Technology Enhanced Family-Focused Treatment

Study Protocol

Document number: NCT03913013

Sept 24, 2020

Date: September 24, 2020

Title: **Technology-Enhanced Family-Focused Treatment for Adolescents at High Risk for Mood Disorders: Phase 2**

Abstract

Adults with bipolar disorder (BD) and major depressive disorder (MDD) often have significant *mood instability* in childhood: rapid shifts among depression, hypomania, anxiety and irritability. Children are considered at high-risk (HR) for the full onset of mood disorders in early adulthood if they have (a) evidence of mood instability, subthreshold mania, and depression/anxiety; and (b) at least one parent with BD or MDD. There is promise in family-focused therapy (FFT) aimed at preventing mood disorders in HR youth who meet these criteria. In four randomized clinical trials, including two trials in youth at high-risk for BD, we showed that pharmacotherapy plus family-focused treatment (FFT) - consisting of intensive psychoeducation for families about illness management and training in communication and problem-solving skills – were more effective than pharmacotherapy plus brief family education in reducing mood symptoms and enhancing functioning over 1-2 years (Miklowitz & Chung, 2016). Nonetheless, responses to FFT are variable: 50%-60% of HR youth have residual mood symptoms and impairment after 18 weeks of FFT. Youth who fail to respond fully to FFT have (a) higher baseline levels of *mood instability* than full responders, and (b) parents who express high levels of criticism, hostility or emotional overinvolvement (*expressed emotion,* EE) during interviews conducted prior to treatment.

Participants in phase 1 (N = 25) and phase 2 (N=60) will be boys and girls (ages 13-19 yrs) who have high mood instability scores, at least one parent with a history of BD or MDD, and at least one parent rated high in Perceived Criticism, a 1-10 child- and parent-rated scale that is a proxy measure for expressed emotion (EE). Each family will receive 12 FFT sessions in 18 weeks, with assessments of EE, mood instability, and symptoms/functional outcomes at intake, mid-treatment, post-treatment (18 wks.) and follow-up (27 wks.). At study entry, all participants will be given access to the MyCoachConnect (MCC) smartphone app with an interactive voice-response (IVR) system. In phase 1, all participants (adolescents and parents) will receive FFT and the fully functional MyCoachConnect (MCC) app. In phase 2, participants will be randomly assigned in a 1:1 split to:

(1) **FFT with the full MCC app *(FFT-MCC)*,** consisting of instructions for daily mood, sleep and family functioning ratings, how to use FFT skills (e.g., symptom tracking, active listening, problem-solving), and how to log efforts to practice these skills; instructional videotapes showing how the skills are used in practice; and weekly and standard interval (every 9 week) assessments completed by the participant on the app. The clinical provider, via the MCC app, will send tailored alerts to parents and youth about mood management strategies and pertinent communication skills for resolving conflicts, which they can practice between sessions. All participants (adolescents, parents) will be instructed to call the automated voice system twice per week and leave a 3-5 minute speech sample surveying how they are doing and how they are getting along with their child (or parent).

(2) ***FFT with the Assessment App (FFT-ASSESS)*,** the same 12 sessions of FFT will be given, but with a scaled-down version of the app consisting of weekly questionnaires to be rated and call-in instructions, plus standard interval (every 9 week) questionnaire assessments. There will be no educational or skill-oriented coaching of participants by clinicians via the app. However, families will still receive the standardized course of 12 sessions/ 4 months of FFT, which is more than families with children with mood disorders ordinarily receive in the community.

The data analyses will examine whether the hypothesis that there will be greater reductions in mood instability and EE in the FFT-MCC condition than in the FFT-Assess condition, and that symptomatic change will be greatest from baseline to 27 weeks in the FFT-MCC condition. Using machine-learning, we will conduct analyses of parents' speech samples to test computational

models that in preliminary studies generated proxies for parents' EE classifications (based on standard coding). We will also explore the use of adolescents' speech samples to test models for estimating **suicidal risk** and **mood instability** as measured by gold standard instruments.

SPECIFIC AIMS

The study will facilitate the translation of a technological augmentation to an evidence-based family intervention, with the goal of increasing treatment access among families with mood disorders. Our proposed strategy is to augment FFT with a mobile app called MyCoachConnect (MCC) that facilitates information exchange between clinicians and families, teaches adolescents emotion regulation skills, and enhances uptake of the communication and problem-solving skills so central to the FFT approach. We hypothesize that FFT-MCC will be more effective than FFT without MCC coaching (FFT-ASSESS) in engaging the targets of mood instability, suicidal ideation and EE and promoting improvements in adolescents' mood symptoms and quality of life over 27 weeks.

Aim #1. Standardization (Phase 1). *1a: To evaluate parents' and adolescents' subjective reactions to FFT with MCC assessments and skills coaching.*

Hypothesis 1a: After a baseline assessment, parents and HR youth will be provided with the adapted MCC app and begin the 18-week FFT protocol. Parents and adolescents will report high subjective usability and perceived utility scores for the mobile app. Based on preliminary data, we expect parents to complete > 80% and adolescents > 70% of the weekly speech samples. Parents and adolescents will report being comfortable leaving confidential information about clinical status on the HIPAA-compliant voice recorder.

Aim 1b. *To determine whether FFT providers in Phase 1 find value in weekly assessment data on the MCC portal*.

Hyp. 1b. Clinicians will report that app-based assessments are concordant with their views of family functioning and useful in treatment planning.

Aim 2 (Phase 2): *Using in-person assessments of moods and EE at baseline, 9, 18, and 27 weeks, and MCC speech samples obtained weekly, we will determine whether targets and outcomes improve over time, and whether these improvements occur to a greater extent in FFT-MCC than in FFT-ASSESS.*

Hyp 2a. We will observe significant improvements over 27 weeks on dichotomous (high vs. low) and dimensional (number of criticisms) ratings of EE and mood instability (targets), and in the clinical outcomes of mood severity and quality of life. These improvements will be greater in FFT-MCC than in FFT-ASSESS. We predict that targets and clinical outcomes will be correlated over time, and that bigger changes in targets will be predictive of larger clinical improvements.

Hyp 2b. In both treatment conditions, we will find prognostic relationships between speech features (collected in call-ins to the voice app) and concurrent or later depression and suicide risk. We do not expect that suicide risk will change more in one MCC condition than in the other.

To more fully investigate hypothesis 2b, we will add two measures to our standard interval assessment (conducted every 9 weeks for 27 weeks) to assess suicide risk: the Suicidal Ideation Questionnaire-Junior (SIQ-Jr)({Reynolds, 1998 #1106}) and the Columbia-Suicide Severity Rating Scale {Posner, 2009 #2158}. We will explore both population-based training as well as within-person training to create personalized prediction models of suicide risk using

machine learning. Because we are collecting speech samples and suicide risk measures over a 6-month (27 week) period, we will be able to conduct analyses to explore the temporal dynamics of suicide risk. This includes understanding prior speech sampling as predictors of change in suicidal ideation or behaviors within and across individuals over time.

Participant eligibility (both study phases)

The **eligibility criteria** for this study are:

(1) The family is English-speaking (although English need not be their first language);
(2) The index adolescent is age 13 years, 0 mos. – 19 years, 11 mos.;
(3) at least one parent has received a lifetime diagnosis of bipolar I or II disorder or major depressive disorder by the MINI International Neuropsychiatric Interview. The protocol does not require participation of this parent in treatment;
(4) at least one parent or step-parent/guardian with whom the subject lives is available to participate in the study and in family sessions, as well as use a mobile app for assessment and treatment;
(5) At least one parent in the family who is planning on attending treatment sessions is rated high in Perceived Criticism (Masland & Hooley, 2017), defined as a score of 5 or higher on a 1-10 scale of criticism frequency, as rated by the adolescent or the parent about him/herself.
(6) The adolescent shows evidence of high mood instability in the previous month. Either parents' ratings of the adolescent on the General Behavior Inventory-10M (PGBI-10M; Youngstrom, Frazier, Demeter, Calabrese, & Findling, 2008) are $\geq$ 6, or the parent's or the child's ratings on the Children's Affective Lability Scale (Gerson et al., 1996) are $\geq$ 20, indicating that the adolescent has significant mood instability and difficulty regulating emotions.
(7) Within the previous month, the adolescent has had current affective symptoms for 1-2 weeks, with either a Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) $\geq$ 11 or a Children's Depression Rating Scale, Rev. (CDRS-R; (Poznanski & Mokros, 1995) score > 29;
(8) Have access to a smartphone, tablet or computer in order to access the study app. There is no requirement for a specific operating system or brand of device.

