAPS Trial in-person visit up to R36 LAPS Registry in-person visit. Modified BMI z-score will be derived 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 study/registry period will be evaluated, although the change from M0 LAPS Trial in-person visit to R36 LAPS Registry in-person visit 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 LAPS Trial in-person visit, gender, and estimated duration of exposure to any antipsychotic drugs and to risperidone or aripiprazole prior to the M0 LAPS Trial in-person 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.

25.3.3 Secondary Analyses

Potential quality of life benefits of multi-year risperidone or aripiprazole treatment will be assessed by examining change over time in PedsQL score, reflecting the participant's quality of life and completed by the parent/guardian/LAR via the Pattern Health mobile application throughout the Registry duration.

Two summary scores will be computed as follows:

1. **Psychosocial Health Summary Score**, as the sum of the items divided by the number of non-missing items answered in the Emotional, Social and School Functioning Scales.
2. **Physical Health Summary Score**, as the sum of the items divided by the number of non-missing items answered for the Physical Functioning Scale.

If more than 50% of the items in the scale are missing, the scale score is not computed. For each of the two dimensions (psychosocial health and physical health), tables will be presented with n, mean (SD), median (min, max) scores at baseline, as well as mean and median score change over time. In addition, mixed effects modeling will be done for each scale, as summary scores can be utilized to measure change over time. The mixed effects model will have the change in score for each scale as the primary outcome and will adjust for antipsychotic drug and covariates of interest.

25.3.4 Exploratory Analyses

Exploratory Objective 1:
Agreement between height and weight data measured at in-person visits, and height and weight data from the Pattern Health mobile application will be evaluated using concordance analysis. Specifically, Lin's concordance correlation coefficient coupled with Bland-Altman plots, including the mean differences, 95% confidence intervals and the 95% limits of agreement will be used to quantify the level of agreement between each pairs of height/weight measurements collected from in-person visits and the mobile application. Pearson's correlation coefficients will also be presented.

Specifically, the following endpoints will be used to evaluate the equivalence of the weight and height measurements from the mobile application with weight and height measurements obtained at in-person visits:

- The paired difference (mean error) or log-transformed ratio between mobile application and in-person weight and height data
- Concordance correlation coefficient (CCC) between in-person measured weight and height data and mobile application collected weight and height
- The proportion of participants whose mobile application and in-person height/weight are within 10% of each other

Two sets of 95% confidence intervals will be calculated separately for height and weight, each set containing confidence intervals for the three endpoints listed above.

In addition, Bland-Altman plots will be graphed to compare the mobile application vs. in-person measured height and weight data. The limits of agreement, which are determined by the bias+/- 1.96 times the standard deviation, will be presented with these plots.

Exploratory Objective 2:

Descriptive analyses will be used to examine the feasibility of using the Pluto mobile application for EHR data transfer and studying real-world health outcomes of early antipsychotic use in children and adolescents.

26 PARTICIPANT CONFIDENTIALITY

Participant information will be extracted from the EHR in collaboration with the Pluto mobile application. Pluto will employ all reasonable means to not hold any PHI. Medical record information is stored locally on a participant's own mobile device and is only shared to consented designated parties. Pluto and LAP01 will work together to ensure that the use and disclosure of PHI obtained during the research study complies with the HIPAA Privacy Rule. Participant confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor, and their agents. This confidentiality extends to the clinical information relating to participating participants.

The mobile application used by Pluto will be password, touchID, or faceID protected to ensure that the participant consents to accessing the data. Data obtained by Pluto will be obtained through participant consent and will be stored locally on their own personal mobile device. However, it is always possible that a password-protected system may be compromised. If there is a known data breach, participants will be notified and told what information was compromised.

Participant access to the Pattern Health mobile application will be authenticated by secret token sent to their registered email address, plus their date of birth. Weight will be collected into the application via a Blue-tooth connected scale. All other data collected via the Pattern Health mobile application will be participant reported. Data collected by the Pattern Health application includes PHI and is encrypted at rest and in transit.

