The Child Bipolar Disorder Network (CBN): A Collaborative Treatment Study of Youth With or at High Risk for Bipolar Disorder

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(1) Project Summary

The **Childhood Bipolar Network** (CBN) is a recently congregated consortium of 5 universities, all of whom have expertise in diagnosing, assessing and treating bipolar spectrum disorders (BSDs) in children and adolescents. BSD refers to bipolar disorder types I (with full manic episodes), II (major depressions alternating with hypomanic periods), or "otherwise specified" (variations between major depression and subthreshold manic episodes). With one year of funding from the Milken Foundation/Baszucki Brain Research Fund, we aim to show that the CBN is able to conduct a naturalistic study of youth with BSDs, with assessments and treatment according to a good practice protocol.

We intend to run the CBN over several years, but the objectives of the first year are to conduct a naturalistic treatment and follow-up study across four sites in the US (UCLA, Univ of Pittsburgh Medical Center or UPMC; Virginia Commonwealth Univ (VCU), and University of Colorado Anschutz Medical Campus (UC-AMC)) with the objective of expanding to sites outside of the US. The network will follow a cohort of up to 80 youth with BSDs for up to 12 months, using harmonized methods of assessment and treatment. The protocol will include standardized diagnostic interviews and rating instruments; a pharmacotherapy decision tool, with guidelines to help physicians on what medications to prescribe for what clinical presentations; and a follow-up assessment protocol, including telehealth interviews and rating scales and an online parent-rated instrument called the Parents' Online Weekly Evaluation and Rating Scales (POWERS) (Post et al., 2017).

(2) Specific Aims

The aims of the first year of this network are to (1) identify and reliably diagnosis youth (ages 9 yrs to 19 yrs) with BD I, II or otherwise specified BD (OSBD, formerly called bipolar disorder

not otherwise specified) across collaborative clinics in the US and Canada; and (2) examine predictors of treatment response in up to 80 youth (up to 20/site) with bipolar spectrum disorders (BD I, II or OSBD) followed over 12 months, using harmonized treatment methods and instrumentation. We will measure mood instability (rapid fluctuations in moods, even when youth are not in an illness episode) and an inflammatory marker based on a blood test (C-reactive protein) as predictors of outcome. Accomplishing these objectives will set up the infrastructure for open trials of novel treatments for youth at high-risk for BD spectrum disorders.

Year 1 has several milestones by which progress can be measured: protocol development, IRB approval, cross-site harmonization of assessment and treatment methods, validation of a mood instability phenotype, and development of an open trial infrastructure for novel treatments. Developing standardized procedures across study centers (and eventually, nations) is a critical component of developing treatment algorithms for use in a wide variety of health settings, with culturally heterogeneous populations of youth with or at risk for BSDs.

(3) Background and Significance

Cross-site networks have led to huge advances in the treatment of childhood diseases. Notably, the development of a pediatric cancer network has led to significant reductions in childhood mortality: doctors are now able to focus on dose optimization for individual patients rather than searching for new drugs to treat heterogeneous populations. Similar advances could come from a multi-center network devoted to understanding and treating pediatric bipolar illness. The timing for developing a collaborative bipolar network (CBN) is right because of advances in the reliable diagnosis of *syndromal BD* (types I or II) in children and adolescents and the identification and early treatment of youth at *high risk for BD*. Much of this work has been done at the member sites. Notably, investigators at University of Pittsburgh Medical Center (UPMC), VCU, UCLA, Colorado and collaborators have developed operational criteria for other specified bipolar disorder (OSBD), which presents in youth as brief and recurrent subthreshold periods of mania or hypomania. OSBD is a neglected bipolar subtype that is genetically and clinically very similar to BD I and II, but can be associated with psychosocial impairment that exceeds BD I and II

conditions (Goldstein et al., 2017). Risk algorithms developed at Pittsburgh indicate that youth with OSBD, depression, anxiety, and mood instability are at significantly increased risk for developing full BD I/II over 5-8 years, especially if they also have a family history of early-onset BD I or II (Birmaher et al., 2018; Hafeman et al., 2017).

Advances in psychosocial intervention research have also contributed to the need for a CBN. In randomized clinical trials with bipolar I/II adolescents and high-risk youth conducted at UCLA, Pittsburgh, Colorado, and Toronto, family interventions combined with pharmacotherapy have been consistently associated with better symptomatic and functioning outcomes over 2-4 years, compared with usual care (or individual supportive therapy) and pharmacotherapy (Miklowitz et al., 2021; Miklowitz et al., 2014; Miklowitz, Schneck, et al., 2020). Specifically, among youth at high risk for BD, the onset of new depressive episodes and suicidal episodes can be reduced significantly in the 2-4 years following a brief trial of family-focused therapy (Miklowitz, Merranko, et al., 2020; Miklowitz, Schneck, et al., 2020).

(4) Key Personnel Roster

Study investigators:

David J. Miklowitz, Ph.D. (overall PI), UCLA School of Medicine;

Site PIs: Danella Hafeman, M.D. and Boris Birmaher, MD, University of Pittsburgh School of Medicine;

Robert Post, MD, Consultant, George Washington University School of Medicine and Bipolar Collaborative Network;

Ekaterina Stepanova, MD, PhD, (site PI) and Robert Findling, MD,Department of Psychiatry, Virginia Commonwealth Univ, Richmond, VA;

Christopher Schneck MD (site PI), Melissa Batt, MD, and Aimee Sullivan, PhD, University of Colorado Anschutz Medical Campus, Aurora, CO.

Benjamin Goldstein, PhD, MD, PI, Toronto Centre for Youth with Bipolar Disorder (consultant on psychodiagnosis and assessment of inflammatory markers);

Statistician: John Merranko, MA, Univ. of Pittsburgh School of Medicine

5. Research Design and Methods

5a. Eligibility of Participants

Inclusion criteria:

1. Age between 9 years, 0 months and 19 years, 11 months
2. English speaking, although English need not be their first language
3. Diagnosis of bipolar I, II, OSBD, or cyclothymic disorder by structured interview;
4. Family availability (at least one parent can rate the CBN POWERS measure)

Children who are at high risk for BD (e.g., youth with OSBD) often have comorbid disorders, including anxiety disorders, ADHD, oppositional defiant disorder, or conduct disorders. Youth with these comorbid presentations will not be excluded.

Exclusion criteria:

Participants will be excluded if they have:

1) a DSM-5 diagnosis of autism or pervasive developmental disorder;

2) diagnosable substance or alcohol abuse or dependence disorders in the 3 months prior to study recruitment, although a lifetime history of substance or alcohol disorders can be present if the child has been abstinent for at least 3 months. We will not exclude

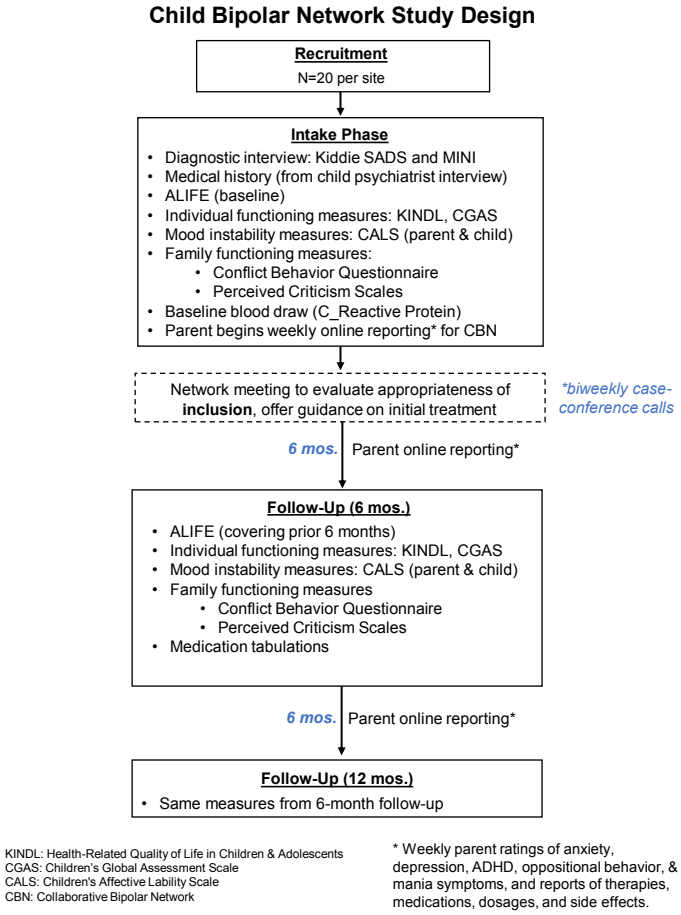
participants who are using only Cannabis regularly, as long as the participant does not meet criteria for a substance abuse or dependence disorder.

3) evidence of a life-threatening eating disorder or other medical disorder that requires immediate hospitalization or other emergency medical treatment;

4) evidence of current sexual or physical abuse of the child, and/or domestic abuse between the adult parents. These situations usually require notification and intervention by the Department of Child Services.

5b. Study Procedures

Below is a summary of study measures and their timing. Procedures for maintaining subjects' confidentiality and limiting access to subjects' identities are described in later sections.



KINDL: Health-Related Quality of Life in Children & Adolescents
CGAS: Children's Global Assessment Scale
CALS: Children's Affective Lability Scale
CBN: Collaborative Bipolar Network

* Weekly parent ratings of anxiety, depression, ADHD, oppositional behavior, & mania symptoms, and reports of therapies, medications, dosages, and side effects.