At baseline, we will interview the youth and at least one parent about the youth's DSM-5 diagnoses using the *MINI International Neuropsychiatric Inventory* (version 7.0.2 for the child and for parents about their child; Sheehan, 2016); there are no exclusions on the basis of children's DSM-5 diagnoses. We will also interview the parents about their own psychiatric diagnoses and history, using the MINI-Plus (adult version of same interview). Disagreements about the teen's diagnosis will be resolved through conjoint interviews of the two parents or the parent and the teen. Structured interviews will be done by minimum MA or PhD/MD clinicians who are trained and reliable on the MINI.

Exclusionary criteria

Subjects will be excluded if they have:

(1) a score 19 or above on the Autism Spectrum Screening Questionnaire (Ehlers, Gillberg, & Wing, 1999);
(2) had an acute DSM-5 manic episode of bipolar disorder within the past two weeks.

(2) significant and persistent psychotic symptoms that historically have not remitted with mood states;
(3) intellectual disability (IQ < 70) from school records;
(4) significant substance or alcohol abuse in the prior 3 months, as revealed by the MINI, resulting in a current DSM-5 substance or alcohol abuse disorder that is not in remission;
(5) already received FFT inside or outside the context of a clinical trial;
(6) there is current sexual or physical abuse or domestic abuse between parents or adult partners. These situations usually require notification of the Department of Child Services and forms of treatment other than FFT (e.g. trauma-focused therapy).

In cases where we exclude participants, appropriate referrals will be made (e.g., treatment for PTSD or autism) if participants are not already engaged in such treatment. We will conduct follow-up phone calls to verify treatment access or offer additional referrals.

Adolescents are not required to take any medications to be in the study, but if they (or their parents) wish, we will refer them to a child psychiatrist for medication management. If they wish, the adolescent and family may receive treatment in the Child and Adolescent Mood Disorders program (CHAMP) at UCLA without participating in the study. We will offer clinical referrals if they have no current providers. They may also continue to see their community provider. This study does not control pharmacotherapy choices or regimens, and does not cover the costs of medications or pharmacological management from a physician, as explained in the consent forms.

All relatives who are in the child's immediate milieu and are relevant to his or her care (biological or stepparents, siblings of any age, grandparents, or aunts/uncles) will be invited to take part in the family intervention sessions, regardless of their own diagnoses or treatment status.

Where will the Participants Come From?

The major source of referrals to the study is expected to be the UCLA Child and Adolescent Mood Disorders program (CHAMP) at the Semel Institute. Additionally, we expect referrals to come from advertisements in local newspapers and on radio stations (see text of **web advertisements**), and **study flyers** posted around campus and in selected community health clinics. Physicians, psychiatrists, pediatricians, social workers and other mental health professionals who have previously referred to our research or clinical programs will be made aware of this new study. Talks or workshops will also be given by the PI and study staff at community mental health clinics, primary care clinics, and local churches or temples. We will advertise the study at patient advocacy groups (for example, Depressive and Bipolar Support Alliance meetings or talks/webinars sponsored by the International Bipolar Foundation).

Procedures: Referral to the Program and Baseline Assessments

Recruitment will start when a teen is referred to the project by a treating psychiatrist or therapist, by another clinician, or by the family itself. When patients are referred by a mental health professional, this professional will give the parents and teen a copy of an IRB-approved study flyer (see attached) explaining the purposes and design of the study. If the teen and parents express interest, the treating clinician will ask the parents to contact the study team directly, using contact information on the flyer. If the family prefers, they can choose to sign a HIPAA authorization to give permission 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 directly to determine their eligibility (some families prefer this option). A copy of the signed authorization form will be provided to the participants.

When adolescents and their families sign up for care at the CHAMP clinic, they may opt to sign a consent form saying they are willing to be contacted by other UCLA investigators for future

studies (IRB#10-001935). Signing this consent determines whether their personal health information can be passed along to UCLA investigators who may be conducting IRB-approved studies relevant to them.

Telephone Screening Interview

After referral to the program, the Project Coordinator will initiate a telephone interview of one or both parents. The coordinator will begin by explaining that the study offers randomly assigned treatment in which all participants get 12 sessions of family therapy involving psychoeducation and skills training, plus use of an experimental mobile application that involves skills coaching and assessment (FFT-MCC) or assessment only (FFT-ASSESS).

The ***Telephone Screening Script and Answer Sheet*** (attached) asks the parent to clarify the child's reasons for referral to the program; depression, mania, or hypomania symptoms over the past 4 months; and current medication and psychosocial treatments (if any). The Coordinator will ask additional questions so that the parent-rated General Behavior Inventory-10 item Mania Scale (PGBI-10M) can be completed. This measure captures subsyndromal mania/hypomania and energy dysregulation.

No inclusion decisions will be made at this point. Instead, if the youth appears to meet the study's inclusion criteria, an appointment will be set for a first meeting. Informed consent and assent forms, written in neutral language, will be mailed to the participants so they can review these forms and assemble their questions prior to the first meeting.

Initial Meeting and Study Description

During this meeting, the project's Research Coordinator will explain the study procedures and treatments to the adolescent, his or her parents, and any siblings the parents would like to involve. The coordinator will address the family's concerns about the study, and will meet separately with the child and parent(s) so that they may raise any additional concerns. The coordinator will explain the IRB-approved consent and assent forms (e.g., youth assent/parent permission and consent/adult consent form, sibling assent form) 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, both orally in this meeting and in writing in the consent and assent forms, that the study involves psychosocial care, interacting with an app (in providing assessment data or assessment data plus receiving informational and coaching alerts regarding family skills), and research assessments. The nature of compensation (see below) will also be described.

The coordinator will determine each individual participant's level of comprehension of the material presented. She will ask the participants to summarize (in their own words) how they understand the procedures and what will be required of them, any possible risks or discomforts involved, the possible benefits, the voluntary nature of the study and their right to withdraw at any time. They will be encouraged to ask questions about the procedures. Participants 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 regarding participation. **Patients who are 18 or above will sign an adult consent form instead of the adolescents' assent form (attached).**

All participants (parents, siblings, at-risk child) will understand that their acceptance or refusal will in no way affect their (or the at-risk youth'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.

Diagnostic Interviews

Adolescent: Once the parents and youth have signed the consent and assent forms, a research assistant (independent evaluator) will administer to the child the MINI International Neuropsychiatric Interview for DSM-5 diagnoses, the Young Mania Rating Scale, the Children's Depression Rating Scale, the AUS/DUS substance use measure, and the Adolescent Longitudinal Interval Follow-up Interview (A-LIFE) covering the 18 weeks prior to the study. A separate research assistant will administer these measures with the parent so that consensus judgements can be made. The interviews will be audio recorded (see Confidentiality sections, below). Based on both sources of information, the independent evaluator will characterize each week of the 18 weeks prior to intake using the 1-6 A-LIFE Psychiatric Status Ratings of depression, mania, hypomania and suicidal ideation/behavior. These are standard structured interviews and will take approximately 1 to 1.5 hours per person. The adolescent will be allowed to take as many breaks as s/he needs, and the interview can be split into two appointments if preferred. Both parents will fill out the PGBI-10M, and both parents and the child will complete the Children's Affective Lability Scale (CALS), with separate versions for each.

Parents: Study children must have at least one parent who has a lifetime diagnosis of bipolar I or II disorder or major depressive disorder by the MINI (adult version) for DSM-5. If there are two biological parents, we will individually interview each parent with the MINI regarding their own psychiatric history to verify that the child has at least one parent with lifetime major depression or bipolar disorder. Adolescents will only be eligible if we can interview at least one parent(s) directly. If the second parent is deceased or otherwise unavailable, we will obtain information about him or her using the other parent's report, with questions guided by the Family History Screen (Weissman et al., 2000) and diagnoses based on DSM-5. However, in these cases we will only include the adolescent/family if the first parent has given sufficient examples to make an unequivocal diagnosis of lifetime mood disorder in the second parent (i.e. ratings of 'probable' or 'definite' on the Family History Screen).

Expressed Emotion (EE) from Five-Minute Speech Sample interviews

We will individually interview each parent or stepparent who is in regular contact with the child (i.e., a minimum of 4 face to face hours/week) using the Five-Minute Speech Sample (FMSS), to determine whether one parent in the child's family is high in expressed emotion based on a standardized FMSS coding system for EE. We will administer the FMSS (Magana et al., 1986) to each parent (or single parent) at baseline and at weeks 9, 18, and 27. The parent is instructed to "talk for 5 minutes (without interruption) about what kind of person your child is and how the two of you get along together." FMSS digital audiotapes will be identified by case number and sent to Ana Magana-Amato, M.A., who developed the FMSS-EE coding system (Saratoga, CA). Ms. Magana-Amato will provide the determination of whether a parent is high or low in EE. Because we will not be able to obtain Ms. Magana-Amato's rating of EE immediately, we will base participant eligibility on whether the child rates one or more parents as 5 or above on the 1-10 measure of Perceived Criticism (Masland & Hooley, 2017; see description below). Scores of 5 or greater on the Perceived Criticism Measure have strong predictive validity in mood disorders samples as a proxy measure of EE.

