**Title: Improving Adherence in Adolescents and Young Adults with Bipolar Disorder**
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***Background**:*

This project will build upon an evidence-based adherence enhancement approach in adult BD and optimize the intervention to meet the specific developmental needs of a population (Adolescents and Young Adults- AYA with BD) for which there are no currently accepted adherence interventions and for which adherence behavior mechanisms are poorly known. This project will use a step-wise approach to characterize the needs of the target population, refine the intervention, and test mechanistic and adherence-related outcomes. This study would be the first to modify and pilot test an intervention that targets adherence barriers in order to optimize adherence in AYAs with BD. Other novel elements include: 1) using iterative qualitative input to optimize a manualized intervention salient to AYAs with BD, 2) assessing the intervention in two geographically distinct sites, and 3) examining mechanisms of adherence behavior in AYAs. The resulting feasibility, acceptability and preliminary efficacy data will lay the groundwork for an RCT with the overarching goal of enhancing generalizability and scale-up.

There is no current standard-of-care for improving adherence in AYAs with BD. An expanding literature suggests that it may be possible to enhance treatment adherence in BD.[1, 2-6] Multiple-strategy interventions are likely to be more effective than a generic single-strategy intervention.[7-10] However, broadly-focused psychosocial interventions that address the full scope of BD problems are not consistently associated with improved adherence.[1,11] Intensive psychosocial interventions are not practical in many clinical settings. Additionally, they are unlikely to be tolerated by non-adherent AYAs with multiple academic, employment and social commitments.[12-14] Similar to the adult BD literature, existing care approaches in AYAs with BD do not specifically target adherence and may not be practical for clinical settings. Miklowitz and colleagues have successfully used family-focused treatment (FFT) for adolescents with BD.[15, 16] However, FFT requires more than 20 sessions and a 9-month intervention duration, a time commitment that is not ideal for AYA, who tend to be oriented toward more immediate rewards. Thus, there is a clear need for brief interventions that are attractive to AYAs and which can rapidly facilitate key health behaviors.

Customized adherence enhancement is a novel intervention that works in BD. Findings from our group, as well as other adherence research [17,1,18,19,20,21-27] suggest that key modifiable adherence barriers in BD include an under-appreciation of illness severity/consequences of non-adherence, substance abuse and other high risk behaviors that impede appropriate medication-taking, difficulties with medication routines, and inadequate ability to communicate with prescribing clinicians regarding drug side-effect concerns. We developed CAE to address key barriers to medication adherence, specifically for non-adherent patients with BD.[28, 29] Complementary and differing sources of qualitative data (focus groups, advisory board input, cognitive interviews) will optimize delivery of CAE to meet the needs of AYAs with BD.

Research in AYAs with chronic health conditions suggests that addressing adherence barriers predicts outcomes: The Pediatric Self-Management Model (Figure 2),[30] developed by Modi (co-I) and colleagues, highlights the individual, family, healthcare system, and community factors that influence disease management and how these processes in turn impact adherence and health outcomes. This model has been applied to a variety of chronic conditions and shares important targets for adherence interventions, including the specific focus on barriers in the current proposal. Modi and colleagues demonstrated that a greater number of adherence barriers correlates with and predicts worse adherence in AYAs with chronic health conditions.[31, 32] Specifically, and aligned with the CAE intervention developed by Sajatovic and Levin, BD knowledge, communication with clinicians and support systems (e.g., family, peers), risk-taking (e.g. substance abuse, unprotected sex), and medication-taking routines appear to be key mechanisms to improve adherence in AYAs. However, there is a need to incorporate the unique issues relevant to AYAs with BD when targeting adherence barriers. Qualitative findings will inform modifications which may include remote technology-facilitated delivery methods (i.e. smart phone) to appeal to AYAs.

***Project Design**:*

**Aim 1:**
**In Phase 1,** we will conduct focus groups in adolescents and young adults (AYAs) with bipolar disorder (BD), their parents/guardians/care partners, and healthcare providers to evaluate barriers & facilitators to adherence. We will use these data, as well as input from an advisory board, to modify an adult intervention that targets adherence barriers in order to optimize adherence, Customized Adherence Enhancement (CAE), with the goal of targeting our hypothesized mechanism, such that it is developmentally specific, appropriate and acceptable to AYAs with BD.

**In Phase 2**, we will conduct cognitive interviews (e.g., "think aloud") with 6-8 of the AYAs with BD (ages 16-21 years) to elicit feedback on the resulting CAE-AYA.