Data collected by the Pattern Health application is transmitted securely to the Pattern Platform via the Pattern API, and stored with the participant's profile, which includes the participant's full name, date of birth, email address, consent and assent documents. Data in the Pattern Platform may be accessed by study staff or authorized Pattern Health support staff via the Pattern Console web application, or via the Pattern API. All Pattern Health support staff are trained to ensure the confidentiality of participant data is maintained in compliance with HIPAA and study protocols.

27 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

27.1 Potential Risks

The risks associated with the registry are limited to the breach of confidentiality risk, described below.

Breach of Confidentiality
See section 15.3 of LAPS protocol.

27.2 Potential Benefits

Benefits to participating in the LAPS Registry include ongoing access to health information. By sharing the study data (via NICHD's Data and Specimen Hub (DASH)), children in the future may benefit.

27.3 Informed Consent Process

Informed Consent for the LAPS Registry will occur using a separate consent document. All participants who consent to the registry may already be consented to the LAPS Trial. The consent may also be signed at the time of initial Informed Consent to the LAPS Trial. Participants interested in participating in the LAPS Registry will sign consent using the Pattern Health mobile application or a web-based platform.

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 parents/guardians/LAR prior to signing consent/assent.

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 or the participant's parent/guardian/LAR electronically to read and note any questions. Study staff will meet with the participant, if developmentally appropriate, and his/her parents/guardians/LAR to further review the consent/assent forms, encourage them to ask any questions they may have, and answer those questions. The registry consent must be signed prior to performing any registry-specific procedures unless documentation of written consent is waived by the IRB of record.

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

Participants who become an adult (of legal age) while participating in the study and who are capable of providing consent (as determined by the SMC) 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 LAR who consents on their behalf.

A copy of the executed informed consent/assent documents will be given to the participant and/or the participant's parent/guardian/LAR via electronic correspondence for their records.

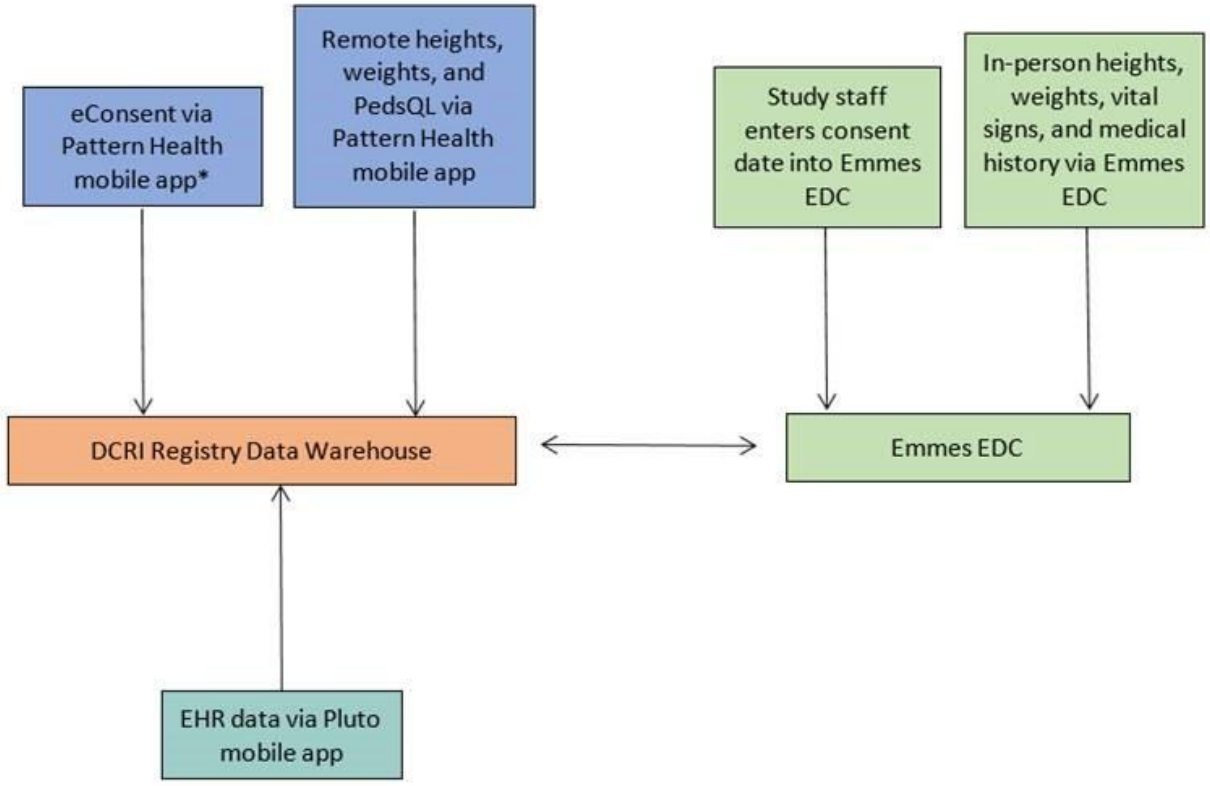
The rights and welfare of the participants will be protected by emphasizing to participants and parents/guardians/LARs that the quality of medical care the participant receives from his/her PPPMP or the site institution will not be adversely affected if they decline to participate in this study.