After reviewing the results of the baseline assessments, the study team will determine eligibility. In the event that there are unanswered questions about eligibility (e.g., whether the child has regularly abused substances in the past 4 months), the relevant parts of the MINI will be repeated with the adolescent and one parent.

Screened but not Eligible

If a child is deemed ineligible, or if the parents or youth are not interested in participating in the study, we will offer at least one session of clinical consultation and informational feedback. A primary goal of this session is to make sure the family members have understood the results of

the evaluation (if one has occurred), and are not having any negative reactions. We often praise the family for finding the program and attempting to find answers to their questions. Regardless of whether the family is accepted into the program, we will offer relevant family-oriented literature on managing mood swings in children and referrals for follow-up care. We will remain accessible for telephone or in-person consultation until the parents and youths are comfortable with the treatment arrangements for their child and family.

Procedures: Follow-up Assessments

The data to be collected for this study are based on:

(1) individual structured interviews (by an independent evaluator)
(2) paper and pencil questionnaires, and
(3) MyCoachConnect (MCC) mobile phone app with an interactive voice system that enables users to leave speech samples or complete standardized questionnaires.

Most of the measures have been used before in our studies of childhood mood disorders. Table 1 describes all instruments and their timing. Standardized measures (for example, parental EE, Perceived Criticism Measure, child's mood instability) will be administered at baseline, mid-treatment (9 weeks), 18 weeks (end of treatment) and 27 weeks post-baseline (hereafter called *standard study intervals*). The interview-based measures of clinical progress (ALIFE Psychiatric Status Ratings, CDRS, and YMRS) are based on a consensus between child and parent reports from direct interviews administered every 9 weeks. We will utilize the MCC app to collect self-report ratings by parents and teens. In the FFT-MCC condition, these ratings will be obtained daily and weekly, as explained below. In the FFT-Assess condition, they will be weekly only.

TABLE 1: Longitudinal Assessment Instruments

Clinical State	Construct	Respondent	Timeline
Mood Rating (5 items)	Current Mood	Child	Daily (FFT-MCC only); weekly (FFT-Assess)
Sleep (sleep/wake times, quality)	Sleep disruption	Child	Daily (FFT-MCC only), weekly (FFT-Assess)
Patient Health Q'nnaire-9, PHQ-9	Depression Symptoms	Child	Stand. interval; weekly
Children's Affective Lability Scale (CALS)	Mood Instability	Child; parent	Stand. interval; weekly
ADHD Rating Scale	ADHD	Parent re: child	Baseline only
Modified Overt Aggression Scale	Aggression	Parent re: child	Standard int.; weekly
Parental General Behavior Inv. 10M	Mood & energy regulation	Parent re: self	Standard int.
Parental 7-Up 7-Down questionnaire	Depressed and manic mood states	Parent Re: child	Standard Int.
Autism Spectrum Disorder Scale	Autism Symptoms	Parent re: child	Baseline only
Children's Depression Rating Scale (CDRS)	Depressive Symptoms	Parent/child consensus	Standard int.
Young Mania Rating Scale (YMRS)	Mania Symptoms	Parent and child	Standard int.

Screen for Children's Anxiety and Related Disorders (SCARED) questionnaire	Anxiety, panic, worry	Child	Standard int.
Adolescent Longitudinal Interval Follow-up (interview)	Depression, hypo/mania, suicidal ideation, psychosis	Parent and child consensus	Standard int.
AUS/DUS Substance Abuse Scale	Substance use/abuse	Child	Standard int.
Suicide Ideation Questionnaire, Jr	Suicidal ideation	Child	Standard int.
Columbia Suicide Severity Inventory (Interview)	Suicidal actions	Child	Standard int.
MINI Child	Diagnostic Impression	Child, Parent re. child	Baseline only
MINI Parent	Diagnostic Impression	Parent	Baseline only
Family Functioning			
Automated MCC Speech Sample	EE, mood instability	Parent, child	1-2 times per week
Perceived Criticism and Perceived Stress Scales	Criticism, family stress	Child, parent	Daily (FFT-MCC only); Standard int. and weekly (both conditions)
In-person 5-Minute Speech Sample	EE, mood instability	Parent, child	Standard int.
Conflict Behavior Questionnaire	Problem-solving and communication behavior	Parent, child	Standard Int.
Child's Functioning			
Treatment Utilization Form	Treatment Utilization	Parent	Study int.
Possible Adverse Events	Adverse events	Parent	Study int.
Children's Global Assessment Scale	Functioning	Staff	Study int.
Reactions to MCC App:			
Usefulness and Usability	Perceived Usefulness, Ease of Use, Subjective Usability scales	Child, parent	Study int.
Experience Scale	Alliance with therapist and helpfulness of the app	Child, parent	Study int.
Clinician's Ratings			
Usefulness and Usability	Perceived Usefulness, Ease of Use, Subjective Usability scales	FFT therapist	Study int.
Subjective Target Estimation Scale	Prediction of family's EE status and child's level of mood instability	FFT Therapist	Study int.
Skill Practice Inventory	Records the adolescent's and family's adherence to assigned homework	FFT Therapist	Weekly (after sessions)

Treatment Progress Form	Ratings of whether delivery of the FFT protocol has been complicated by patient or family nonadherence or other complications	FFT Therapist	Study int.

Clinical State. Mood instability scores will be measured at each interval with the parent- and child-rated CALS. Parents also fill out the 7-UP/7-Down questionnaire, a measure of mood symptom severity, in which the child's behavior on 7 high/manic items and 7 depressed items are rated on a 0-3 scale (example: Have there been long periods in your child's life when he/she felt sad, depressed, or irritable most of the time?) (Youngstrom et al., 2013). Parents will fill out the Modified Overt Aggression Scale (Kay, Wolkenfelf, & Murrill, 1988) and the adolescent will fill out the Screen for Children's Anxiety and Related Emotional Disorders (SCARED; Birmaher et al., 1997) at standard study intervals. Mood severity - as measured by the interview-based Young Mania and Children's Depression Rating Scales and the A-LIFE PSRs - will also be administered at these times. The evaluators will administer a brief interview- the Alcohol/Drug Use Scale (Mueser et al., 1995) – to the adolescent to determine the frequency and impairment associated with alcohol or drug use during the preceding interval.

Adolescents and parents in the FFT-MCC condition will receive text message prompts from the app every evening to complete a daily mood rating, whereas adolescents and parents in FFT-ASSESS will receive prompts once per week. A link to the mobile survey will be included in each message. Responses will be selected on the webpage by clicking on the appropriate choice for each item. Participants will be asked to rate mood on a -3 (very depressed) to +3 (very excited or elated) scale, with '0' indicating normal mood. Adolescents will also record their sleep/wake times and make an overall rating of sleep quality.

Family functioning. In both treatment conditions, we will assess the key study construct of EE using five-minute speech samples collected in person from the parent(s) at standard study intervals. We will also use the MCC app to obtain weekly automated speech samples from parents to compute EE proxy measures, and adolescents to measure mood instability and reactivity when discussing parents. At weekly intervals using MCC, we will administer the Perceived Criticism Measure, in which patients rate each of their parent(s) on four items using 10-point scales, two of which cover perceptions of the parent's criticisms (e.g., "How critical do you think your (mother/father) is of you?" "How upset do you get?") and two items that cover the child's own behavior (e.g., "How critical are you of ____?"). The family is considered high-EE by the PCM if the teen rates either or both items a 5 or higher. Parents will fill out the same PCM measure weekly, with questions taking the form "How critical do you think you are of (son/daughter)? How upset does he/she get?" Finally, adolescents and parents will rate the Conflict Behavior Questionnaire ((Prinz, Foster, Kent, & O'Leary, 1979)), a measure of family interactional behavior, at standard intervals.

Adolescents' functioning and treatment use. At each interval, evaluators will make a 1-100 point CGAS rating covering the prior two weeks. Evaluators will interview parents at each interval to assess treatment utilization.

Behavior change/process outcomes: In the FFT-MCC condition, we will use the app to remind participants to practice their skills taught in FFT-psychoeducational (e.g., mood management) strategies and communication skill strategies. These reminders will be sent on a weekly basis during treatment and each of the 9 weeks after treatment. Participants will be asked

to log : (1) what skill they implemented during the week, when they tried using the skill, a 5-point rating of "How did it go"? and a text box in which they record "Thoughts on how it went."

There will be no prompts to use the skills in the FFT-Assess condition. All reminders to use skills will occur in the FFT sessions themselves. For both conditions, we have added a short questionnaire for clinicians to complete on the app after every session, rating how frequently and how well the child or parent used each skill (the "*Skill Practice Inventory*", or SPI, attached in Study Summary).