5.c. Recruitment

Participants at UCLA will be recruited and followed at the Child and Adolescent Mood Disorders (CHAMP) clinic, A floor, UCLA Semel Institute (D. Miklowitz, Dir). The clinic is equipped with psychiatric interview rooms, office and laboratory space, a medical exam room, and access to emergency psychiatry services.

When youth and parents are initially recruited for treatment in the CHAMP clinic, they have the option of signing a consent form that allows them to be contacted in the future about research projects for which they may be eligible. In addition, participants from prior studies who have provided written consent to be contacted for future studies may be contacted directly. The project coordinator will conduct all recruitment calls, which will be by phone or by Zoom (participant's choice). The participant's current therapist or physician will not be the one making this contact.

At the VCU site participants will be recruited at the Virginia Treatment Center for Children (VTCC). The VTCC has a wing specifically designated for clinical research with interview rooms, laboratory space for blood draws, exam room. This space is located in the same building with outpatient and inpatient psychiatric services.

Participants at the University of Pittsburgh will be recruited and followed at the Child and Adolescent Bipolar Spectrum Services (CABS) clinic. The program is part of Western Psychiatric Hospital of UPMC. The offices are equipped with all of the necessary computing software and hardware to complete the proposed research. Assessments for the proposed study will occur in private offices, either in person or virtually through a HIPAA compliant platform. If a psychiatric emergency should arise, the site PIs are well-trained to assess the need for higher level of care, and refer to appropriate treatment (e.g., emergency room, intensive outpatient program, etc.).

Participants at the University of Colorado Anschutz Medical Campus will be recruited from the Johnson Depression Center (a clinic serving children/adolescents up to adults) as well as the Summit Child Clinic (a general psychiatric clinic that has a child sub-clinic). The offices are equipped with all of the necessary computing software and hardware to complete the proposed research. Assessments for the proposed study will occur in private offices, either in person or virtually through a HIPAA compliant platform. If a psychiatric emergency should

arise, the site PIs are well-trained to assess the need for higher level of care, and refer to appropriate treatment (e.g., emergency room, intensive outpatient program, etc.).

We propose to recruit, diagnose, treat and follow 20 subjects at UCLA and at each of the collaborative sites, for a total of 80 subjects followed for up to one year. In light of recent research collaborations, several of the sites have already established infrastructures for conducting longitudinal and treatment studies of BD or high risk for BD in youth, and collectively, have adequate case flow to achieve the expected sample sizes. Based on our prior experiences, we expect that referrals will be of one of two types: (1) parents who have bipolar disorder who want to have their children evaluated for the disorder; (2) referrals of children with established BD, major depression, hypomania, or significant mood cycling that may meet our eligibility criteria.

It is likely that we will have study attrition (i.e., participants who agree to the study but, upon evaluation are found not to meet the diagnostic criteria; participants who move away before the study is completed or who leave the study for other reasons). Based on our past studies we are estimating that 80% of participants who sign the initial consent and assent forms will complete the 12-month study. Thus, we will need to recruit 25 participants/site to have a completer sample of 20/site.

On a monthly basis, a Network Oversight Committee consisting of the site PIs and consultants will review proposed participants that present diagnostic complexities, and decide whether the individual meets eligibility criteria for the study. Case information (i.e., results of the Kiddie Schedule for Affective Disorders and Schizophrenia, diagnostic interview) will be presented by the diagnostic assessor from the relevant site at these teleconferences, but no PHI will accompany this presentation (i.e., no names or other identifying information).

The Network Oversight Committee will also offer advice to the treating psychiatrist on appropriate medications, dosing, and adjustments. The treating physician will take these recommendations under consideration but will have the final say, in consultation with the parents and child, as to what treatments will be pursued.

5.d. Study advertising

All sites will place advertisements in local newspapers and on local radio stations, and post flyers online, on campus billboards and in selected community health clinics. Physicians, psychiatrists,

and social workers/clinic workers who have previously referred to the program will be made aware of this new study. Regular talks or workshops by study staff at community mental health clinics, primary care clinics, and churches or temples have generated referrals in the past.

UCLA has an established infrastructure for recruiting children into randomized trials, with UCLA ACCESS, which refers youths to specialty clinics and studies. Additionally, the Child and Adolescent Mood Disorders Program (CHAMP; www.semel.ucla.edu/champ) has a community presence, with a 10-year history of diagnosing and treating bipolar spectrum children and teens. The CHAMP Clinic, which has a staff of five licensed psychologists and three psychiatrists, assesses 2-3 new children or teens each week and verifies all diagnoses with structured diagnostic interviews. Referrals to the clinic have been generated by advertisements and community lectures given by Drs. Miklowitz and other staff members.

At the VCU site participants will be recruited through advertisements in the community, pediatrician offices, as well as clinicians' referrals from the outpatient clinic at the Virginia Treatment Center for Children. The VTCC outpatient clinic serves over 3,000 patients per year, resulting in over 14,000 visits. Additionally, children and their families that are currently participating in other research trials at the VTCC will be offered an opportunity to participate in this study. All referrals will be sent to the study coordinator.

The University of Pittsburgh offers several mediums for participant recruitment which include the CTSI Research Participant Registry/Pitt+Me, the CTSI Pediatric PittNet Network, and several outpatient clinics at Western Psychiatric Hospital, including the Child and Adolescent Bipolar Services (CABS) clinic.

As indicated above, participants at the University of Colorado Anschutz Medical Campus will be recruited from the Johnson Depression Center and the Summit Child Clinic, as well as through advertising and private referral.

5.e. Diagnoses

Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KSADS-PL; Kaufman et al., 2013, 2016). The KSADS-PL is a standardized, semi-structured diagnostic interview. Once the parents and youth have signed the consent and assent forms (see Consenting Procedures), a research clinician will administer the KSADS Depression

and Mania Rating Scales (scales adapted from the original KSADS that allow for (1) to (6) ratings of severity, instead of absent, subthreshold, or threshold). The KSADS will be administered to the child and at least one parent separately regarding the child's psychiatric history. The KSADS Depression and Mania Rating Scales will be followed with the MINI International Neuropsychiatric Interview (Sheehan, 2016) for DSM-5, child version, to classify anxiety, ADHD, oppositional, psychotic, and other disorders. The MINI consists of a series of questions about current and past psychiatric symptoms, each of which is rated as present or absent.

The entire diagnostic evaluation is expected to last 1.5 – 2.0 hours with the child and 1.5 - 2.0 hours with one parent. When discrepancies between child and parent reports occur, we will interview the child and parent together to determine a consensus rating. After reviewing the results of the KSADS and MINI, the study psychiatrist assigned to the case will conduct a separate psychiatric evaluation with the child and parent and then meet with the KSADS interviewer to make a best estimate consensus diagnosis.

The KSADS/MINI interviewer(s) will have undergone cross-site reliability training. Sites will decide whether the interview should be done by a single interviewer who interviews each person or by two interviewers, depending on personnel availability. Interviews may be conducted online using Zoom or anther university-approved, HIPPA compliant telehealth system. The diagnosticians will meet after the interviews and decide on primary and secondary consensus diagnoses based on all sources of information. If the child has prior medical records, we will obtain those after the child and parent sign a HIPAA release of information form.

5.f. Diagnostic Criteria for Inclusion

For a diagnosis of bipolar 1, the youth must meet DSM-5 criteria for at least one manic episode. They may or may not have had a major depressive episode previously, but DSM-5 only requires one prior manic episode. For a diagnosis of bipolar 2 disorder, the youth must have had at least one major depressive episode and one hypomanic episode meeting DSM-5 criteria.

For other specified bipolar disorder, we will use criteria adapted from the Course and Outcome of Bipolar Youth (COBY) study (Towbin et al., 2013), the presence of (1) or (2):

1. Subjects do not meet the DSM-5 criteria for BD-I or BD-II, but must have *recurrent, distinct periods* of abnormally elevated, expansive, or irritable mood plus the following: (1) two DSM-5 manic symptoms (3 if the mood is irritability only) that are clearly associated with the onset of abnormal mood, (2) a clear change in functioning, (3) mood and symptom duration of a minimum of 4 hours within a 24-hour period for a day to be considered meeting the diagnostic threshold, and (4) a minimum of 4 days (not necessarily consecutive) meeting the mood, symptom, duration, and functional change criteria over the subject's lifetime, which could be two 2-day episodes, four 1-day episodes, or another variation. Symptoms and mood changes that occurred during substance use or antidepressant treatment do not count toward a bipolar diagnosis.

2. A full hypomanic episode (i.e., a minimum of 4 consecutive days) without a history of a major depressive episode.

These brief periods of mania are often embedded in, or alternate with, periods of significant depression and/or irritability (i.e., mixed or dysphoric hypomania).

The following are not indicative of a hypomanic episode: multiple or extended temper tantrums in a day without accompanying symptoms such as decreased need for sleep, increased energy and activity, of grandiosity; or "rebound irritability" that occurs in ADHD when stimulants wear off.

5.g. Family History and Developmental Assessments

Family History Screen. We will ask each parent to talk about their own psychiatric history, as well as any such history in their parent(s), siblings, and other biological children. Diagnostic ratings will be made using the Family History Screen/Research Diagnostic Criteria (Weissman et al., 2000). The Family History Screen enables the interviewer to make ratings of each of the parent's first-degree relatives (all of whom will be first or second-degree relatives of the index child) on each of the various diagnostic categories (bipolar, schizophrenia, substance abuse, depression, etc), using a Family History RDC Scoresheet. Each first- or second-degree relative is rated on each

diagnosis as 0 (no diagnosis), 1 (possible), 2 (probable) and 3 (definite). There is a manual to guide these interviews.