**Aim 2:** In Phase 3, we will conduct a pilot randomized-controlled trial of CAE-AYA vs. enhanced treatment as usual (ETAU) to examine changes in medication adherence (primary outcome) in AYAs with BD.

**Hypotheses 1:** At 6 month follow-up, compared to ETAU, individuals in CAE-AYA will have greater improvement in adherence measured by the Tablets Routine Questionnaire (TRQ) and electronic adherence monitoring.

**Hypotheses 2**: We expect greater improvements in secondary outcomes, including health related quality of life and symptoms in CAE-AYA vs ETAU group.

**Aim 3:** Exploratory analyses will investigate CAE-AYA mechanistic effects by evaluating whether adherence barrier change (BD knowledge, communication with clinicians/parents/guardians/care partners, medication routines and substance use/risky behaviors) is related to adherence change.

**Hypotheses 3:** Change in knowledge, communication with clinicians/parents/guardians/care partners, medication routines and substance use/risk-taking behaviors will mediate improved adherence.

***Number of Study Participants***
We plan to enroll a total of up to 82 participants across all 3 phases and both sites (see breakdown below):
Phase 1: focus groups/advisory board (n=up to 54; all at CWRU)
Phase 2: cognitive interviews (n=up to 8; all at CWRU)
Phase 3: The total number of subjects that may be enrolled in to the RCT across both sites (CWRU and UC) is 40.

***Inclusion and Exclusion Criteria***

**Phase 1 Focus Group/s and Advisory Board**
We will conduct 2-3 focus groups in AYA with BD (6 individuals per focus group with a total of 12-18 individuals), 2-3 focus groups of parents, legal guardians or care partners (e.g., spouse, grandparent, adult sibling, etc.) who are involved in the care of and live with an AYA with BD (6 individuals per focus group with a total of 12-18 individuals), and 2-3 focus groups of healthcare providers that care for AYA with BD (6 individuals per focus group with a total of 12-18 individuals). AYA and parent/guardian/care partner focus group participants will be referred by clinicians or self-referred in response to IRB-approved advertisements. To optimize generalizability, some of the prescribing healthcare providers will be community-based.
We will then convene an advisory board (AB) of AYAs with BD (n= up to 10), parents/guardians/care partner of AYAs with BD (n= up to 10), and a group of healthcare providers (e.g., physicians, therapists, pharmacists, and nurses) that care for AYAs with BD. AYA and parent/guardian/care partner AB members will be a representative subset of the members of the focus groups. Healthcare provider AB participants will be physicians, therapists, pharmacists, and nurses that care for AYAs with BD.

**Inclusion for AYA focus group and AB members**
1. Individuals between the age of 16 and 21 years old.

2. DSM-5 diagnosis of bipolar disorder (BD)
3. If <18 years, able and willing to give written informed assent and have a legal guardian provide written informed consent. If > 18 years, able and willing to provide written informed consent.
4. Fluent in English.

**Inclusion for parent/guardian/care partner focus group and AB members**

1. Individuals of age 18 years or older.
2. Parent, legal guardian or other person who is closely involved with the care of and lives with an adolescent/young adult who meets the study criteria.
3. Willing/able to provide written, informed consent for their participation.
4. Fluent in English

**Inclusion for provider focus group and AB members**

1. Individuals of age 18 years or older.
2. Physician, therapist, pharmacist, or nurse that cares for AYAs with BD.
3. Willing/able to provide written informed consent for their participation.
4. Fluent in English

**Exclusion for all focus groups and AB members**

1. Unable to receive care in the outpatient setting due to illness severity
2. A DSM-5 diagnosis of an autism spectrum disorder or primary psychotic disorder.
3. Documented or suspected IQ< 70.

**Phase 2 Usability testing and feedback:**

In Phase 2, CAE-AYA will undergo usability testing and feedback with 6-8 AYAs with BD, representative of age, gender, and ethnicity. Participants will be referred by clinicians or self-referred in response to IRB-approved advertisements.

**Inclusion for Phase 2 participants**

1. Individuals between the age of 16 and 21 years old.
2. DSM-5 diagnosis of bipolar disorder (BD), type I or II.
3. Poor adherence defined as missing ≥ 20% of prescribed evidence-based BD medications, i.e., mood stabilizer (e.g., lithium, valproic acid, or carbamazepine) or second generation antipsychotics, on the TRQ at any point since being diagnoses with bipolar disorder.
4. If < 18 years, able and willing to give written informed assent and have a legal guardian provide written informed consent; if > 18 years, able and willing to provide written informed consent.
5. Fluent in English.