Treatment Progress Form. The FFT clinician will be asked to complete a brief form at mid-treatment and end of treatment on the mobile app. The 7-item form asks clinicians whether administering the FFT treatment was made more difficult by factors such as the patient's or family's nonadherence (e.g., repeatedly missing sessions; coming late) or any of the listed complications, such as medical problems or accidents. There are text boxes where clinicians can indicate how these complications affected progress of the treatment, such as whether they had to add extra sessions. There is a separate Adverse Events rating form completed by the independent evaluator (see below).

MCC Usability: Usability of MCC will be assessed in adolescents, parents, and treating clinicians (see description of provider portal). We will draw on the Technology Acceptance Model (Davis, 1989) which includes scales on *Perceived Usefulness* (6-items) and Ease of Use (6-items). In addition, participants will be asked to complete the *Subjective Usability Scale* (Bevan, Kirakowski, & Maissel, 1991) which enables comparison to a broad set of information technology studies. Finally, youth and parents will fill out the *My Experience with the Program scale* (Hatcher & Gillaspy, 2006), which contains 18 items concerning their alliance with the therapist and how much they think they learned from the study app. Adolescents, parents and clinicians will complete these scales at 9-week study intervals. Finally, we will use data logs from the MCC app for both providers and patients including number of times the app was accessed, pages/modules accessed, and time spent on each page/module.

MyCoachConnect (MCC) Application

Participants will utilize the MyCoachConnect application for daily or weekly ratings of mood and behavior as well as weekly calls to the interactive voice response tool. The full MCC app consists of a mobile web application paired with text messaging (SMS) "push" notifications regarding completing assessments, practicing skills or calling in to the interactive voice response system. The scaled down version of MCC to be used in the FFT-Assess condition consists of the same mobile application for collection of weekly questionnaires, "push" notifications regarding weekly assessments, and reminders to call in using the interactive voice system.

MCC weekly online measures: In both conditions, participants will receive text messages in between FFT sessions encouraging them to complete weekly mobile assessments by clicking a link to the app in the message. Clicking the link will open a web page on their smartphone, tablet or desktop computer to access the MCC app. They will then complete survey questions and access informational content online using their browser. **No app needs to be downloaded or installed on the participant's phone as the web application is accessed through the participant's web browser.** Participants can access the online measures via the MCC mobile web app on the phone, tablet or desktop computer. These measures will be completed by parents and adolescents weekly during the 18 week active phase of treatment using the MCC mobile app; the assessment battery will be completed in approximately 15 minutes. If the participant has not completed the weekly measure, the system will send reminders based on the preferences that they indicate at study enrollment. For example, "Hi [participant's name]. We haven't heard from you in a while. Please complete the weekly survey by clicking here [link]. Thanks!".

MCC weekly voice measures: Participants in both conditions will be prompted (via push SMS and/or displaying a prompt on the mobile web app) to call the interactive voice response system of the app to provide a speech sample up to twice per week. Once again, participants can use any phone (smartphone not required) to dial a toll-free number and authenticate using their assigned ID and PIN number. Both youth and parents will answer open-ended questions about how they are doing and their family interactions. Transcriptions will be used for speech analytic analyses of mood stability/instability, suicidal ideation, and for parents, expressed emotion.

While the participant will be instructed to call the system twice per week, they may choose to call additional times per week. If the participant has not called in to the system for one week, the system will send reminders. Study staff will have access to a secure webpage where they can review audio responses from callers and manually enter transcriptions of the voice responses.

Family-Focused Therapy Protocol

The FFT protocol for early-onset youth, to be given in both conditions, consists of 12 one-hour family sessions (8 weekly, 4 biweekly), usually completed within 18 weeks. (The full FFT manual and handouts are accessible through www.semel.ucla.edu/champ/dowloads). The system for rating fidelity using the Therapy Competence and Adherence Scales consists of 11 items (e.g., communication training, problem-solving) rated by an independent rater from (1) no fidelity (e.g., therapist did not use this strategy) to (7) excellent fidelity (therapist used this strategy frequently and effectively) (Marvin, Miklowitz, O'Brien, & Cannon, 2014).

Family engagement (sessions 1 and 2). The clinician schedules an initial meeting with the teen and available family members (usually parents or siblings), and reviews the stages of FFT and use of the MCC app: (1) how to call the server and provide a speech sample; (2) how to respond to questionnaire items; and (3) what to expect in terms of weekly reminders. Treatment goals from the adolescent's, parents', and clinician's viewpoints are clarified.

Psychoeducation (sessions 2-5) assists the family in recognizing early signs of mood episodes in the adolescent, and distinguishing mood instability from developmentally appropriate emotional reactivity. A major goal of this phase is for family members to understand that the youth's aversive behavior may be due to a biologically-based illness, and is not always under his/her control. Adolescents and parents/siblings are encouraged to identify triggers for their mood swings (e.g., sleep/wake changes; negative family interactions). Adolescents are assisted in developing their own mood management plan, which usually includes (a) monitoring moods and sleep/wake rhythms, (b) learning to anticipate factors that destabilize mood, and (c) a list of "go-to" emotion regulation strategies to arrest mood escalation or deterioration (e.g., mindful breathing, behavioral activation).

Family Skills Training (sessions 6-12) consists of 4 sessions of communication training and 3 of problem-solving skills training. In role-plays, parents and adolescents learn to express positive feelings, listen actively (ask questions, paraphrase, maintain eye contact), make positive requests for change, communicate clearly, and constructively express negative emotions (e.g., pause and put difficult feelings into words). In problem-solving, families learn to break down large issues into small ones, generate and evaluate pros/cons of solutions, and choose which approaches to implement. Skill practice homework assignments for the weeks between sessions help the skills to generalize to the home setting.

Pharmacotherapy

The study coordinator will make clear that taking medication is not a requirement for participating in the study and that the child will not be experimentally assigned to receive a specific medication. If the parents and child opt for pharmacological treatment, we will refer them to the appropriate provider at UCLA or in the community. However, families/patients will be expected to

pay for such care. This decision reflects the fact that pharmacotherapy is part of the standard of care for childhood onset bipolar or unipolar disorder or high-risk conditions and not part of the study protocol.

Participatory Workgroups

Our approach to tailoring and implementing technology interventions is participatory and iterative, involving patients, parents, and providers. This proposal will seek to tailor MCC to the FFT context. This includes feedback on the MCC app requirements (which are different in the two treatment conditions), the frequency and timing of coaching push notifications, and the degree to which families find the app useful vs. cumbersome. To improve our ability to understand how individuals used the app and the context in which they did, we will conduct post-treatment workgroups for parents, adolescents and providers who have completed FFT-MCC or FFT-ASSESS. We will audio-record the workgroups and analyze for themes related to behavioral change theory constructs, usability and specific use cases.

The groups will be conducted during or following the 4-month treatment and will consist of parents and adolescents who are taking part (or took part) in the treatment (and who consent for these groups), and clinicians who participated in the same FFT condition (that is, FFT-ASSESS families will meet with other FFT-ASSESS families). We anticipate conducting approximately 2-3 workgroups for each of the different stakeholder types (parents, adolescents, clinicians).

The Full MyCoachConnect App: Augmenting FFT with a Tailored Mobile App for Families and Providers (FFT-MCC)

Mobile Assessment: The MCC mobile app, currently in use in the CHAMP clinic as an assessment device, is delivered through Chorus, a platform previously created by the study's Co-PI, Armen Arevian, MD, PhD. MCC includes a mobile web app paired with text messaging "push" notifications and an interactive voice response (IVR) system. Because the mobile app is accessed via the browser, it is compatible with all smartphone brands, tablets and desktops and no download/installation is required. In fact, participants can use any phone (smartphone <u>not</u> required) to dial the toll-free number and authenticate using their assigned ID and PIN.

(1) Participants will receive text messages in between FFT sessions encouraging them to complete weekly mobile assessments by clicking a link to the app in the message.
(2) After completing the assessments, participants will be prompted on the webpage to call the IVR component of the app to provide a 3- to 5-minute speech sample. During the call, parents will be asked four open-ended questions: "In the past week, "how have you and (him/her) been getting along?" "What have you noticed about [child's name]'s behavior that is positive?" "What have you noticed about [child's name]'s behavior that needs to improve?" "How have <u>you</u> been doing?"
(3) For teens, we will ask: "Tell us about something that happened in the last few days that you liked." "Now, tell us about something that upset you." "Tell us something that happened (good or bad) with you and one of your friends." "Now, talk about something good or bad that happened in your family," Speech samples will be audio recorded and saved to the Chorus server, then transcribed by study staff (see protections of privacy described below).

MCC Intervention Support: Individuals in FFT-MCC will have access to an interactive, mobile intervention via MCC. This intervention consists of supportive text messages sent to participants (both youth and parents) in between FFT sessions with content based on material covered that week and tailored by FFT providers, based on the participants' needs.