General Information and Medical History Questionnaires. These questionnaires gather basic information about the child and family (e.g., parent's job and contact information, socioeconomic status), the mother's pregnancy and birth information relevant to the child, and the child's medical treatment history. These questions are standard in a good psychiatric evaluation.

The Pubertal Development Scale (Peterson et al., 1997) is a self-report questionnaire for children ages 10 and older to determine pubertal status at baseline and one year (prepubertal versus post-pubertal). It will be administered to the child at intake and at 12 months.

Autism Spectrum Disorders (ASD) Prescreen Questionnaire (Ehlers et al., 1999). This brief "true/false" screening measure asks parents to report whether the child has ever had symptoms of autism spectrum disorders, such as language impairment, social impairment, or repetitive/stereotypical behaviors. An example item is "Has your child ever said the same thing over and over in exactly the same way, or insist on you saying the same things over and over again?" Although this is unlikely to occur, children who score "true" on 6 or more items will be assessed with a lengthier pervasive developmental disorder assessment (a separate module of the KSADS-PL). Children who meet criteria for autism will be excluded from the study and given referrals for appropriate treatment.

Childhood Adverse Experiences. There is evidence that adversity in childhood, such as physical or sexual abuse, is associated with poor outcomes of childhood bipolar disorder and possibly, onset of bipolar I or II disorder in high-risk youth (Post & Miklowitz, 2010). To capture the variability in adverse childhood experiences, we will ask youths to fill out the Childhood Trust Events Survey – Children and Adolescents (long version 1.0; Oh et al., 2018). The inventory will only be requested at baseline. It contains the following instructions:

"It is important for us to understand what may have happened to you. The questions below describe some kinds of upsetting experiences. Since we give these questions to everyone, we list a lot of possible events that may have happened at any time in your life. If one or more of these experiences has happened at some time in your life, please circle Y for Yes. If not, circle N for No."

Example items include "Were you ever so badly hurt or sick that you had to have painful or scary medical treatment?" "Have you ever had a parent swear at you, insult you, put you down, or say hurtful things such as "You are no good," "You will be sent away because you are bad," or "I wish you were never born"? "Has someone in your home ever been physically violent toward you, such as whipping, kicking, or hitting hard enough to leave marks?" "Has someone ever touched your private sexual body parts when you did not want them to?"

The child is asked to estimate the age at which these events occurred, and to give a brief description. Children will be reminded that they do not have to answer any questions that make them uncomfortable. We will follow all state laws regarding reporting instances of childhood abuse or domestic violence, whether current or past.

5.h. Blood Draw and Inflammatory Marker Assays

Within 2 weeks after the initial interview is completed, study-eligible participants will complete a blood draw. Blood draws must be scheduled between the hours of 8 am and 11 am, and will be scheduled at a laboratory at the UCLA (or VCU, Colorado, or Pittsburgh) hospital. Following the blood draw, inflammatory cytokines (particularly C-Reactive protein, but also IL-1, IL-2, IL-6, IL-8, IL-10, TNF-alpha) will be obtained. The assays will only be obtained at baseline. The cytokine assays provide us with potential potent biomarkers with which to predict the course of early-onset BD and the response to pharmacological treatments.

5.i. Outcome Assessment Battery

A battery of symptom and functioning interviews and questionnaires will be administered at baseline, at 6 months, and 12 months. The measures are arrayed below, with information on the construct measured, the time period covered, and the respondent.

5.i.1. Child Functioning: Symptom Assessments

Parents' General Behavior Inventory, 10 item Mania Scale. This 10-item questionnaire measure captures subsyndromal depression or dysthymia, mania/hypomania, and biphasic or cyclothymic symptoms, each rated on a 1 (never) to 4 (very often) scale. Scores of 12 or above have the best positive and negative predictive power for bipolar spectrum diagnoses (Youngstrom et al., 2008). The scale will first be administered at baseline and again at 6 and 12 months.

Parents' Online Weekly Evaluation and Rating Scale (POWERS)**.** In the first 12 weeks of prospective observation, parents will rate their child on a weekly basis on a secure website developed from an active online protocol (Post et al., 2017). The secure website, called the Chorus Platform, is described below. The POWERS involves weekly ratings on a series of scales that range from 0 (symptom absent) to 4 (severe). Parents rate the child for the prior week on severity of anxiety, depression, ADHD, oppositional behavior, and mania symptoms. It includes reports of any therapies or medications used and side effects.

Chorus Platform. The "MyCoachConnect" mobile app was built using the Chorus platform. MyCoachConnect will be used to collect the POWERS data and the child's ecological momentary assessment data (below). Chorus is a web platform that allows individuals to create websites, mobile apps, and interactive text messaging. Chorus is hosted on a secured, SOC2 Type 2-compliant AWS server infrastructure and is HIPAA-compliant. Chorus has been used in over 50 IRB-approved research studies (many conducted at UCLA), including collection of PHI. All data sent to or from the server and Chorus apps are transmitted over encrypted, industry-standard connections like SSL. The server is protected using standard practices including being located behind a network firewall and accessible only by designated users. Data are regularly backed up. No data are stored locally on user's devices (such as local browser storage or temporary storage) that access Chorus apps.

Chorus has been approved by the UCLA Office of Information Security for use in research projects including those that collect protected health information, and is used by multiple IRB-approved studies at UCLA. Study staff will be able to export data in comma-separated format (CSV) from Chorus to the study's primary repository (a Semel network drive associated with the CHAMP program) for storage and analysis.

Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE). To examine the severity of youths' mood symptoms at each study interval, independent evaluators will administer the A-LIFE interview to the youth and one parent, and rate each week of the prior 6 month interval (i.e., 6 months prior to intake, then months 1-6 and 7-12) on Psychiatric Status Ratings (PSRs) of depression, hypomania, mania , and suicidality (Keller et al., 1987). The depression PSR is scored on a 1 (symptoms absent) to 6 (severe symptoms) scale, whereas the mania and hypomania PSRs

will be combined into a single 8-point hypo/mania scale ranging from 1 (no symptoms) to 6 (syndromal hypomania), with scores of 7-8 indicating severe or extremely severe mania. To enhance recall, interviewers query participants as to life events or seasonal change points (e.g., beginning of school year, holidays) during the retrospective interval that might have been associated with changes in mood. Interrater reliabilities (intraclass rs) for weekly PSRs for depression and hypo/mania in a past multisite study were 0.88-0.99, calculated across raters at three sites (Miklowitz, Schneck, et al., 2020).

The ALIFE will enable us to capture the timing of symptom recovery (depression and hypo/mania PSRs $\leq$ 2 for $\geq$ 8 consecutive weeks) and recurrence or first episode onset (PSRs $\geq$ 5 for $\geq$ 1 week for hypo/mania or $\geq$ 2 weeks for depression). We will collect data on the participant's variability in episode length to determine whether the criteria for OSBD capture the unique cycling patterns of youth who are at high risk for BD I or II.

5.i.2. Questionnaires

The following questionnaires will be administered to the youth and at least one parent at baseline, 6 months, and 12 months.

Mood and Feelings Questionnaire. At each major study interval, child participants will fill out the Child Self-Report Moods and Feelings Questionnaire (MFQ), Long Form, covering the prior 2 weeks (Costello & Angold, 1988). The MFQ consists of 33 items rated "not true" (0), "sometimes true (1) or "true" (2). Example items include "I didn't enjoy anything at all," "I thought about death or dying," and "I slept a lot more than usual." Parents will rate the parent version of the same form (e.g., "S/he didn't enjoy anything at all" in the past 2 weeks). The MFQ is an effective means of assessing suicidal ideation. It generates a depression score which helps discriminate youth who do and do not meet DSM criteria for a major depressive episode.

The Self-Report for Childhood Anxiety Related Disorders (SCARED), is a 41-item child-rated scale with five factors corresponding to different categories of anxiety and worry (Birmaher et al., 1997).

Drug Use Screening Inventory, Revised (DUSI-R). Although we will exclude youth with active substance misuse disorders, there will still be variability in use of illicit and licit drugs and alcohol. To supplement the K-SADS-PL module that assesses substance use, we will administer the DUSI-R (Tarter, 1990) questionnaire at baseline and at every follow-up (covering the prior month) to the child only. Participants are instructed to "darken the circle that applies to the number of times you have used each of the drugs listed below in the last month" (with range 0 – 20 or more times). Scores reflect gradations of severity and frequency of substance use.