**Exclusion for Phase 2 participants**

1. Unable to receive care in the outpatient setting due to illness severity.
2. A DSM-5 diagnosis of an autism spectrum disorder or primary psychotic disorder.
3. Documented or suspected IQ<70.
4. Prior enrollment in CAE.

**Phase 3 Randomized Clinical Trial:**

Once a referral has been made, either by self or clinician referral, a research assistant will telephone the potential participant, give a brief description of the study, and invite them to an appointment to assess their eligibility. Individuals who provide informed consent (or assent with informed consent provided by their legal guardians if they are < 18 years old) will then proceed with screening and enrollment for the RCT.

**Inclusion for RCT participants**

1. Individuals between the age of 13 and 21 years old.
2. DSM-5 diagnosis of bipolar disorder (BD), type I or II as diagnosed by the Structured Clinical Interview for DSM-5 (SCID-5).

3. Poor adherence defined as missing ≥ 20% of prescribed evidence-based BD medications, i.e., mood stabilizer (e.g., lithium, valproic acid, or carbamazepine) or second generation antipsychotics, on the TRQ for the past week or past month.
4. If < 18 years, able and willing to give written informed assent and have a legal guardian provide written informed consent. If > 18 years, able and willing to provide written informed consent.
5. Fluent in English.

**Exclusion for RCT participants**

1. Unable to receive care in the outpatient setting due to illness severity.
2. A DSM-5 diagnosis of an autism spectrum disorder or primary psychotic disorder.
3. Documented or suspected IQ< 70.
4. Have recently (in the past month) started a new psychotherapy/behavioral intervention

***Special/Vulnerable Populations**:*

**Minors**

The CAE-AYA intervention is meant to be an adjunct to routine clinical care. The AYA with BD participant and their legal guardians (if < 18 years) will be informed and it will be understood that acceptance or refusal to participate in any phase of the study will not influence their ability to receive clinical care at any affiliated hospital or clinic setting or elsewhere, and that they are free to withdraw from study participation at any time. The informed consent/assent process will be documented for each participant. Specifically, for all participants, it will be documented that information was provided regarding the risks, benefits, and alternatives to study participation.

Consistent with the Federal guidelines, all participants/guardians will be informed, verbally and in the written consent/assent form, of the federally mandated reporting laws for child abuse and neglect. Specifically, the consent form will read, "the state of Ohio, mandates all those working with children report suspected incidents of abuse or neglect. In addition, research records, just like hospital records may be subpoenaed by a court order. If some information about abuse is revealed that must be reported, or if a court order to release the reports is received, an attempt will always be made to inform you before the Department of Human Services or any other agency is consulted. Within the bounds of confidentiality permitted by the law, no information about you (or your child) will be shared with any individual or agency without your prior consent." Thus, except under circumstances covered under the mandated child abuse reporting laws, and/or situations in which the adolescent/young adult and/or a family member is judged to be a danger to him- or herself or others, no information about the adolescent/young adult or family will be shared with any individual or agency without prior consent.

**Students/Employees**

UHHS or CWRU employees or students will not specifically be recruited for this study, however, they will be allowed to participate if they fit the inclusion criteria and do not directly report to the Psychiatry Department. Students and employees may directly benefit from participation. Anyone with an employment or academic relationship to CWRU or UH will be informed that their participation in the study or refusal to do so, will in no way influence their grades, employment, or subsequent recommendations. Employees will never be made to feel that their job, promotion, salary, or status in any way depends on participation in the research study. The Principal Investigator or any other coinvestigator will not be responsible for directly recruiting and/or obtaining informed consent from any person under his or her direct supervision/employee.

***Setting:***

1) Research will be conducted at the Research offices of the PIs, Dr. Sajatovic in Cleveland and Dr. DelBello in Cincinnati.
2) Participants will be referred by local clinicians who have been informed of the study by study staff, by self-referral in response to IRB flyers, and by email as described in the Recruitment section.
3) The Cleveland offices are in the W.O. Walker Center, 10524 Euclid Ave., Cleveland, OH 44106.

The consent process may be conducted remotely via video conferencing, using either UH Zoom, CWRU restricted Zoom, Zoom for Healthcare or WebEx, and REDCap (individual link emailed directly to the participant/guardian) if necessary. All other study procedures may also be conducted remotely via telephone or

via video conferencing, using UH Zoom, CWRU restricted Zoom, Zoom for Healthcare or WebEx and REDCap (individual link emailed directly to the participant/guardian), if necessary.