The assent process for the registry consent will occur as appropriate, as described, per protocol.

28 DATA HANDLING AND RECORD KEEPING

The investigator will conduct this study in accordance with the protocol, applicable state laws, and the ICH E6 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.

An overview of the data workflow is provided:



*eConsent may occur via Pattern Health web-based platform as a backup option

28.1 Data Handling

The investigator will ensure the accuracy, completeness, legibility, and timeliness of the data reported at in-person visits. Data collection forms (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. Sites should not erase, overwrite, or use correction fluid or tape on the original.

In-person visit 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.

Because the majority of data will be recorded remotely by participants through the mobile applications, sites will not have the same level of oversight for data collected remotely as the data collected during in-person visits.

The Pluto mobile application gives participants control and access to their personalized medical records on their personal device(s). Using encryption and API technology, Pluto will allow participants to access their medical records by mining the clinics and health care system EMRs. This data will then be aggregated from across disparate medical systems and the participant can then chose who to share their data with. For this study, data will be transferred from the participant's device directly to the DCRI's Registry Data Warehouse. The data will be transferred to the DCC at the end of the study.

Data collected via the Pattern Health mobile application will include participant-entered data and weight via a Blue-tooth connected scale. The Pattern Health mobile application is HITRUST certified and provides a secure platform for both the providers and participants. The Pattern Health mobile application holds data in a 21 CFR Part 11-compliant platform. Data held on the Pattern Health secure platform will be transferred to DCRI's Registry Data Warehouse at pre-determined increments.

An SQL Server database called the Master Data Management Repository will function as the 21 CFR Part-11 compliant DCRI Registry Data Warehouse.

28.2 Data Management Responsibilities

All CRFs must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Data collection is the responsibility of the SS and the SMC at the site under the supervision of the Site Investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

The Emmes Company, LLC. will serve as the DCC for the in-person data collection portion of the LAPS Registry and will be responsible for data management, quality review, analysis, and reporting of the study data. The DCRI, and/or their designee, will be responsible for data management and quality review, as needed, of the data collected via the mobile applications.

28.3 Data Capture Methods

Some of the data for the LAPS Registry will be collected directly from the participant or their designee via a mobile application. Data collected via the aforementioned mobile applications, Pluto and Pattern Health, may be transferred and merged to data collected in the LAPS Trial. This data will be managed by the DCRI. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

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