Table 1. Summary of Assessment Instruments

Measure	Key Variable	Initial Interviews		Follow-up (every 6 mos. until 12 mos)	
		Child	*Parent*	*Child*	*Parent*
DIAGNOSTIC HISTORY					
KSADS-PL with Mania and Depression Rating Scales, plus MINI for comorbid disorders	Diagnosis and current symptoms; comorbid disorders	X	X		
Parents' General Behavior Inventory-10 item Mania Scale	Mood Symptoms, history of present symptoms or illness		X		X
Blood Assay	Inflammatory Markers	X			
General Information Questionnaire assessing psychiatric history	Treatment and medication history, SES		X		
Family History Research Diagnostic Criteria Screen	Family history of mood disorders in all 1st and 2nd degree relatives		X		
Autism Spectrum Disorders (One parent re: child)	Autism Score		X		
Childhood Trust Events Survey – Children and Adolescents (child re: self)	History of traumatic events	X			
FAMILY FUNCTIONING					
Perceived Criticism Scale (4 items)	Low/high expressed emotion	X	X	X	X
Conflict Behavior Questionnaire	Family conflict	X	X	x	x

CHILD FUNCTIONING					
A-Life (weekly Psychiatric Status Rating grid)	Depression and mania syndromal status	X	X	X	X
Ecological Momentary Assessment of Mood States (Chorus Platform)	8 mood items, queries every 2 hours for 7 days	X		X	X
Moods and Feelings Questionnaire	Depression/irritability	X	X	X	X
Parents' Online Weekly Evaluation and Rating Scale (POWERS) on Chorus Platform	Symptom severity weekly		X		X
Children's Affective Lability Score	Mood Instability	X	X	X	X
CGAS/CGI Severity	Functioning Scores	X	X	X	X
Drug Use Screening Inventory	Usage score	X		X	
SCARED Anxiety Q'nnaire	Anxiety score	X		X	
KINDL Quality of Life	Quality of life	X		X	
Treatment Utilization Form	Personal psychiatric service use		X		X
Physician's Report Form	Filled out by MD after every med visit				

5.j. Mood Instability

Mood instability is a behavioral phenotype that characterizes many disorders, but appears to have strong prognostic utility in early-onset BD. Mood instability refers to frequent, sudden, and unpredictable shifts in emotional states. We will use multi-method assessments to capture mood instability during various phases of the study.

1. The Children's Affective Lability Scale (CALS Gerson et al., 1996) is given in both child-rated and parent-rated versions. It consists of 20 items covering the prior 3 months: "Suddenly becomes tense or anxious…has bursts of being overly affectionate or silly….starts to laugh or cry…suddenly appears sad, depressed, for no reason." It is a measure of mood lability, and has subscores for elevation/activation, irritability, and anxiety-depression. It will be given to parents and children at each study interval.

2. Ecological momentary assessments. On six consecutive days (4 week days, 2 weekend days of the first week following the initial assessment), we will issue six prompts on the

weekend days and three prompts on the weekdays asking the child to rate themselves on eight emotions (e.g., anger, sadness), each on a 5-point Likert scale. These ratings will enable us to measure mood lability by modeling changes in negative and positive emotions across assessments. The queries can be set up using the Chorus platform. These 6 days of self-ratings will be collected at entry into the study, and again at six months and at 12 months (each scheduled for the week after the follow-up interview). Participants will be compensated $30 for completing these measures.

5.k. Psychosocial and Family Functioning Measures

The KINDL (Quality of Life Questionnaire for Children) (Ravens-Sieberer & Bullinger, 1998) is a 30-item parent- rated questionnaire that measures quality of life in the areas of physical health, overall sense of well-being, self-concept, family, friends, school, and when hospitalized, feelings about illness and treatment. Parent items are written so that they pertain to the child's quality of life. The KINDL requires approximately 5-10 minutes of the parent's time, and is only administered to one parent. The measure will be given at baseline, 6 months, and 12 months.

Perceived Criticism Scale. In the PC scale, child participants make a 1-10 weekly rating of "How critical is your (mother/father) of you?" and "When s/he criticizes you, how upset do you get?" PC is one of the most well-validated predictors of symptomatic outcome across a variety of disorders (Masland & Hooley, 2017). PC appears to measure how much criticism gets through to the child.

Conflict Behavior Questionnaire. At each follow-up assessment, child and parent participants filled out the Conflict Behavior Questionnaire (CBQ; Prinz et al., 1979), a measure of family functioning. The CBQ assesses the degree of aversive communication and conflict experienced in a child/parent dyad over the prior 3 months. The 20 scale items are rated "true/false" and cover argumentativeness (e.g., "At least three times a week, we get angry at each other"), frustration in communication, degree of empathy (e.g., "My mother understands me"), and relationship quality (e.g. "I don't think we get along very well"). The child fills out separate CBQs regarding conflict with each primary caregiver.

Treatment Utilization Form (Miklowitz et al., 2020). This brief form asks parents to summarize the child' use of health services in the last 3-6 months, including medications, psychotherapy, or other treatments. Parents also make a rating of the child's compliance or consistency with medication regimens.

6. Treatment Protocols

6.a. Pharmacotherapy for Primary Mood and Comorbid Disorders

The youth who enter this study will have had clinically significant elevations of depressive, manic, or hypomanic, or comorbid symptoms that will usually warrant psychopharmacological intervention. Psychiatrists associated with the study will undertake pharmacological interventions using good practice guidelines for high-risk youth (Schneck et al., 2017) and children or adolescents with established BD I or II (Yatham et al., 2018). If the child is not taking mood stabilizing or atypical antipsychotic medications, these agents may be started; if the child is already taking medications, they may be augmented with other agents or dosages increased. In some cases, an existing agent will be discontinued (e.g., a child is clearly rapid cycling following initiating an SSRI). We will not put the child at further risk by delaying medication treatment.

We will not require that the child take medicines to be in the study. They may be followed over time without taking medications, as long as we are able to collect information on medications and medication adjustments from their community psychiatrist. Youth and parents who opt to see their own doctors will be asked to sign HIPAA Research Authorization forms to allow this communication.

As indicated, there will be a **Pharmacotherapy Advisory Committee** available to the treating psychiatrist for consultations about treatment of complex cases. However, psychiatrists will not be under any obligation to follow a specific protocol; they will be encouraged to treat each child as per best community practice, as outlined in the above-cited guidelines.

If willing, all participants will be assigned to a psychiatrist upon entry into the study, with the understanding that the cost of care will be borne by the child/family's own insurance or other payment options the child's family has arranged. Psychiatric treatment is a regular part of the community care of bipolar disorder and would be necessary whether or not the child took part in

the study. These terms will be spelled out in the consent and assent forms.

In a baseline psychiatric evaluation, study psychiatrists will determine whether (a) medications need to be started, (b) current medications and dosages are appropriate, or (c) current medications need to be adjusted, augmented, or discontinued. Attempts will be made to preserve current regimens; that is, medications will be changed only if necessary, as determined by clinical, psychosocial or academic dysfunction of the child..

Because all study psychiatrists are experienced in the treatment of childhood mood disorders, we will maximize the chances that at-risk or fully syndromal children with BD are appropriately treated. Furthermore, there will be regular monitoring and monthly advisory sessions offered to study psychiatrists when treating complex patients.

During the study, pharmacotherapy can be initiated or modified at any time based on clinical need. If the patient is not taking any medications that would treat his or her condition, then new medications will be instituted, with the goal of decreasing acute symptoms to the point where functioning improves.

Participation in the study will help ensure that the child receives best-practice pharmacotherapy. However, the ultimate choice to start or change medications or dosages will lie with the participating youth and parent(s); no participant will be dropped from the study because of unwillingness to follow the prescribed medication plan.

6.b. Pharmacotherapy Decision Rules

The high-risk and bipolar I/II pharmacotherapy protocols were designed to clarify good clinical practice procedures in these populations. For example, when children have active manic symptoms associated with OSBD or BD I/II, it will usually be necessary to stabilize their mood symptoms before introducing a psychostimulant (Scheffer et al., 2005). Again, there is no requirement that children take any medications in order to be in the study; there are forms of prodromal bipolar disorder that are not severe enough to require medication.

The choice of medications will depend on the patient's current regimen, and his or her current psychiatric state. For example, if the patient has impairing ADHD symptoms and is not taking medications, we will offer to prescribe a psychostimulant or nonstimulant ADD medication and adjust as necessary. If the patient is currently taking an ADHD medication, we will recommend dose adjustments as needed. If the patient has manic symptoms requiring

treatment, we will consider treatment with an atypical antipsychotic, lithium, or another mood stabilizer. If the patient is already taking such a medication, we will recommend dose adjustments as necessary.

Treatment of depressive symptoms is often more complex. Current treatment guidelines suggest that severe depression may need to be treated with an SSRI antidepressant with careful monitoring for the emergence of suicidal behaviors or ideation or mania/hypomania. We recognize that in the population at high-risk for BD, participants are likely to be treated with SSRIs (Chang, 2010) and may be at higher risk of treatment-induced manic or mixed episodes. We will discuss with the family whether to begin treatment with an SSRI, an atypical antidepressant such as bupropion, or other agents used in the treatment of bipolar depression such as lamotrigine or lurasidone. These agents are considered appropriate treatments for children and adolescents with bipolar depression (Kowatch et al., 2005), and their use can be extrapolated to children with depression who are at high-risk for BD (Schneck et al., 2017). If an antidepressant is chosen, we will start with a relatively low dose and monitor carefully for any emergence of manic or mixed symptoms.

For those youth who are prescribed medications upon enrollment or are considering starting medications, we suggest the following parameters as a tool to help clinicians, as reflected in the most recent data on high-risk bipolar conditions (Post et al., 2020):

6.b.1. Prescriber support tool when making pharmacotherapy decisions

Prescribers may choose to begin pharmacotherapy with medications that have evidence from RCTs that support its use (depending on the polarity of the current episode). For example:

- For manic/mixed symptoms: risperidone, olanzapine, aripiprazole, quetiapine, ziprasidone, asenapine, lithium
- For depressive symptoms: lurasidone, quetiapine, lamotrigine, or an antidepressant

The dosing of the medications will be adjusted as clinically necessary and based on clinician's discretion. If the first agent does not lead to symptom resolution, it can be switched to a different agent from the same class or a medication from a different class.