***Recruitment Methods***

Participants will be recruited for Phases 1 & 2 of the study at CWRU. It is expected that most participants will be referred from the child, transitional care and the general adult psychiatry clinics in the Department of Psychiatry at CWRU/UH or (for Phase 2) be self-referred in response to IRB-approved flyers advertising the study which will be posted with permission of staff at Community Mental Health Clinics, physician offices, and other organizations serving this population. Healthcare providers will also be recruited by email for focus groups and advisory boards. Follow-up methods will include both email and phone calls.

Participants for Phase 3 of the study will be recruited from CWRU/UH and child and adult clinics in Cincinnati. Once a potential participant has been identified by their clinician, the clinician will ask if they are interested in hearing more about the study and ask permission for someone from the study team to call them. Potential participants may also self-refer in response to IRB-approved flyers advertising the study which will be posted with permission of staff at Community Mental Health Clinics, physician offices, and other organizations serving this population. Once the referral has been made, either by self or clinician referral, a research assistant will talk with the potential participant over the phone, give a brief description of the study, and invite them to an appointment to assess their eligibility.

At the CWRU site, we will recruit participants through their clinicians from the Department of Psychiatry at UHCMC, the Division of Child and Adolescent Psychiatry at UHCMC, and affiliated community mental health centers. The CWRU site will also recruit using ResearchMatch. social media ads, Google search ads and bus ads. Social media ads will be posted on Facebook originating from the main UH Facebook page. Bus ads will run on the RTA bus system. Social media ads, Google search ads and bus ads are being done in coordination with UH Marketing & Communications and Brokaw ad agency. We will also query TriNetX to identify potential participants. Address, phone numbers and email addresses will be collected so that parents/guardians/potential participants can be contacted (by letter or email, followed by a phone call). The letters will mention specifically that individuals can opt out of the follow up phone call. Potential participants/their parents/guardians who do not opt out of the follow-up phone will be contacted and, if they express interest in the study, a screening visit will be scheduled. Up to 4 attempts will be made to contact the potential participant. Research personnel will leave a voicemail if the person does not answer. For those participants who cannot be contacted, refuse participation, or otherwise do not qualify for the study, only aggregate numbers will be retained to keep track of recruitment efforts. The personal information will only be kept for as long as necessary (i.e. until the participant is enrolled or documented as a pre-screen failure). We will request a partial waiver of HIPAA to be able to collect PHI for recruitment purposes.

In Cincinnati we will recruit participants from The Mood Disorders Clinic at the University of Cincinnati Medical Center, The Division of Child and Adolescents Psychiatry at Cincinnati Children's Medical Center, and the Central Clinic Community Mental Health Center. The UC site will also recruit using ResearchMatch. We will also run an electronic medical record query at this site as well, using the same method as described above for the CWRU site.

Clinicians at the above mentioned clinics will be given information about the research study and will be asked to consider referring AYA patients of theirs with BD and ask them if they would be interested in hearing more about a research study. The research assistant will then call patients who have agreed to being called, give them a brief description of the study, and prescreen them for basic inclusion/exclusion criteria over the phone. If patients are still interested, an appointment will be made to meet with the RA in person to consent the participant and complete the screening visit.

The CWRU outpatient clinics from which we will recruit provided care to 2,212 unique individuals in 2018 who were between the ages of 14-20. Patients are seen for follow-up every 1-3 months.

The University of Cincinnati (UC) outpatient clinics from which we will recruit patients provide care to approximately 3,500 unique individuals annually. Typically, patients are seen for follow-up every 1-3 months.

Research will be conducted at the Research offices of the PIs, Dr. Sajatovic in Cleveland and Dr. DelBello in Cincinnati. Participants will be referred by local clinicians who have been informed of the study by study staff, by self-referral in response to IRB flyers, and by email as described in the Recruitment section. The Cleveland offices are in the W.O. Walker Center, 10524 Euclid Ave., Cleveland, OH 44106.

***Consent Process***

At the CWRU site, the consenting will take place at the PI's research offices within the Department of Psychiatry in the W.O. Walker Center. The consent process may also be conducted remotely over video conferencing, using either UH Zoom, CWRU restricted Zoom, Zoom for Healthcare or WebEx, and via REDCap/electronic written consent (individual link emailed directly to the participant/guardian) if necessary. Before enrollment in the study, an authorized member of the investigational staff will explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. The research staff will present the consent form in detail, and make sure the participants understand the study by encouraging them to ask any questions they may have, and asking them to explain what the study will involve in their own words. The participant and their parent/guardian (if applicable) will be given sufficient time to read the informed consent form and the opportunity to ask questions. Participants or their parent/guardian (if applicable) will also be asked to sign a Photograph, Image and Audio Release Form.