The app will send text messages with information related to family engagement, psychoeducation and skills training as the family transitions from one of these treatment modules to the next. Individuals can also initiate contact with the mobile app by clicking buttons to explore skills and relevant didactic material in more depth, and to obtain coaching related to responding in specific family conflicts (e.g., when anticipating a conflict, reminders about active listening and specific negotiation skills). The MCC app can be used on-demand (e.g., when an adolescent has worsening symptoms) by both parents and youth. The app will send push notifications to indicate whether or not the participant or parent have recorded use of a skill for that week.

Rewards. Participants are assigned an emoji avatar when they enter the study. They can "level up' each week and receive other emoji rewards by completing daily mood ratings, weekly app questionnaires, recording at least one voice message per week, and recording at least two skills per week (e.g., having a family meeting and practicing active listening).

The FFT Assessment Only App (FFT-Assess)

This version of the app, given in conjunction with the same 12-session FFT given in the FFT-MCC condition, differs in one important way: it only captures the online symptom/social functioning and voice assessments, but does not contain the didactic psychoeducational or skill-oriented information contained in the FFT-MCC app nor the reminders to practice skills between sessions. There will be no emoji rewards for completing the weekly assessments of mood states, family functioning, sleep, or stress (although all participants receive compensation for completing research measures, as described below). Participants are reminded to complete the weekly questionnaires and leave voice messages in the interactive voice portion of the app.

Provider Feedback and Tailoring

Assessment results will be made available in real-time to providers in both conditions via a provider portal. Following each session (and prior to the next one), FFT providers will be able to log into the MCC web portal and review the family's assessment results for the period up to the current session, including a graph of the adolescents' weekly mood ratings and family functioning scores.

In the FFT-MCC condition, providers will tailor the interactive content/skills coaching based on a review of these assessments and their own observations during FFT sessions. They will select a "highlighted" module/topic for each week (e.g., communication strategies to reduce conflict over homework). When participants access the MCC mobile app, they will see this prioritized topic at the top of a list of topics and be prompted to explore the topic further within the app in between sessions. Providers' access to participants' adherence data will enable providers to discuss possible barriers to adherence and relevant solutions during FFT sessions. As discussed above, providers in both conditions will fill out Subjective Usability, Perceived Usefulness, and Ease of Use scales to describe their experiences of using the MCC app as an aid to therapy.

Estimation of Treatment Targets through Speech Analytics

Audio recordings of weekly speech samples provided by participants will be manually transcribed within five business day and entered into to the MCC app. An analysis script will be initiated to extract the relevant lexical features from the samples and calculate the estimated target scores to be displayed on the MCC provider portal. ***We will use machine learning algorithms to obtain weekly ratings of (1) parental EE (high vs low), (2) estimated suicidal risk scores concurrently and at later study timepoints, and (3) adolescents' degree of mood instability based on their respective MCC speech samples.***

Speech data used in the analysis will be from audio recordings obtained when participants (youth and parents) call in to an automated voice response system and leave open-ended responses to questions reflecting on 1) how they are doing overall and 2) interactions within the family. Recordings are manually transcribed by study staff. We will utilize both lexical (primary focus of analysis) as well as acoustic features from the voice samples.

Lexical features: Using the transcriptions, we extract several lexical features to use as inputs for analysis. We plan to extract features that are similar to those extracted previously. These include several overlapping methods containing affective features, including SentiWordNet, Affective Norms of English Words (ANEW),and Linguistic Inquiry and Word Count (LIWC). LIWC is a broad and commonly used feature set that contains features including metrics of word usage (such as total count, words per sentence, count of parts of speech) and measures of word norms across multiple domains of word meaning including social, cognitive processes, perceptual processes, biological process, time orientation and others. Finally, we will extract simple statistics of the word norms: average, minimum, maximum and standard deviation.

Acoustic features: Acoustic features of speech have been shown to be correlated with several mental health ratings including depression and mania. We will implement methods used previous by our group based on prior reports[15], including measures of pitch, intonation, vocal formants, fundamental frequency, and inter-word pause length.

PROTECTION of HUMAN SUBJECTS

Potential Risks

This study will be of minimal risk to participants. There is a low risk of harm to patients receiving psychoeducation or family skills training. Prior studies have demonstrated the easy tolerability and efficacy of FFT for adults and children with bipolar disorder, children and adolescents at high risk for bipolar disorder, children with depression, and adolescents/young adults at high risk for psychosis (for review, see Miklowitz & Chung, 2016). This study has no manipulations of drug treatments. Pharmacotherapy is not required and when parents and children opt for it, they will be referred to psychiatrists in the UCLA outpatient services, other community clinics, or if they prefer, their own chosen providers. There is no additional risk conveyed by the more vs. less intensive MCC augmentation.

Children and parents may at times feel inconvenienced by the time required to complete the questionnaires, although the MCC platform will reduce the amount of time they spend on these measures. 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. In our pilot work, several participants told us that the open speech sample format of the MCC (e.g., “talk for a few minutes about how things are going this week”) is therapeutic in itself.

Discussing the adolescent’s psychiatric problems may at times be upsetting to the adolescent or family. If these reactions occur, the research staff, all of whom are well-trained and supervised by an attending psychologist or psychiatrist, will offer the participants emotional support and validation. Participants will also be informed that they can receive and follow-up on referrals for counseling outside of the study at any time, although they may have to be discontinued from the protocol. They can receive clinical services within the CHAMP clinic regardless of whether they participate in the study.

The children recruited for this study will have high levels of mood disturbance and mood instability. Children with significant mood variability have an increased risk of school failure, substance abuse, suicidal ideation or actions, and psychiatric hospitalizations compare to children without mood instability (Marwaha et al., 2014). The rate of hospitalization among children and adolescents with bipolar spectrum disorders is approximately 13% in one year (Goldstein et al.,

2009). ***There is no reason to suspect that rates of these illness complications will be higher if the child receives treatment in the study instead of a community treatment setting***. Because of the psychosocial protocols administered in this study, the availability of between-session communication for the adolescent and parent provided by the app, and the referral to good practice pharmacotherapy, rates of adverse events associated with the disorder may be lower than if patients were treated in the community. Nonetheless, the independent evaluator who administers the standard interval assessments will track all adverse events that occurred during a study interval – whether study related or not - using an **Adverse Events Form** developed in our prior studies.

Reducing Participant Burden

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 may complete their initial or follow-up interviews and questionnaires over two visits if they prefer.

The amount of time needed for therapists to review daily/weekly data and integrate the findings into treatment sessions should be minimal because of the availability of a clinicians' portal summarizing all recently collected data about the relevant patient. The MCC output is designed so that information about the child's Perceived Criticism ratings or mood instability of study participants can be absorbed quickly by clinicians (for example, by viewing weekly mood charts) in the 5 minutes before a session. After the session the clinician can quickly choose communication or problem-solving skills or educational content areas (e.g., relapse prevention plans) to "push" so that families will be encouraged to rehearse these skills or content areas before the next session. The clinician's choice of content can be made with a single click of an option in a drop-down menu. Thus, the time required for clinicians for the MCC protocol is well-integrated into the session by session plans.

Maximizing Confidentiality: Access to Subjects' Identities

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.

FFT sessions will be videotaped for later fidelity coding. Digital video and audio files will be stored on a password-protected internal server, and will be coded by study ID number and only accessible by research staff members. Digital video files 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, and tapes will be erased if the participant so desires. To help assure the confidentiality of participants, digital files and questionnaires will only contain numbers and not names. Each individual will receive a unique I.D. number consisting of two parts: a family I.D. number and an individual I.D. number. Data from the interviews and questionnaires will be stored in password-protected computer files maintained by the UCLA Semel Institute Biostatistics lab, and identified only by ID number. The PI will keep a separate paper/pencil list of pairings of names and participant identification numbers. This list will be kept in a locked file cabinet separate from the paper and pencil questionnaires and coded digital files. 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.

Chorus Platform and Data Protection

The MyCoachConnect interactive voice response system and weekly online survey assessments will be provided through the Chorus Platform. Chorus was developed by Dr. Arevian and the IP is owned by the UC Regents. Chorus is a web platform that allows individuals to create websites, mobile apps, and interactive text messaging and interactive voice applications (www.joinchorus.com). Chorus has been used in over 50 IRB-approved research studies, including with collection of PHI, and is approved for use by the UCLA Office of Information Security. 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 security practices including being located behind a network firewall and accessible only by designated users. No data is stored locally on user's devices (such as local browser storage or temporary storage) that access Chorus apps.