The prescriber will note the rationale for choosing a particular medication on the Physician's Report Form (PRF). If the clinician believes that the medications with evidence for

pediatric bipolar disorder will only be partially effective in a particular patient, other agents (both those with and without FDA regulatory approval) may be considered as add-ons or substitute agents in the current regimen. In every instance, the rationale will be recorded for choice of this agent. The prescriber will also note the dosing of the medication, and the rationale for any deviations from regulatory guidelines.

For patients with comorbid conditions, prescribers will list the psychiatric comorbidities for which they are providing pharmacotherapy. The medications being used and their doses to treat those conditions will be recorded on the PRF. If medications are discontinued, the rationale for this decision will also be recorded by the prescriber.

6.c. Pharmacotherapy Training, Supervision, and Adherence Monitoring

During an initial study launch meeting in year 1 (online or in-person), the study physicians will be trained in the study guidelines for treatment of bipolar I, II, or OSBD patients with or without comorbid conditions. Drug treatment will be monitored throughout the study by the pharmacotherapy oversight committee (Drs. Schneck, Post, and Findling), who will have monthly conference calls with physicians to discuss complex study cases, decisions to modify treatments, and handle adverse events. Study physicians can receive additional supervision at any other time via teleconference or e-mail.

6.d. Monitoring Adverse Events

Psychiatrists will track any adverse events associated with medications on the Physician's Report Form. The independent evaluators, clinicians, and psychiatrists will record other adverse events (e.g., illnesses, car accidents) on the Adverse Event Form and enter it onto the UCLA REDCAP data capture system. Severe adverse events such as ER visits, hospitalization or suicide attempts, whether study related or not, will be recorded on this form and reported to the local IRB. The Adverse Event Form asks the respondent to describe the event, the likelihood that it is an effect of having a mood disorder, and the probability the event was caused by or related to the study treatments or assessments.

6.e. Psychosocial Treatments

Study psychiatrists and study coordinators will refer patients to appropriate psychosocial interventions as these become available either in the study clinics or in the community. Generally, psychosocial interventions will include psychoeducation and stress management (e.g., mood tracking, development of a relapse prevention plan). In some of the study centers, family interventions may be offered, involving combinations of psychoeducation, communication enhancement training, and problem-solving skills training. Mindfulness therapy groups, cognitive behavioral therapy groups, or dialectical behavior therapy will be offered when available and warranted. The psychoeducational interventions are add-ons to standard care. There are no randomized manipulations of treatments or placebo interventions.

6.f. Study Termination

Study participation will end after the 12-month follow-up. At that point, participants may opt to stay with their study provider (by mutual agreement); if an agreement cannot be reached, the clinician and study staff will provide appropriate referrals for pharmacological and psychological treatment and will continue to treat the participant until such treatment has been arranged. If a new psychiatrist is enlisted, we will send them a treatment report outlining the history of any medication adjustments made during the study. Disclosure of treatment information will require signed HIPAA authorization forms from the parent and child specifying what information will be disclosed and to which doctor.

7. Data Analyses

The data to be collected for this study are based on paper and pencil questionnaires, structured interviews, and pharmacotherapy sessions. Most of the measures have been widely used in studies of childhood mood disorders, including our own studies (Miklowitz et al., 2020). The data will be used only for the purposes of research.

Data used as part of this study will be stored primarily on a shared networking server provided by the UCLA Semel Institute. The network server is located in a locked server room and cabinet and complies with UCLA Health data security protocols and is approved for storage of protected health information. The Semel IT administrators perform regular and encrypted backups of the data. The server is protected using standard security practices including being located behind the UCLA firewall, accessible only by designated users from our staff located at UCLA or

connected through the UCLA VPN from an offsite location. Data transferred using devices (such as USB drives and laptops) will be encrypted following UCLA Health device encryption policies. Storage and access procedures are in full compliance with UCLA Health data security policies.

Our primary analytical techniques will be generalized linear mixed models (GLMMs) and survival analyses, run on an intent-to-treat basis. GLMMs estimate a slope and intercept for each individual and can handle missing data on key outcome variables. Our primary outcomes are symptom severity (i.e., the 1-6 ALIFE Psychiatric Status Ratings) and secondary are remission or recurrence (also recorded on the A-LIFE). The GLMM and survival models will be fit initially without covariates, following standard practices (Kraemer, 2015). We will use logistic regression to identify factors associated with attrition and data loss, and control for these factors in sensitivity analyses. We will protect against multiple comparisons by focusing on a limited set of a priori primary outcomes and contrasts and by reporting results within each hypothesis using false discovery rate procedures (Hochberg & Benjamini, 1990).

For example, when examining the association between study sites and study outcomes, we will code site as a between-subjects variable, symptoms (for example, ALIFE Psychiatric Status Ratings of depression) as the dependent variable, and study visit (baseline, 6 months, or 12 months) as the repeated time variable. These models will examine site by time interactions. There will be subject level random effects to account for individual variation in response trajectories. Covariates may include the child's sex, diagnostic status (bipolar I, II or OSBD), race, ethnicity, or socioeconomic status.

Secondary analyses will concern repeated dependent variables (e.g., parent POWERS ratings) computed from all relevant information at each time point, including information gathered through the MyCoachConnect mobile app. We will determine the degree to which inflammatory variables are associated with changes in symptom severity over 12 months. The correlations between data collected through MyCoachConnect and data collected through interviews and questionnaires will be examined using mixed effect regression models. Using all available variables, we will compute a clinical forecasting model consisting of inflammatory variables at baseline as predictors of symptoms at 0, 6, and 12 months.

7.a. Data Management, Programming Support and Statistical Consulting Services

Management of study data will be accomplished through the REDCAP system. REDCap is a secure, HIPAA-compliant online database that consists of password protected accounts. Demographic, psychiatric, and behavioral data will be stored in REDCap. Prior to analyses, the data will be exported from REDCap into another program such as Excel or R. The data will be immediately stripped of any identifiers (e.g., email, IP address) and the deidentified data will be stored on the UCLA server behind the School of Medicine firewall. All incoming data are purposely filtered, sanitized, and escaped.

REDCap also maintains a built-in audit trail that logs all user activity and pages viewed by every user, including contextual information (e.g., the project or record being accessed), data entry, data export, modifying a field, running a report, or adding/modifying a user. The built-in audit trail in REDCap allows administrators to be able to determine all the activity and all the data viewed or modified by any given user. The REDCap administrator is also available to assist with technical support on research projects. All requests for analysis of datasets must be approved by the PI and site PIs before they are accessed from REDCap.

The UCLA servers are located on the UCLA network behind the School of Medicine (Mednet) firewall and linked to the web server via an internal IP connection. All the servers have 256-bit SSL to provide security for transmission of any sensitive or confidential data and are backed up both locally (incrementally on a daily basis and the full system monthly) and off site (with an encrypted copy of the monthly full back-up image sent to AWS S3 storage.) In addition to the regular IT back-up, there is a secondary full daily back-up for programming code on the web server. The networking server features an hierarchical system of password protected logins.

Study personnel (e.g., Robin Brown at UCLA) will perform ongoing quality checks of the database, monitor the data correction process, and assist study staff with all aspects of system usage and other programming and IT needs. They will coordinate with the site project coordinators and independent evaluators (responsible for entry of paper/pencil forms) to coordinate the timely completion of data deliverables.

Data storage and access procedures will be in full compliance with UCLA Health data security policies. Data transferred using devices (such as USB drives and laptops) will be encrypted following UCLA Health device encryption policies. The default mechanism for electronically transferring files from the sites to UCLA, or from UCLA to individual sites includes either sending through encrypted connections (e.g., SSL/SSH/VPN) and/or encrypting files (256-bit AES

approved using software that supports .zip format, e.g. WinZip) into a single archive, in compliance with UCLA Health data security policies.

7.b. Analysis of Inflammatory Markers

We will examine whether inflammatory markers (C-reactive protein and cytokines such as IL-6 and IL-10) at baseline as a predictors of the symptomatic course of illness over 1 year. At UCLA, blood draws will be done by nurses from the Clinical Treatment Research Center (CTRC) and shipped to the Center for Pathology Services for analysis of inflammatory markers. First, whole blood samples are collected in EDTA tubes. After collection, the samples are centrifuged at 4°C, and plasma harvested into multiple aliquots, and then stored in a -70°C freezer until assayed. Plasma concentrations of inflammatory cytokines are measured in duplicate. Using a Bio-Plex 200 (Luminex) Instrument, Bio-Plex software v4.1, and a 5-parameter logistic curve fit, plasma levels of each cytokine are quantified by means of high sensitivity bead-based multiplex immunoassays (Performance High Sensitivity Human Cytokine, R& D Systems, Minneapolis, MN). All multiplex assays are performed on plasma samples diluted 2-fold according to the manufacturer's protocol, and all calculated concentrations ≥0.1 pg/mL generated by the BioPlex Manager software are included in data analyses. All observations deemed undetectable are assigned a value equal to one-half of the plate-specific lower limit and retained in the analysis.