The consent process will begin when the research assistant first talks on the phone with the potential participant and explains the study to them. If possible, potential participants (if > 18 years old), will be given a copy of the consent form ahead of time by mail or email and they will be asked to read it carefully. RCT participants will be allowed to take the consent/assent form home to think it over and schedule another time to come back to finish the screening visit if they wish.

The research staff will present the consent form in detail, and make sure the participants understand the study by encouraging them to ask any questions they may have, and asking them to explain what the study will involve in their own words. Once the researcher has confirmed the identity of the subject, the researcher, subject and their parent/guardian (if applicable) sign either a physical copy of the consent form or an electronic version of the consent form in REDCap. For those consenting via e-consent, identity will be confirmed by asking the potential participant to show his/her driver's license or if not available, any state or government-issued picture identification card. If they do not have picture identification available, they will be asked to provide the last four digits of the social security number, their date of birth and one of the following: account number, street address, insurance carrier name, insurance policy number, medical record number, birth certificate or insurance card.

At each visit the participant will be asked if they want to continue with the study. The research assistant who consents the participants will not be in any way involved with their clinical care. The AYA with BD participant and their legal guardians (if < 18 years) will be informed and it will be understood that acceptance or refusal to participate in any phase of the study will not influence their ability to receive clinical care at any affiliated hospital or clinic setting or elsewhere, and that they are free to withdraw from study participation at any time.

Research Participants who are not yet adults (children and teenagers) will parental permission be obtained from one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. Signed consent form will be documenting the parental/guardian permission. If a participant has a legal guardian, they will be allowed to sign consent for the participant. Participants who are 14-17 years old will sign the consent form and their parent will countersign it. Participants who are 13 years old will sign the assent form and informed consent from participant's parent will be obtained and documented using an IRB-approved consent.

***Waiver of Written Consent for Clinicians***

We will be asking the clinicians of subjects who participate in the RCT portion of the study to complete a questionnaire giving their impressions of the intervention their patient received and asking them what types of adherence improvement or support approaches are used in their clinic. When participants enroll in the study, they are asked to sign a release of information so we may talk to their treating clinician. Study staff will use that contact information to reach out to clinicians to complete this questionnaire. Clinicians will be sent a survey link via REDCap. The initial page of the RedCap survey will include an electronic consent form. Consent will be implied by completion of the survey. Alternatively, the clinician may complete their questionnaire over the phone or by having it mailed to them for them to mail back to the study site. In those cases, study staff will review with them in detail the language in the consent form that explains the purpose of the study, the procedures involved, potential risks and benefits, how to withdraw from the study, confidentiality, and informs respondents that participation is voluntary. A copy of the informed consent may be sent to the potential subject for them to review prior to consent should they request this. After reviewing the consent form with the clinician and answering any questions they may have, verbal consent will be obtained over the phone from the clinician.

Those who enroll via mail will be mailed a copy of the consent form along with their questionnaire. Clinician participation involves the completion of an online survey and involves no more than minimal risk. A survey such as this, conducted outside of the research context would not require written consent.

***Study Design/Procedures***

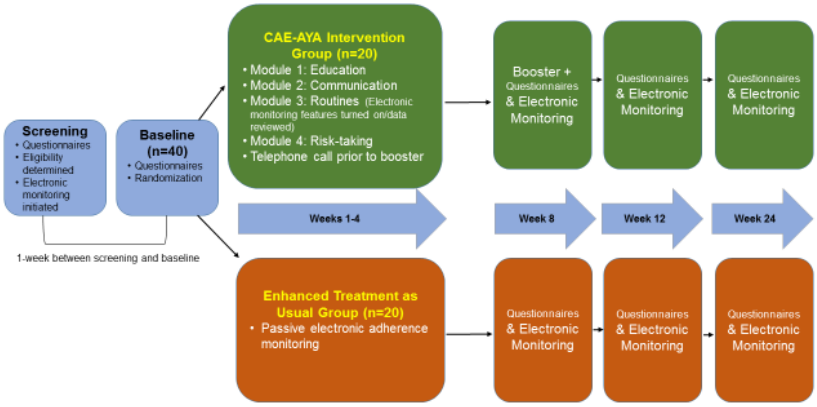
**Phase 1: Investigation of AYA Needs in Adherence Promotion:** Adaptation of CAE and development of new content will be guided by focus groups and key informant interviews with a representative advisory board (AB) of AYAs with BD (n= up to 10), their parents/guardians/care partners (n= up to 10), and a group of healthcare providers (e.g., physicians, therapists, pharmacists, and nurses) that care for AYAs with BD. To optimize generalizability, some of the prescribing providers will be community-based. Focus groups and AB meetings may take place in person or via a video conferencing platform with optional telephone call-in if needed.