The voice recordings are experimental and used only for research. Using the same protocol as in our previous FFT studies, voice recordings will not be directly entered into the clinical record. This will be explained in the consent procedures for participants. Voice recordings are obtained through Chorus, a HIPAA-compliant platform, approved through the UCLA Office of Information Security for personal health information. Therefore, we follow all standard security procedures to protect data stored on the server and the privacy of all patients and family members. No written or voice recording data will reside on the individual's Smartphone.

Sessions of FFT will be recorded on a video server so that the FFT supervisor (D. Miklowitz) can review the session with the FFT clinician and advise on issues such as: content to emphasize in between-sessions via the mobile app; how to use communication skills training when assisting the family in problem-solving; or how to encourage compliance with the online assessments and treatment assignments. FFT supervisors will rate randomly selected FFT sessions on the Therapy Compliance and Adherence Scales. Moreover, session videotapes may be transcribed and speech features used to inform machine learning models for the prediction of clinical outcomes.

Digital files will be named using the study ID number and date of the session. The video server, which is housed in a secure data room in a locked rack, retains videos for approximately two months and then are written over in order of age, oldest first. Users have accounts and passwords to log into the system; video permissions are restricted to view/playback only those videos belonging to their individual groups. Users who require access to the system must have supervisor approval and technical staff assistance to install the application. All workstations in the Enterprise environment are encrypted and require a valid login ID. Once sessions have been downloaded to a desktop computer, they will be erased from the server.

Limits to Confidentiality

We are using a HIPAA-compliant, secured platform to reduce the risk of data breaches. As indicated above, there are circumstances, such as in the case of child abuse, where we will need to make a state-mandated disclosure. In the unlikely event that there is an unauthorized data breach (for example a server compromised by hackers despite best security practice implementation), participants involved as well as the UCLA IRB will be notified.

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 California state's Dept. of Child and Family Services. 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 at-risk child is actively abusing alcohol or drugs in a way that is life-threatening or otherwise a danger to him- or herself 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 family sessions. If we disclose these behaviors to parents, we will use extra family sessions to help resolve family conflicts and introduce preventative measures. Additional counseling sessions beyond the required number will be tabulated and included as covariates in the treatment/outcome analyses.

Privacy

All research interviews and therapy sessions will be conducted in clinical interview rooms in the Semel A-Floor CHAMP clinic or via Zoom, the HIPPA secure online platform, where the content cannot be overheard by others. CHAMP has a glassed in waiting area where participants come before their appointment. There will be no private conversations between research staff and participants in the waiting room.

We will follow protocols implemented in our prior studies with MCC speech samples. Voice samples submitted by participants will be reviewed promptly (usually within 24 hours) by study staff and transcribed. We will always have a clinician (psychiatrist or psychologist with training in assessment and management of suicidal conditions) available when voice samples are reviewed by study staff. This will usually be one of the PIs (Miklowitz or Arevian) but may also include other CHAMP clinicians (e.g., Patricia Walshaw, Ph.D.) as needed. If participants report thoughts or actions related to self-harm, the study clinician on-call will be contacted by study staff to review the response. The clinician will then determine, using clinical best practices, what the subsequent course of action should be. If an elevated risk of suicide is evident, the clinician will contact the participant and/or family to discuss further (see below). If there is continued concern after reviewing the case, the clinician will provide safety recommendations, contact additional providers, or emergency services as needed.

Preventing Suicidal Episodes

Children of parents with mood disorders are at elevated risk for suicide (Goldstein et al., 2005). We have no reason to suspect that participation in this study will elevate suicidal risk. Nonetheless, special precautions will be undertaken to prevent the onset of suicidal crises in all family members, including adolescents, parents and siblings. When a participant (an at-risk youth, a parent, or a sibling) expresses suicidal thoughts, the study staff members, or attending psychiatrists or psychologists working in the CHAMP clinic, will conduct a thorough lethality and safety assessment with the relevant family member and arrange hospitalization if necessary.

1. First, we will learn of new onsets of suicidal ideation or new attempts because we will have regular contacts with adolescents and parents for at least the 6-month study protocol, including two months after treatment has been concluded. Information about suicide will be obtained by the family clinician during treatment sessions, by the research team analyzing speech samples from the MCC, or the independent evaluator in face-to-face research assessments. Independent evaluators will contact the PI and the treating psychiatrist (if applicable) when mood deteriorations are detected so that appropriate rescue treatments can be introduced.
2. The study coordinator will begin with a telephone assessment of the participant to determine the severity of the suicidal ideation; whether there is intent, plan, and means; degree of certainty of acting on the thoughts; and history of suicide attempts. All events that trigger this safety protocol will be logged by study staff.
3. If the risk is deemed moderate to severe and the participant is not seeing a community psychiatrist, the study coordinator will ask the participant to come in for a face-to-face

evaluation with one of the attending psychiatrists in CHAMP (Drs. Suddath or Elizabeth Horstmann) or the PI (Dr. Miklowitz) or Dr. Walshaw (Study Co-Director, Clinical Psychologist). These on-call clinicians will perform a more thorough risk assessment and offer crisis counseling. They will facilitate emergency care (e.g., an evaluation at the UCLA emergency room) if necessary. The study clinic is within walking distance of the UCLA emergency room. Depending on the circumstances, the participant may be admitted to an inpatient bed at the Resnick Neuropsychiatric Hospital or referred to another hospital with an open bed.

4. If the study coordinator and on-call clinician are unable to reach the participant within 12 hours, or after 3 phone call attempts, they will contact the participant's parent or other emergency contact.
5. If the suicide risk is deemed low, we will intervene through offering referrals to care or crisis resources, and developing a safety plan (i.e., identifying triggers for suicidal thoughts; listing who the participant will call if he or she feels suicidal; getting in touch with the attending psychiatrist or psychologist and what to do if they are unavailable), and problem-solving to eliminate triggers of suicidal thoughts and prevent the escalation of suicidality.

The family clinician will intervene to prevent deterioration, following procedures outlined in Miklowitz & Taylor (2006). Usually, prevention includes additional family sessions or individual sessions with the child or parents. The FFT manual has a supplementary module for addressing suicidality, which includes (a) conducting chain analyses to assess the precipitants and consequences of suicidal thoughts or actions, (b) providing education about the biological linkage between suicidal thoughts and mood disorder, (c) developing a suicide prevention contract (i.e., identifying triggers for suicidal thoughts; clarifying the steps by which parents can get in touch with the psychiatrist or therapist and what to do if they are unavailable), (d) enhancing family members' expressions of support, concern, and compassion; and (e) family problem-solving to eliminate triggers of suicidal thoughts and prevent their worsening.

Protocol for Monitoring Safety of Speech Samples

We will follow protocols implemented in our prior studies with MCC speech samples. Voice samples submitted by participants will be reviewed promptly (usually within 24 hours) by study staff and transcribed. We will always have a clinician (psychiatrist or psychologist with training in assessment and management of suicidal behavior) available for study staff to contact when they are concerned about the content of a participant's speech samples. This will usually be one of the PIs (Miklowitz or Arevian) but may also include other study PhD or MD clinicians as needed. If participants report thoughts or actions related to self-harm – either in voice samples or on daily or weekly questionnaires - study clinicians will be contacted by study staff to review the reports. The clinician will then determine, using clinical best practices, what the subsequent course of action should be. If an elevated risk of suicide is evident, the clinician will contact the participant and/or family to discuss more intensive treatment options, such as inpatient care or partial hospitalization. Often, this process requires having one or more emergency treatment sessions. If there is continued concern, the clinician will provide additional safety recommendations, contact the participant's other providers, and refer to emergency services as needed. If the risk is lower, the family clinician will address risk factors related to suicidal ideation in their weekly family therapy sessions, or offer referrals to individual therapy should the participant want them.

Availability of Ancillary Treatments

Participants who do not respond to study-based treatments may require out-of-protocol emergency or other services. These participants will be retained in the protocol whenever possible. A child who needs to be hospitalized (e.g., for suicidality) will be reentered into the protocol after hospital discharge if the child and family agree to continue participating. Family sessions will be conducted in the hospital if necessary. Children or families will not be withdrawn if they seek weekly individual psychotherapy outside of the study (for example, individual therapy, group therapy, school-based counseling).

If family members request ancillary treatment, or in the family clinician's judgment referral to an outside therapist or physician is clinically indicated, we will refer the relative to the appropriate care providers. Referrals for pharmacotherapy evaluations will also be made. If family members require hospitalization, we will follow the same advocacy procedures described above for the at-risk child.

Family members (parents or siblings) can also pursue ancillary treatments without jeopardizing the family's involvement in the study. Thus, they 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. **Families will be withdrawn from the study only if they request and pursue referrals for family or marital therapy outside of the context of the study protocol.** Family intervention is the modality we wish to systematically examine and it would not be in the family's best interests to undergo two simultaneous forms of family therapy. Families will be made aware of this contingency (orally and via the consent forms) during the initial consent phase. We will record each patient's, parent's, and sibling's non-protocol treatments (medications received, frequency and type of extra psychotherapy sessions) using the ***Treatment Utilization Form***.