8. POTENTIAL RISKS

This study will be of minimal risk to participants. There is a low risk of harm to youth with BD spectrum disorders from receiving the good practice pharmacotherapy procedures or assessment instruments outlined in this protocol. Pharmacotherapy is not required and when parents and children opt for it, the study psychiatrists will follow standards of best practice, as outlined earlier. Parents can enroll their child in pharmacological treatment from a physician of their choosing if they do not want to see one of the study-affiliated psychiatrists. In these cases, the study psychiatrist will conduct an initial diagnostic evaluation and recommend a treatment plan to the youth's outside psychiatrist, unless the family does not want this recommendation. Assessment reports generally consist of an evaluation summary followed by phone calls if the

outside physician would like further clarification. The youth and parents must sign our HIPAA release form for us to send this treatment information. Of course, the outside physician and family are under no obligation to follow the recommendations of the study psychiatrist.

Children and parents may at times feel inconvenienced by the time required to complete the research assessments. The assessment battery has been designed to minimize participant burden but to cover the domains and constructs relevant to the study's hypotheses (see table above). Participants will be compensated for completing each assessment battery ($40 for initial intake assessment, $20 for the 6- and 12-month assessments). Research interviews will be scheduled at the times (for example, after school; immediately following the medication visits) and locations most convenient for the youth and family, or (if participants prefer, or COVID safety regulations demand it) via a Zoom telehealth visit. Participants who leave the study early will still be paid for those research assessments completed up to that point. The default arrangement will be that compensation will be divided evenly between parents and children, although there may be cases where the family would prefer another arrangement.

Participants may at times experience sadness or discomfort when discussing family issues, personal problems, or psychiatric symptoms, but no more than they would if they took part in psychotherapy or pharmacotherapy sessions in the community. Discussing the child's psychiatric problems may at times be upsetting to the child or family. If these reactions occur, the research staff, all of whom are trained psychiatrists and psychologists will offer the participants emotional support and validation. Clinicians will acquaint the child and family with methods to manage and control mood symptoms and enhance day-to-day functioning. Participants will also be informed that they can receive and follow-up on referrals for counseling outside of the study at any time, without being dropped from the protocol.

The children and adolescents recruited for this study are believed to have already developed or are at high risk for developing BD. Children with BD are vulnerable to disturbances in school and social functioning, substance abuse, and suicidal ideation or actions. There is no reason to suspect that rates of these illness complications will be higher if the adolescent receives treatment in the study instead of a community treatment setting. Because of the careful pharmacotherapy and follow-up protocols administered in this study, rates of adverse events associated with the disorder may be lower than if patients were treated in the community.

Participating in alternative treatments in the community has its own risks. Treatment in the community often does not explore the illness management strategies relevant to bipolar spectrum disorders. Pharmacotherapy as practiced in the community will usually involve the same classes of medications as proposed here, but may not include the careful pharmacological oversight by experts provided in this study.

9. ADEQUACY OF PROTECTION AGAINST RISKS

9.a. Recruitment

Training of staff. All study research staff will be trained in recruitment and informed consent procedures before collecting data for this study. We will develop a study procedures manual that clarifies how to explain the study to participants and parents and address questions about medications, assessments, privacy, or other study-related matters. Training will require that study staff read through and discuss the manual and participate in role-plays of the recruitment and informed consent process (for example, how to determine if the child and parents fully understand the protocol before signing informed consent or assent documents). The PIs at all sites will carefully supervise the recruitment of all study participants. All research staff proposed for the study have received on-line CITI human subjects training.

Referral to the program. Recruitment will start when a case is referred to the project by a treating psychiatrist or therapist, or by the family itself. When patients are referred by a mental health professional, this professional will give the participants a copy of a study flyer explaining the purposes and basic design of the study (attached). If the parents express interest, there are two options for contacting the study personnel: (1) the treating clinician will ask the child and one of his or her parents to sign a HIPAA Authorization Form. The purpose of the form is to obtain permission from the prospective participants for the treating clinician to release protected health information (name, age, working diagnosis, address, telephone number) to the research team. This will enable the team to contact the participants to determine their eligibility. A copy of the signed authorization form will be provided to the participants and placed in the medical chart; (2) if the prospective participants are not comfortable signing the form, or would like more time to think about contacting the research personnel, the psychiatrist or therapist will give them the study flyer so that they may contact the study investigators themselves.

Telephone Screening Interview. After referral to the program, the project coordinator at each site will initiate the Script to Phone Screen Potential Participants, conducted with one or both parents (see attached). The coordinator will begin by explaining that the study offers a diagnostic evaluation, pharmacotherapy, and follow-up research assessments. Families will be told that their child will receive a full diagnostic workup (including evaluations from a psychologist and a psychiatrist) and, if appropriate, pharmacotherapy as administered by a study psychiatrist for one year.

The Script to Phone Screen Potential Participants (attached) asks the parent to clarify the child's reasons for referral to the program, depression, mania, or hypomania symptoms over the past 6 months, and current medication and psychosocial treatments (if any). No diagnoses will be made at this point. Instead, if the child appears to meet the study's inclusion criteria, an appointment will be set for a first meeting. Informed consent and assent forms will be mailed to the participants so they can review these forms and assemble their questions prior to the first meeting.

9.b. Consent Procedures

Initial meeting, study description, and KSADS Interviews**.** During the initial meeting, to be held at the site's clinic (for UCLA, CHAMP Clinic A8-256 UCLA-NPH and associated interview rooms), the project coordinator will explain the study procedures and treatments to the child and their parents. The coordinator will address the family's concerns about the study together in a conjoint meeting and separately (i.e., child alone, parents/siblings alone) in break-out portions of the same session. The coordinator will explain the IRB-approved consent and assent forms (youth assent form, parent permission forms) and assure that the participants have had ample time to read and review them before signing. The parents and children will once again be informed, via information given orally and in the consent and assent forms that the study involves research assessments, and that their participation is optional. Access to pharmacological intervention is optional.

The research staff will determine each individual participant's level of comprehension of the material presented, based on whether the subjects are able to paraphrase the information in the consent or assent form, to comprehend it adequately, and to ask reasonable questions about

their participation. The coordinator will ask the participants to explain back to her (in their own words) how they understand the procedures and what will be required of them, any risks or discomforts involved, the possible benefits of the study, the voluntary nature of the study and their right to withdraw at any time. Subjects who wish to do so will be encouraged to speak separately with other family members, friends, and physicians about the consent or assent forms before making their decision to participate.

If the family has any prior treatment relationship with the project coordinator, the PI, or any of the other study clinicians, the consenting procedure will be carried out by a staff member who is not the current therapist. This will avoid a situation in which family members feel obligated to participate.

The parents will be told that their own emotional/behavioral functioning will be evaluated, in addition to the child's. **All participants will understand that their acceptance or refusal will in no way affect their (or the child's) ability to receive appropriate psychiatric care from their chosen providers, and they are free to withdraw their consent and discontinue participation in the study at any time without any penalty.** If the family needs more time to think about the procedures and consent forms before signing, a second session will be scheduled. All remaining questions that were not addressed in the first session will be answered by the project coordinator at this second session or, if the family prefers, by the PI.

In cases of youth who meet OSBD (high risk) criteria, we cannot be certain whether they will develop a full episode of mania or depression during the study interval. To avoid the negative effects of diagnostic labeling, we will explain to children that they are participating in a study of mood swings, and specifically, what kinds of treatments are helpful in stabilizing moods and improving functioning at school, with friends, and at home. If parents or siblings ask whether the child will get bipolar disorder, we will explain that having a familial predisposition to the disorder, even with subsyndromal symptoms, does not necessarily mean an inevitable trajectory toward the disorder. If parents or youth desire it, we will give them statistics on the likelihood of developing BD if one has a first-degree or second-degree relative with the disorder, making clear that many protective and risk factors can affect a child's developmental trajectory and his or her likelihood of developing the illness.

Thus, the consenting procedure will consist of four key components: (1) consent or assent will be obtained by research personnel who have completed all required human subjects and

HIPAA training; (2) the subjects will be consented or assented in a quiet setting that is free from distraction; (3) the subject's autonomy and comprehension will be assessed by asking them, after the study is explained, to explain back to the researchers the purposes and procedures of the study in their own words; and (4) all participants will receive a copy of their consent or assent form.

9.c. Protections Against Risk

The PIs and study staff will maximize each participant's (including the parents') safety through providing crisis intervention, recommendations or referrals for adjunctive medical/pharmacological interventions, and when necessary, referral to inpatient, partial hospital, or intensive outpatient treatment. All research personnel have been trained by the PIs to recognize early signs of mood escalation or deterioration. Research staff will be continuously supervised by the PIs and Project Coordinators and instructed to inform the attending psychiatrist and PI if a child is showing signs of mood escalation or deterioration.

9.d. Maximizing Privacy and Confidentiality: Access to Subjects' Identities

During the initial meeting, the project coordinator will explain the study procedures and treatments to the child and their parents. Privacy will be assured during the consenting process. Participants will be given ample time to read the consents/assets and ask questions (see Consenting Procedures).

All of the medical and clinical information obtained during therapy sessions, interviews, or questionnaire assessments will be kept confidential, unless participants provide a written request for release of information. All guidelines of the HIPAA privacy act will be followed. Confidentiality assurances will be provided to participants via initial written consent and oral explanations throughout the study.

The videotapes, audiotapes and questionnaires will be retained for research purposes only. When not in use, the tapes will be kept in locked research laboratories which are only accessible to project research staff. Tapes will be kept for 10 years after the study has been completed and then erased. If participants would like to review any of the tapes they may do so. Tapes will be erased if the participant so desires. To help assure the confidentiality of participants, tapes and questionnaires will only contain numbers and not names. Each individual

will receive a unique 5-digit I.D. number, with the first digit referring to site and the next three digits their order in the randomization. Lastly, parent and child data are identified with codes that indicate the respondent to a particular interview or questionnaire (e.g., 0=child, 1=mother, 2=father). Data will be stored in password-protected computer files in a centralized database on a HIPAA-compliant UCLA server. The site will keep a list of its pairings of names and participant identification numbers. This list will be kept in password-protected computer files in the site PI's or project coordinator's offices, separate from any of the paper and pencil questionnaires or numbered digital audio- or videotapes.