Prior to the first AB meeting, we will conduct 2-3 focus groups in AYA with BD (6 individuals per focus group with a total of 12-18 individuals), 2-3 focus groups of parents, legal guardians or care partners who live with an AYA with BD (6 individuals per focus group with a total of 12-18 individuals), and 2-3 focus groups of healthcare providers that care for AYA with BD (6 individuals per focus group with a total of 12-18 individuals) to assess perceived adherence barriers and facilitators. Focus groups will be organized, conducted, and analyzed in the format described by Morgan and Krueger. [34] All focus group participants will complete a demographics form that should take no more than 5 minutes to complete. This form will be completed either on paper or in REDCap via a survey link sent to the participants email address. The focus groups and AB will be convened at CWRU and led by Sajatovic & Levin. All focus groups and AB meetings will be video or audio-recorded and transcribed verbatim (any reference to names or other PHI will be removed/coded to ensure deidentification) to undergo thematic analysis and reviewed by the members of the study team at CWRU, UC, Cincinnati Children's Hospital Medical Center (CCHMC), and University of Florida (UF). In the event that a participant agrees to be in a focus group, but is unable to attend the focus group because of scheduling or other problems, the study team may conduct an individual interview (either in person or by phone) following the same set of questions that would have been administered in the focus group.

Following the focus groups, the AB will meet twice. At the first meeting, we will present a summary of the perceived barriers/facilitators from focus groups and present a first draft of the CAE-AYA intervention. We will elicit additional suggestions on barriers/facilitators and receive input on the CAE-AYA draft. In the second AB meeting, we will present a revised draft and solicit input for a final product. Those participating in the AB who did not participate in a focus group portion of phase 1 will be asked to complete a demographics form that should take no more than 5 minutes to complete The resulting intervention will combine CAE elements and focus on adherence barriers within a development framework [33] that articulates the involvement of support networks (e.g., family, peers, and clinicians), acknowledges the presence and variability of support network stress, engagement in risk-taking behaviors, and is sensitive to the needs of AYAs with BD.

**Phase 2: Intervention Refinement Based on Patient Input:** CAE-AYA will undergo usability testing and feedback with 6-8 AYAs with BD, representative of age, gender, and ethnicity. AYA will all have self-reported difficulties with adherence (missing > 20% of BD medication at any point since being diagnosed with bipolar disorder). We will determine usability by systematically observing AYAs under controlled conditions to detect issues that can lead to lack of engagement.[35] Specifically, we will evaluate the acceptability, comprehensibility, and relevance of each CAE module. Each participant will undergo a 1-hour session of testing to minimize the burden of the evaluation and to ensure that each module is reviewed by 2-3 AYAs with BD. After brief explanation by a trained facilitator, participants will be asked to 'think aloud' as they work through one

Figure 4. Pilot RCT Design



module, thus allowing us to evaluate the thought processes of the AYA as he/she works through the modules.[36] Sessions will be video recorded, and notes will be taken by the facilitator. Modifications will be made after each AYA completes testing, as they play a crucial role in developing the intervention content and materials. The recordings may be transcribed verbatim (any reference to names or other PHI will be removed/coded to ensure deidentification) and reviewed by the members of the study team at CWRU, UC, CCHMC, and UF. These sessions may take place in person or via a video conferencing platform with optional telephone call-in if needed

**Phase 3: Pilot Testing of CAE-AYA:** Once the CAE-AYA treatment manual is completed, we will conduct a 6-month, prospective, 2-site pilot RCT testing the effects of CAE-AYA (N=20) vs. enhanced treatment as usual (ETAU) (N=20). Participants will be consented/assented, screened for inclusion/exclusion, and receive their electronic monitoring device. One week later, those who meet screening criteria and complete baseline evaluation will be randomized to Control (Enhanced Treatment as Usual; ETAU) or Treatment (CAE-AYA). 20 AYAs with BD will receive CAE-AYA and 20 AYAs with BD will receive ETAU, with 10 of each group at each site. Participants will be in the study for a total of 6 months and measures will be completed at Screening, Baseline, and Weeks 8, 12 and 24 as noted in Figure 4 and Table 2. Study visits may take place in person or via a video conferencing platform with optional telephone call-in if needed

**Treatment Randomization:** Individuals will be randomized on a 1:1 basis to participate in either CAE-AYA or ETAU. Block randomization with block sizes ranging randomly between 3-5 consecutive patients will ensure equal numbers of CAE-AYA and ETAU patients balanced on demographic and clinical characteristics. The randomization list will be computer-generated by CWRU personnel who are not members of the study staff. We will stratify by site (UC vs. CWRU) and age (13-17 vs. 18-21 years old).