Circumstances That May Require Study Withdrawal

Noncompliance. Participants will be withdrawn from the protocol if they are noncompliant with the study procedures (for example, miss 3 consecutive family therapy sessions without calling ahead, or refuse to provide speech samples). The circumstances that may require administrative withdrawal will be spelled out in the consent forms.

Substance or alcohol abuse. Youth who meet DSM-5 substance or alcohol abuse or dependence DSM-5 criteria will not be included. If the child shows evidence of regular substance or alcohol use after randomization (during the study protocol) and/or develops a DSM-5 substance/alcohol abuse or dependence disorder, we will retain him or her in the study protocol for as long as possible and work toward abstinence. In most cases 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. 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.

Participants will have been 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 at UCLA. They can have regular pharmacotherapy or psychotherapy at CHAMP or another relevant 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.

Tolerability of the Baseline and Follow-up Assessment Batteries

Our prior experience with assessment batteries similar to the one proposed has been that they are well-tolerated by children and adults. We estimate that the initial assessment battery (MINI, YMRS, CDRS, questionnaires) will require approximately 2 – 2.5 hours from the parent and youth, which can be spread over two sessions. The follow-up interview and questionnaire battery averages -1.5 hours and will be administered at 9, 18, and 27 weeks.

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 help assure the integrity of the data. Children will be allowed to take breaks as often as they require.

This project includes the addition of daily and weekly assessments through the MCC app. Questionnaires and speech samples are obtained weekly by the app, and ratings of mood and sleep obtained daily in the FFT-MCC condition and weekly in FFT-Assess. We have minimized the assessments required through the app and estimate that the weekly abbreviated questionnaires and speech samples will average no longer than 15 minutes to complete. We expect that the ease of completing the assessments through a mobile app will lessen the assessment burden. Prior studies using the MCC app (Arevian et al., in press) have shown generally good tolerability and compliance with online mood assessments.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

Compensation

Families will be compensated up to $410 over the 6-month study: $40 for the intake assessment (paid to the parents and separately, the child) and $25/each for the standard follow-ups at 9, 18 and 27 weeks. Additionally, $90 is paid to the parent(s) (and separately, $90 to the child) for completing the weekly mood and sleep ratings and the online speech samples for the 6-month study (Table below). We will pay teens $4 cash per call up to $16 per month for use of the app voicemail system; teens in active treatment will be compensated at their next appointment while teens in the follow-up phase will be compensated at their final research assessment. We will reimburse parents for the costs of their on-campus parking (about $12) for the research visits at baseline, 9, 18 and 27 weeks. Research interviews will be scheduled at the times (for example, after school; immediately following treatment visits) most convenient for the family. If the parents or child decide to stop the study early, they will be paid for those research assessment sessions completed up to that point. Families in the two treatment conditions will be compensated equally.

The table below summarizes the plan of research assessments and payments.

Task	**Payment to Family**	**Approximate time requirement**	**When paid?**
Baseline in-person assessment and MCC questionnaire battery	$40 to child, $40 to parents	2.0 hours	After completing baseline assessment
9 Week in-person assessment and MCC questionnaire battery	$25 to child $25 to parents	1.5 hours per person	After completing assessment

18 Week in-person assessment and MCC questionnaire battery	$25 to child $25 to parents	1.5 hours per person	After completing assessment
27 Week in-person assessment and MCC questionnaire battery	$25 to child $25 to parents	1.5 hours per person	After completing assessment
Weekly MyCoachConnect calls (answering brief questionnaires, providing speech samples)	$90 to parent(s), $90 to child; additional payment for calls by teens is $4 per call up to $16 per month	6 hours over 6 months	Week 27 (payment proportionate to assessments completed); calls will be paid out at the next in person appointment

The $90 paid for completing weekly ratings will be dispensed at the end of the study (week 27). It will only be dispensed in full if the participant has completed at least 50% of the required assessments. For example, if they complete 25% of the assessments, they will be paid $90 x .25 = $22.50; if they complete 50%, they will be paid $45. These payment schedules are made clear in the consent and assent forms.

Cost: Benefit Ratio

In our opinion, the benefits of this study to participating families outweigh its risks. All families will receive an 18-week, 12 session course of family psychoeducation about mood disorders (personalized to the symptoms and course trajectories of their adolescent offspring), and family skills training (communication and problem-solving skills). Parents report that specialized treatments for children with mood disturbances are rare in Los Angeles and where they do exist, are often quite expensive. The information obtained from the study may help guide the subsequent care of the child in the community.

At-risk youths will receive a diagnostic evaluation and, as appropriate will be referred for psychiatric care sessions from a child psychiatrist. The mood and family management skills learned in sessions may translate into a better course of symptoms for the adolescent. Through in-session learning (and in FFT-MCC, practicing at home via the MCC app), parents may gain a greater knowledge of how to cope with their child's mood swings and resolve family conflicts, which may improve their own mood states, decrease subjective burden and distress, and reduce levels of expressed emotion. Likewise, in both conditions the adolescent will receive important informational tips on regulating mood states. All child and adult participants will receive support, help in solving problems, advice, reassurance, and information as needed from project staff members for the 6-month study. After the study, they will receive appropriate referrals for pharmacological and psychosocial follow-up care, including care at the same clinic if appropriate. The study staff members will continue to provide treatment and crisis counseling until such referrals have been contacted and treatment initiated.

Clinical emergencies (e.g., suicidal crises) may at times require additional family sessions. These will be offered as clinically appropriate. The research assessments are time-consuming but the interviews and five-minute speech samples are often experienced positively by the participants, because they are administered by sensitive, clinically-trained staff members. The results of these assessments should also be useful in informing treatment plans for the child following participation in the study. Finally, participants (at-risk child or adolescent) will be financially compensated for completing the research assessments.

IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Successful implementation of this study will generate much-needed empirical data on how to treat youths with mood instability, the behavioral mechanisms associated with clinical change, and clues as to how to make family interventions more accessible to a larger number of people. Our long-term objectives are to promote symptom stabilization, reduce symptom severity over time, reduce the eventual onset of more severe mood disorders, and enhance individual and family functioning. Utilization of real-time technology to assess moods and behavior, and to augment treatment with frequent between-session skills coaching will enhance our ability to achieve these long-term objectives. The potential clinical gains for participants and to the field are likely to outweigh the minimal risks to participants.

References

Arevian, A. C., O'Hora, J., Jones, F., Jones, A., Booker-Vaughns, J., Banner, D., . . . Wells, K. B. (in press). Participatory technology development to enhance community resilience *Ethnicity and Disease*.

Bevan, N., Kirakowski, J., & Maissel, J. (1991). What is usability? In H. Bullinger, -J. (Ed.), *uman Aspects in Computing: Design and use of interactive systems and work with terminals.* . Amsterdam: Elsevier.

Birmaher, B., Khetarpal, S., Brent, D., Cully, M., Balach, L., Kaufman, J., & Neer, S. M. (1997). The screen for child anxiety related emotional disorders (SCARED): Scale construction and psychometric characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 545-553.

Davis, F. D. (1989). Perceived usefulness, perceived ease of use, and user acceptance of information technology *MIS Quarterly, Vol. 13*(3), 319-340.

Ehlers, S., Gillberg, C., & Wing, L. (1999). A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. *Journal of Autism and Develeopmental Disorders, 29*(2), 129-141.

Gerson, A. C., Gerring, J. P., Freund, L., Joshi, P. T., Capozzoli, J., Brady, K., & Denckla, M. B. (1996). The Children's Affective Lability Scale: a psychometric evaluation of reliability. *Psychiatry Research, 65*(3), 189-198.

Goldstein, T. R., Birmaher, B., Axelson, D., Goldstein, B. I., Gill, M. K., Esposito-Smythers, C., . . . Keller, M. (2009). Family environment and suicidal ideation among bipolar youth. *Archives of Suicide Research, 13*(4), 378-388.

Goldstein, T. R., Birmaher, B., Axelson, D., Ryan, N. D., Strober, M. A., Gill, M. K., . . . Keller, M. (2005). History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. *Bipolar Disorders, 7*(6), 525-535.

Hatcher, R.L. & Gillaspy, J.A. Development and validation of a revised short version of the working alliance inventory. *Psychotherapy Research*, 2006, 16 (1).

Kay, S. R., Wolkenfelf, F., & Murrill, L. M. (1988). Profiles of aggression among psychiatric patients: I. nature and prevalence. *Journal of Nervous and Mental Disease, 176*, 539-554.

Magana, A. B., Goldstein, M. J., Karno, M., Miklowitz, D. J., Jenkins, J., & Falloon, I. R. H. (1986). A brief method for assessing expressed emotion in relatives of psychiatric patients. *Psychiatry Research, 17*, 203-212.