The findings from this study will be published in journal articles or books. However, the participants' names and all other protected health information will never appear in these writings. Data will be analyzed at the group rather than the individual level.

9.e. Limits to Confidentiality

If the researchers have reasonable cause to believe that child abuse or neglect is occurring, or there are circumstances which might result in child abuse or neglect, they will comply with state laws by filing a child abuse report with the state's Department of Child Protective Services. The same procedures apply to instances of domestic violence or elder abuse. In the unlikely event that materials from the study are court-ordered for use in a custody or other court hearing, the project staff members will make every reasonable effort to protect the confidentiality of the participants. They may, however, have to respond to these subpoenas as they would with any client under their care.

If the research staff believe that the adult or child participants are at risk of harming someone else, they are required to take necessary actions. These actions include notifying the parent of the participant's intentions, notifying others who might be affected (i.e., intended victims), or notifying the police or the Department of Child Services. In these cases, the research staff will be unable to preserve the adult's or child's confidentiality. These limits to confidentiality will be spelled out in the participants' consent and assent forms.

We will notify parents if we learn that the child is actively abusing alcohol or drugs in a way that is life-threatening or otherwise a danger to themselves or others. If a teen participant has experimented with a drug or alcohol on a single occasion, notifying the parents may not be indicated. Nonetheless, it will be necessary to monitor this behavior in the psychopharmacology

or family sessions. If we disclose these behaviors to parents, we will offer family intervention sessions to help resolve family conflicts and introduce preventative measures. We will coach parents on how to communicate and problem-solve with the child regarding the self-injurious behavior, and counsel the youth on how to discuss these matters with their parents.

9.f. Chorus Mobile App Platform and Data Protection

The MyCoachConnect online survey assessments will be provided through the Chorus Platform. Chorus was developed by Dr. Armen Arevian at UCLA, and the internet protocol address is owned by the UC Regents. Chorus is a web platform that allows individuals to create their own automated text-messaging, interactive voice and mobile web applications in an easy-to-use and accessible visual web interface.

Chorus is hosted on a secured, SOC2 Type 2-compliant server infrastructure and is HIPAA-compliant. Chorus has been used in over 50 IRB-approved research studies, including with collection of PHI. All data sent to or from the server and Chorus apps are transmitted over encrypted, industry-standard connections like SSL. The server is protected using standard practices including being located behind a network firewall and accessible only by designated users. No data are stored locally on user's devices (such as local browser storage or temporary storage) that access Chorus apps.

The Chorus platform has been approved by the Office of Information Security at UCLA for collection and storage of PHI in research projects as well as patient care activities. The Chorus website uses standard SSL technology to encrypt all traffic to and from the server over HTTPS connections. Server management is conducted via encrypted SSH connections. There are standard practices for backup and encryption of data. Security, backup, and disaster recovery protocols are overseen and approved by Chorus, Inc.

For each stage of the research process, the following procedures will be implemented:

1. Training staff on data sensitivity and data safeguards being employed.
2. Processing sensitive data in a centralized location with established access control procedures.
3. Electronic files used by study staff will be stored on secured, password protected computers accessible only to study staff members.

4. Storing sensitive hardcopy in locked files when not in use.
5. Restricting access to shared disk files through appropriate use of file permissions.
6. Printing sensitive material only when absolutely necessary. When it is necessary, project staff will ensure that an authorized person is at the printer when the sensitive material appears.
7. Using Certified mail, return receipt requested, for sensitive data and Registered mail for very sensitive data when transferring materials by mail.
8. Re-training staff and reviewing sensitive data inventory and data safeguards annually.
9. Reporting all serious violations of the Data Safeguarding Plan in writing to the Principal Investigator, with a copy to the UCLA Privacy Resource Office.

9.g. Managing Risks Related to Blood Assays

Participants may experience brief physical discomfort associated with the blood draw. Any participant who shows an adverse reaction to a blood draw will be treated on site. At UCLA, the blood draws will occur either at the Cousins Center for Psychoneuroimmunology, which has been conducting these studies for many years; or in a UCLA CHS laboratory room with a trained, licensed phlebotomist. Participants may experience brief anxiety related to the blood draw. They will be accompanied to the blood draw by a study staff member and their parent to help alleviate any anxiety that may arise prior to the blood draw.

9.h. Maximizing the Participants' Safety Through Appropriate Pharmacotherapy

To reduce the risks of negative outcomes, we will implement the carefully supervised medication protocol (above) to assure that, when medications are warranted, psychiatrists proceed in a manner that is consistent with good practices in the empirical literature. The study coordinator will explain that the study psychiatrist who conducts the initial evaluation may recommend medications to help stabilize the participant's mood. They will make clear that the study is committed to using best available practice procedures, that the child will not be experimentally assigned to receive a specific medication, and that if new and relevant information about medication efficacy or side effects is published during the course of the child's treatment, the child's treatment regimen will be amended accordingly. The coordinator will also make clear

that taking medication is not a requirement for participating in the study, and that the costs of medication management will be borne by the participant.

Study psychiatrists experienced in treating childhood mood disorders, all of whom will be supervised by internationally-recognized experts from the study's pharmacotherapy oversight committee (Drs. Robert Post, Robert Findling, Christopher Schneck, and others), will apply criteria set forth in the study pharmacotherapy protocol to assure best practice administration of medications.

Psychiatrists will fill out the comprehensive Physician's Report Form (Miklowitz, Schneck, et al., 2020) at each study pharmacotherapy visit. The form records the current medication regimen and dosages, dosage modifications or medication switches since the previous visit, reasons for these switches symptoms during the previous 2 weeks, suicidal ideation or behavior, adverse events. This form, which has evolved over the past 10 years to track a variety of information important to clinical decision-making, includes physician-rated Clinical Global Impression – Bipolar Disorder (CGI-BP; Spearing et al., 1997) and Child's Global Assessment Scale (CGAS; Shaffer et al., 1983) ratings. The CGI-BP rates current depressive, manic, and overall bipolar symptoms on a 1 (normal) to 7 (extremely ill) point scale, and the CGAS uses a 1-100 scale of functioning.

Data from the Physician's Report Form will be important to the guideline adherence scores made by the Pharmacotherapy Oversight Committee. The Committee will measure the adherence of physicians in implementing the protocol based on ratings of each study visit on a 1 (nonadherent), 2 (partially adherent) or 3 (fully adherent) scale. Our prior studies of bipolar adolescents and adults have found that study psychiatrists can remain adherent to a protocol algorithm with regular supervision from experts, with little drift across time (e.g., Miklowitz et al., 2014).

9.i. Pharmacological Treatment of Acute Illness Episodes

If a child shows a clinically significant elevation of mood disorder symptoms at any time during the study (i.e., a sudden worsening of mood or behavior), study psychiatrists will introduce emergency prophylactic medication as clinically indicated to forestall the development of a syndromal mood episode. If the child is not taking mood stabilizing or atypical antipsychotic

medications, these agents will be introduced; if the child is already taking medications, these agents will be augmented with other agents, or dosages will be increased. Thus, there will be no delays in the initiation of rescue pharmacotherapy when a child's mood worsens.

If a study youth shows the early warning signs of mania (e.g., decreased need for sleep, irritable or elevated mood, grandiose thinking) or begins to sink into depression (pessimistic thoughts, decreased energy, insomnia), the independent research evaluator will notify the treating psychiatrist immediately, who will institute appropriate changes to the medication regimen (or initiate new medications) as per good clinical practice. When there are questions or difficult cases, psychiatrists will consult with the pharmacotherapy oversight team to determine how to modify drug treatments in the most clinically appropriate manner. Typically, changes will include adding a second mood stabilizer or an atypical antipsychotic agent.

Family members will be instructed to notify their assigned psychiatrist and case coordinator if they observe sudden deteriorations in the mood or behavior of the child at home or in the school setting. When clinically appropriate, psychiatrists will instruct the family as to how to get the youth to the nearest hospital emergency room. The clinicians will facilitate communication between the family and the hospital. In all cases, they will re-contact the family within 24 hours to be sure that contact has been made with the appropriate care provider.

Parents or siblings of the youth may also require referral for pharmacological treatment. For example, a parent with bipolar I disorder may have a recurrence and require initiation of pharmacotherapy or a reevaluation of their regimen. In all cases, we will refer relatives to an appropriate clinical provider and obtain ongoing information on their treatment regimen, using the Treatment Utilization Form (Miklowitz et al., 2020), administered at each follow-up visit.

9.j. Preventing Suicidal Episodes

Children with or at risk for bipolar disorder are at heightened risk for suicide (Goldstein et al., 2005). Special precautions will be undertaken to prevent the onset of suicidal crises. We will learn of new onsets of suicidal ideation or new attempts because we will have regular contacts with children and parents (a minimum of once monthly). Information about suicidal ideation will be obtained by the psychiatrist during the psychopharmacology sessions, by weekly online parent reports, and by the research assessor in face-to-face assessments. The project coordinator

and assessors will contact the study psychiatrist and PI if mood deteriorations are detected so that rescue medications or crisis counseling can be introduced.