***Measures and Assessments***

Table 2 shows the measures to assess outcomes, symptoms, barriers, mechanisms, and visits at which the measures are given. All scales have been used successfully with AYAs. Phase 3 participants will be evaluated for DSM-5 diagnoses using the Structured Clinical Interview for DSM-5 (SCID-5)[37] and the separation anxiety module of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)[88], administered by a trained rater with established diagnostic reliability. All comorbid psychiatric diagnoses determined by the SCID-5 and K-SADS, including ADHD, will be recorded and considered in analyses. Both sites have extensive experience administering the structured diagnostic interviews and clinical symptom and self-report assessments that will be used in the proposed study.

Demographic variables will include age, sex, race/ethnicity, living situation, parental education level, educational/school, and socioeconomic status. The primary outcome measures include two adherence measures: TRQ and electronic monitoring via the SimpleMed pillbox. Participants will be encouraged to be as candid as possible in reporting adherence, although we acknowledge that some individuals might over-report adherence. In the proposed study, there will be a hierarchical plan for determining adherence in which the TRQ will be the primary measure and SimpleMed pillboxes will be used to validate these adherence data. The TRQ evaluation will include adherence data for each BD drug.

The SimpleMed boxes can assess adherence for multiple medications and we will examine adherence for each BD drug. Participants will be instructed on the use of the pillbox and will be given a handout with simple instructions. Participants load their weeks' worth of medication into the pillbox each week. When it is time to take their medication, the participant removes the dose for that day/time. SimpleMed sends the data about whether or not the compartment was opened via an internal cellular modem which only requires a battery that is rechargeable. The data is linked only to the SimpleMed ID and kept in the SimpleMed cloud portal that the study staff can access. The link to the participant study ID will be kept separate with the study's secure documents. A dose will be counted as "taken" if the cell on the pillbox is opened within two hours of the prescribed time. Using the TRQ, we will collect information on the type and number of prescribed BD drugs, dosing frequency and adherence. We will also collect information on drugs prescribed for psychiatric comorbidity, including drug name/class, dose, dosing frequency and TRQ. We will assess prior treatment duration for each medication. For follow-up, we will inquire about any drug changes. For the primary outcome, we will calculate an average TRQ based on TRQ scores for each BD drug, but also plan to explore differences across BD drugs and drug classes in additional exploratory analyses. Data from 35 AYA with BD prescribed 2 medications in our prior study suggest that of the 19 (54%) were non-adherent to either medication, and most of those who were poorly adherent (n=16,

84%) were non-adherent to both medications. Analyses will also consider medication changes, number of medications, and medications prescribed for psychiatric comorbidity as possible variables that impact outcomes. The adult CAE RCT demonstrated that TRQ scores by blinded vs. un-blinded raters were similar, likely because the TRQ is a self-report measure. However, the SimpleMed data will be analyzed by staff blind to intervention assignment. In the event a subject's SimpleMed box is not working or the subject does not wish to use the SimpleMed Box for any period of time, the subject will track their medication compliance using a paper form.

Adverse effects will be collected systematically at each study visit using open-ended questions. Severity and duration and its relation to BD medications and/or CAE-Y will be evaluated and recorded by a study clinician. All adverse events will be reviewed by the DSMB biannually.