Marvin, S. E., Miklowitz, D. J., O'Brien, M. P., & Cannon, T. D. (2014). Family-focused therapy for youth at clinical high risk of psychosis: treatment fidelity within a multisite randomized trial. *Early Intervention in Psychiatry*. doi: 10.1111/eip.12144

Marwaha, S., He, Z., Broome, M., Singh, S. P., Scott, J., Eyden, J., & Wolke, D. (2014). How is affective instability defined and measured? A systematic review. *Psychological Medicine 44*(9), 1793-1808.

Masland, S., & Hooley, J. M. (2017). Perceived Criticism: a research update for clinical practitioners. *Clinical Psychology: Science and Practice*.

Miklowitz, D. J., & Chung, B. D. (2016). Family-focused therapy for bipolar disorder: reflections on 30 years of research. *Family Process*, 1-17. doi: 10.1111/famp.12237

Miklowitz, D. J., & Taylor, D. O. (2006). Family-focused treatment of the suicidal bipolar patient. *Bipolar Disorders, 8*, 64-651.

Mueser KT, Drake RE, Clark RE, McHugo GJ, Mercer-McFadden C, Ackerson TH. Toolkit for evaluating substance abuse in person with severe mental illness. Cambridge, MA: Evaluation Center at Human Services Research Institute; 1995.

Poznanski, E. O., & Mokros, H. B. (1995). *Children's Depression Rating Scale, Revised (CDRS-R) Manual*. Los Angeles, CA.: Western Psychological Services.

Prinz, R. J., Foster, S. L., Kent, R. N., & O'Leary, K. D. (1979). Multivariate assessment of conflict in distressed and nondistressed mother-adolescent dyads. *Journal of Applied Behavior Analysis, 12*, 691-700.

Sheehan, D. V. (2016). *MINI International Neuropsychiatric Interview: Child and Adolescent Version for DSM-5*: Harm Research Institute.

Weissman, M. M., Wickramaratne, P., Adams, P., Wolk, S., Verdeli, H., & Olfson, M. (2000). Brief screening for family psychiatric history: the family history screen. *Archives of General Psychiatry, 57*(7), 675-682.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity, and sensitivity. *British Journal of Psychiatry, 133*, 429-435.

Youngstrom, E. A., Frazier, T. W., Demeter, C., Calabrese, J. R., & Findling, R. L. (2008). Developing a 10-item mania scale from the Parent General Behavior Inventory for children and adolescents. *Journal of Clinical Psychiatry, 69*(5), 831-839.

Youngstrom EA[1], Murray G, Johnson SL, Findling RL. (2013). The 7 up 7 down inventory: a 14-item measure of manic and depressive tendencies carved from the General Behavior Inventory. Psychol Assessment, 2013, 25(4), 1377-83.

Appendix

DATA SAFETY PLAN

Responsibility for Data Safeguarding

The principal investigators, Drs. David Miklowitz and Armen Arevian, have ultimate responsibility for data safeguarding. All project staff will have completed the CITI IRB training and UC HIPAA training (UCLA personnel) or other HIPAA training (non-UCLA personnel), and will sign a Confidentiality Agreement (in compliance with university policies and procedures to protect the privacy of the research data) for their entire tenure on this project.

Data Storage

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.

Data management, programming support and statistical consulting services

These services will be provided by SIStat, the biostatistics core in the UCLA Semel Institute for Neuroscience and Human Behavior (C. Sugar, Director). SIStat is made up of senior consulting faculty from the departments of Biostatistics and Psychiatry, as well as full-time staff statisticians, database and application development programmers, database managers and web designers. Its personnel have extensive experience providing support for multisite studies involving longitudinal trials, including prior studies by the PI. Services for this project will include the creation of a customized online database that will eventually incorporate a randomization system, data dictionary, adverse event reporting system, data entry forms for all clinical and behavioral measures, project management and tracking tools, and a query and dissemination system to control the flow of data and provide information to investigators and the DSMB committee. Development of this customized database is already well underway because the online database for our high-risk early intervention study (MH093676) used many of the same measures.

SIStat databases feature a variety of built-in quality assurance processes including double entry to verify data correctness, automatic logic and range checking, and strict protocols for data confidentiality, transfer, security and backup. All systems and tools are located on a shared networking server at UCLA, are protected by 128 bit SSL (the secure socket layer technology used for sensitive transactions on the web), and feature an hierarchical system of password protected logins, allowing differential access to project team members as appropriate for their

roles. All requests for analysis datasets will be made through the online query system and must be approved by the PI before they are prepared and distributed by SIStat staff.

Databases are backed up daily on the servers and at regular intervals to tape which is stored off site. Snapshots of the datasets distributed for analyses, along with the corresponding queries, will also be permanently preserved. SIStat personnel 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 study's data technicians, responsible for entry of completed paper/pencil forms) to coordinate the timely completion of data deliverables. SIStat will also notify the Research Coordinator when 9-week follow-ups are coming due.

Data Transmittal

Digital audiotapes containing Five-Minute Speech Samples (FMSSs) will be sent to a transcription service affiliated with UCLA that has been chosen because of its consistency with HIPAA and UCLA rules about confidentiality and privacy. Tapes of FMSSs (coded by study ID) will also be transmitted to Ana Magana Amato, MSW, a private contractor who will be responsible for coding of expressed emotion. All personal health information will be stripped from the tapes before transmittal. The default mechanism for electronically transferring files 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.

MCC Mobile App

The MCC mobile app (including both patient- and provider-facing versions) was built using the Chorus platform. Chorus is a web application that allows individuals to create websites and mobile apps to collect and display data similar to sites such as SurveyGizmo. Chorus was created by Dr. Armen Arevian at the Center for Health Services and Society at UCLA and is hosted by a server at that center. It has been approved by the UCLA Office of Information Security for use in research projects including those that collect protected health information. The server is located in a locked server cabinet and server room with access only by Center IT administrators. Data are regularly backed up. All communication to and from the server is encrypted using SSL certificates. The server 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 (Semel network drive described above) for storage and analysis.

Audit and Monitoring Plans

Speech samples provided by parents and adolescents will be transcribed and reviewed within 3 days of completion. Study staff will screen transcripts for evidence of thoughts of self-harm or of harming others, including child or elder abuse. If study staff detect the presence of these thoughts or statements, we will implement a standardized notification protocol. This includes immediately alerting the PI and co-PI for further review. If warranted, one of the PIs or a covering licensed MD

or psychology PhD will contact the participant. They will leave up to three voicemails and if unable to reach the participant on the same day, they will contact the participant's emergency contact (usually a parent). Once contacted, the staff member will interview the participant to further clarify their risk of self-harm or of harming others. They will determine an intervention as clinically appropriate based on that risk (see Section on Minimizing Risks).

Data Safeguarding: Standard Procedures

UCLA staff will also abide by the basic set of procedures which are generally utilized to protect identifiable private and proprietary data. For each phase of the study, the following procedures will be implemented:

1. Training staff on data sensitivity and data safeguards.
2. Processing sensitive data in a centralized location with established access control procedures.
3. Storing sensitive hardcopy in locked files when not in use.
4. Restricting access to shared disk files through appropriate use of file permissions.
5. 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.
6. If it is necessary to transfer materials by mail, we will use certified mail, return receipt requested, for sensitive data or communications; and registered mail for the most sensitive data or communications.
7. Re-training staff and reviewing sensitive data inventory and data safeguards annually.
8. Reporting all serious violations of the Data Safeguarding Plan in writing to the PI, with a copy to the Privacy Resource Office.

DATA SAFETY MONITORING BOARD

This study will have a separate DSMB committee, consisting of a clinical psychiatrist or psychologist, a statistician, and a community stakeholder (e.g., a parent of a child with mood disorder). The PI has already approached several individuals at UCLA and outside UCLA who have agreed to serve on the committee. The purpose of the DSMB is to review the implementation of the human subjects protocol and help assure the safety of participants. The board will review all serious adverse events (e.g., hospitalizations, suicide attempts) and other adverse events (e.g., medication nonadherence, contact with police, school truancy) in relation to treatment phase (psychoeducation, communication skills, problem-solving skills). The DSMB will make recommendations to the NIMH and the University IRBs if it believes that participants are being endangered by the study procedures or the trial should be stopped. It will make recommendations as to ways to improve the quality of care and confidentiality of the participants. As in our prior studies, this study's DSMB will work with the PI to inspect samples of data and help assure the confidentiality, reliability, and validity of the data collection, entry and management process. The DSMB board will meet yearly (or more frequently if warranted) and receive reports from the PIs about study progress and safety issues. The Board will then issue its own reports to the UCLA IRB and the NIMH, along with suggested corrective courses of action.