When a participant (an at-risk youth or a family member) expresses suicidal thoughts, the treating psychiatrist will conduct a thorough lethality and safety assessment with the relevant person and arrange hospitalization if necessary. Rescue medications will be introduced by the psychiatrist as medically appropriate. The participant will be referred for evaluation at the hospital emergency room if the treating psychiatrist cannot be reached.

If the suicide risk is deemed low, the treating psychiatrist will intervene to prevent escalation of the suicidal thoughts or behaviors. This will usually include additional psychiatric sessions for the child and/or family. Addressing suicidality usually includes (a) conducting chain analyses to assess the precipitants and consequences of suicidal thoughts or actions, (b) providing training in distress tolerance skills (e.g., deep breathing for anxiety); (c) developing a suicide prevention contract (i.e., identifying triggers for suicidal thoughts; lists of who the child or adult will call if he or she feels suicidal; how the parents can get in touch with the psychiatrist or therapist and what to do if they are unavailable); (d) enhancing family communication focused on supportive interactions that encourage the family members' expressions of compassion and concern, and (e) problem-solving to eliminate triggers of suicidal thoughts and prevent the escalation of suicidality.

9.k. Availability of Alternative Non-Protocol Treatments

We will explain to participants that, instead of receiving psychiatric treatment from a study psychiatrist, the youth may initiate or continue medication treatment with his/her existing psychiatrist or primary care physician. If the family so chooses, the study psychiatrist will assemble a report detailing his or her evaluation of the child and send it to the family's chosen physician. It will be up to the primary care physician and family to determine whether or not to follow these recommendations.

Participants who have recurrences of their illness may require emergency services. A child who needs to be hospitalized (e.g., for suicidality) will be reentered into the study after hospital discharge if the child and parents agree to continue participating.

Because bipolar disorder runs in families, one or more of the child's relatives may have bipolar I or II disorders themselves, or other mood, substance, or anxiety disorders. Parents with BD will have been identified on the basis of the Family History screen, as well as via spontaneous self-report during the evaluation or treatment sessions. If family members request ancillary treatment for themselves or another relative, or if in the psychiatrist's or family clinician's judgment referral to an outside therapist or physician is clinically indicated, we will refer the relative to the appropriate care providers, including referrals for pharmacotherapy evaluations as needed. If family members require hospitalization, we will follow the same advocacy procedures described above for the symptomatic child participant.

Family members of the youth (parents or siblings) can pursue ancillary treatments without jeopardizing the family's involvement in the study. Thus, participants or family members may take part in individual therapy, support groups, chemical dependency programs (such as A.A.), or domestic violence prevention programs without being terminated from the study. If parents would like to join a multifamily group, they may do so without jeopardizing their involvement in the study.

9.l. Protocol to Maximize Retention of Study Subjects

We will make every attempt to retain all participants in the longitudinal protocol for as long as possible. We have found that retention hinges on maintaining excellent rapport with children and parents, communicating optimism and hopefulness, and fostering the attitude that every participant is important. Relatedly, it is essential to get to know each member of the family as a person and emphasize personal strengths.

On a practical level, retention requires obtaining telephone numbers, addresses, and email addresses for participants and their parents, including parents' cell phone numbers and workplace numbers. This information must be repeatedly updated throughout the study. We will retain contact with participants who are difficult to reach unless the participant has stated that he/she (or the parent) no longer wants to participate and no longer wishes to be contacted. In cases where a participant declines a research interview or family session, we will ask permission to recontact him/her in the near future. With the participants' permission, we will obtain contact information for grandparents and other extended family members so that we can locate the family if the contact information we have is no longer valid.

The following procedures have also helped us to maximize retention: (1) be flexible about the time of day that assessment or treatment sessions are offered (i.e., after school, early evening, weekends); (2) sending birthday and holidays cards to the child and parents; if the cards are returned because of a wrong address, immediately track the new address; (3) check in with participants about their goals and expectations early in treatment, and revisit these goals from time to time to make sure they are being addressed; (4) provide appointment reminder cards; (5) offer between-session phone consultations as needed; (6) offer the parents or the child extra support as needed through additional therapy sessions, (7) serve as a source of treatment or medical referrals for the family; (8) remunerate children and parents for completing each follow-up interview and questionnaire battery, with compensation divided evenly between them.

9.m. Circumstances That May Require Study Withdrawal

Noncompliance. Participants will be withdrawn from the protocol if they are noncompliant with the study procedures (for example, refuse the research assessment interviews). Participants will not be dropped from the protocol if they are noncompliant with their medication regimens. The circumstances that may require administrative withdrawal will be spelled out in the consent forms.

Substance or alcohol abuse. The Drug Use Screening Inventory, Revised (DUSI-R; Tarter 1990), a self-report questionnaire, will be administered to supplement the MINI substance abuse module at baseline and follow-ups, covering the prior month. Scores reflect gradations of severity and frequency of use of alcohol and substances. If the child shows evidence of regular substance or alcohol use during the study protocol, has a positive toxicology screen, and/or develops a DSM-5 substance/alcohol abuse or dependence disorder, we will retain him or her in the protocol for as long as possible and work toward abstinence. In most cases involving significant substance or alcohol abuse, we will make referrals for adjunctive chemical dependency treatment. We will make this determination on a case-by-case basis as medically or ethically appropriate. Referrals can include age-appropriate modified 12-step programs with psychiatric oversight, drug rehabilitation facilities, and various forms of individual treatment (i.e., motivational enhancement, cognitive-behavior therapy). Study staff members will follow-

up to assure that the youth and family have pursued adjunctive treatment. Adjunctive chemical dependency treatment will not preclude continued participation in the study protocol.

If the child is using alcohol or drugs regularly and (a) psychiatric treatment is jeopardized (for example, the child comes to sessions intoxicated, cannot function during sessions, consistently no-shows) and (b) refuses adjunctive substance or alcohol abuse counseling or other chemical dependency treatment, we will inform the child and parents that the substance use must stop or the child will be discontinued from the study. We will continue to monitor the child's clinical status and substance abuse behavior for the next 4 weeks. If the child continues to meet DSM-IV substance abuse/dependence criteria (i.e., persistent use) and is unable to participate in treatment, he or she will be discontinued from the study. In all cases, children will be referred to the appropriate substance abuse treatment clinic. In our previous studies, we have not had to withdraw any subjects due to persistent substance abuse.

Participants will be informed of these rules during the recruitment phase of the study, both through information given orally and via our informed consent procedures. We will make clear that discontinuing participation in the study will in no way jeopardize their access to other treatments. Thus, they can have regular pharmacotherapy or psychotherapy at the relevant study outpatient clinic even if no longer participating in the study. Whenever possible, we will continue to follow these children using the research outcome battery so that they can be included in intent-to-treat analyses. We will record the nature of the adjunctive drug/alcohol treatment services received (i.e., number of sessions, frequency, and costs) using the ***Treatment Utilization Form.***

9.n. Tolerability of the Baseline and Follow-up Assessment Batteries

Our prior experience with assessment batteries similar to the one proposed for this study has been that they are well-tolerated by children and adults. We estimate that the initial assessment battery (i.e., KSADS, MINI, questionnaires) will require approximately 2-3 hours from the parent and the youth, which can be spread over two sessions. The follow-up interview and questionnaire battery currently averages 1.0-1.5 hours every 6 months.

The research personnel are trained to be attentive to fatigue, especially when the child is actively symptomatic. Where appropriate, the interviewer will subdivide the assessments across

two or more sessions to decrease the participants' fatigue and assure the integrity of the data. Children will be allowed to take breaks as often as they require.

10. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

In our opinion, the benefits of this study to individual participants outweigh its risks. Families with youth who have or are at risk for BD have significant difficulty finding services in the community because of the shortage of child psychiatrists or specialty programs focused on bipolar spectrum disorders. As a result, parents of bipolar persons often report high levels of subjective burden (Perlick et al., 2007). The information obtained from the KSADS and MINI interviews and study questionnaires may help the child to obtain a more definitive diagnosis and get better treatment either within or outside the context of the study.

If they so choose, youths will receive a pharmacological evaluation and psychiatric care sessions from experts in childhood mood disorders. As a result of study participation, the youth and parents may gain a greater knowledge of how to cope with their child's mood swings, which may improve their own mood states and decrease their subjective burden and distress. All child and adult participants will receive support, help in solving problems, advice, reassurance, and information as needed from project staff members for the year-long study period. They will receive appropriate referrals for pharmacological follow-up care at the end of the study, and study staff will continue to provide treatment and crisis counseling until such referrals have been contacted and treatment initiated.

The research assessments are time-consuming but are often experienced positively by the participants, because they are administered by sensitive, clinically-trained staff members. Participants (parents and child, to be divided as they see fit) will be financially compensated for completing the research assessments. The results of these assessments may be useful in informing treatments received after the child finishes participation in the study.

11. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Little is known about whether different clinical centers can diagnose and treat youth with or at risk for bipolar disorder using the same instruments and strategies. There is a need for

standardized diagnostic and treatment guidelines for use across national centers and potentially, across cultures.

Successful implementation of this study will generate much-needed empirical data on how to treat youth who are at risk for BD. Our long-term objectives are to promote symptom stabilization, reduce symptom severity over time, reduce the onset of bipolar I or II disorder, and enhance individual and family functioning. Additionally, little is known about biological predictors of treatment response among youth at risk for BD. The potential clinical gains for participants and to the field are likely to outweigh the minimal risks to participants.

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