**Study Timeline**:

| *Phase 3 RCT Schedule of Events* | Screen | Baseline | W1-W7 | W8/V1 | W12/V2 | W24/V3 |
|---|---|---|---|---|---|---|
| **Estimated time requirement of visit** | 90-120 minutes | 60-90 minutes | 45-60 minutes | 60-90 minutes | 60-90 minutes | 60-90 minutes |
| Informed Consent | X | | | | | |
| Structured Clinical Interview for DSM-5 [37]<br>Separation anxiety module of the Kiddie Schedule for Affective Disorders and Schizophrenia[88] | X | | | | | |
| Family History | X | | | | | |
| Demographics Form | X | | | | | |
| **BIPOLAR SYMPTOMS** | | | | | | |
| Young Mania Rating Scale[56] | | X | | X | X | X |
| Clinical Global Impression (CGI)-Severity Scale[57] CGI-Improvement Scale[57] | | X | | X | X | X |
| The Columbia Suicide Severity Rating Scale[58] * | X | X | | X | X | X |
| Suicide Risk Assessment | | | X | | | |
| Hamilton Depression Rating Scale (HAM-D)[55] | | X | | X | X | X |
| **PRIMARY OUTCOMES** | | | | | | |
| Tablets Routine Questionnaire [59, 60] *** | X | X | | X | X | X |
| SimpleMed Boxes (Vaica) / Compliance log | | X | | X | X | X |
| **SECONDARY OUTCOMES** | | | | | | |
| Quality of Life Inventory (PedsQL™)[61,62] | | X | | X | X | X |
| Longitudinal Interval Follow-up Evaluation (LIFE) -modified mental health, medical and crisis service utilization.[63, 64] | | X | | | X | X |
| **ADHERENCE BARRIERS** | | | | | | |
| Oxford Bipolar Knowledge Questionnaire[65] | | X | | X | X | X |
| Adolescent Patient-Provider Interaction Scale[66] | | X | | X | | X |
| Self-Report Habit Index[67] | | X | | X | X | X |
| Bipolar Disorder Routines Questionnaire (adapted from Asthma Routines Questionnaire)[68] | | X | | X | X | X |
| Teen-Addiction Severity Index (Chemical Use section only) [69] | | X | | X | X | X |
| Rule Breaking Subscale of the Antisocial Behavior Questionnaire[70, 71] | | X | | X | X | X |
| **DEVELOPMENTAL MECHANISM** | | | | | | |
| Attitudes Towards Mood Stabilizers Questionnaire, a modification of the Lithium Attitudes Questionnaire[72] | | X | | X | X | X |
| Transition Readiness Assessment Questionnaire (TRAQ) [73] | | X | | X | X | X |
| Global Decision-Making Scale [74] | | X | | X | X | X |

| | | | | | | |
|---|---|---|---|---|---|---|
| Conflict Behavior Questionnaire - 20[75] | | X | | X | X | X |
| Inventory of Parent and Peer Attachment[76] | | X | | X | X | X |
| **FEASIBILITY, ACCEPTABILITY, AND SATISFACTION OF TREATMENT** | | | | | | |
| Patient & Clinician Acceptability & Satisfaction Questionnaires (W8) | | | | X | | |
| Attendance Tracking Sheet (W1-W8) | | | X | | | |
| Evaluation of adherence with scheduled routine mental health care appointments (no shows) and number of routine mental health care appointments in past 6 months | | X | | | | X |

**Table 2: Assessment Strategy for Phase 3**

| | Questionnaire/Assessment | # of items/Description/Reliability-Validity |
|---|---|---|
| **DSM-5 DIAGNOSIS** | | |
| | Structured Clinical Interview for DSM-5[37], Family History & separation anxiety module of the Kiddie Schedule for Affective Disorders and Schizophrenia[88] | Structured Clinical Interview for DSM-5 and separation anxiety module of the Kiddie Schedule for Affective Disorders and Schizophrenia will be administered by a trained rater with established diagnostic reliability (diagnostic kappa > 0.9). Family History will be assessed by asking the subject if they have any immediate family members (parent, grandparent, aunt/uncle, siblings ) with bipolar depression, anxiety disorder, PTSD, schizophrenia, substance use/abuse or other psychiatric illness, and if so, who has them. |
| **BIPOLAR SYMPTOMS** | | |
| Depression | Hamilton Depression Rating Scale (HAM-D)[55] | 17-item observer-rated questionnaire to assess depressive symptoms with excellent reliability and validity |
| Mania | Young Mania Rating Scale[56] | 11-item observer-rated questionnaire to assess manic symptoms with high reliability and validity |
| Illness Severity & Illness Improvement | Clinical Global Impression (CGI)-Severity Scale[57] CGI-Improvement Scale[57] | A well-established observer-rated 7-point scale to assess overall illness severity and change from baseline |
| Suicidality | The Columbia Suicide Severity Rating Scale[58] Suicide Risk Assessment**** | Assessment for suicidality. If any subject experiences worsening suicidality, the Child/Adolescent mental health clinician on the study team will evaluate them and determine the most appropriate course of action, referral and/or management. The study team has established high inter-rater reliability with all rating scales (ICC >0.85) |
| **PRIMARY OUTCOME** | | |
| Adherence | Tablets Routine Questionnaire [59,60] *** | Self-report measure noted to be reliable for use in BD and shows a high correlation with lithium levels.[62, 63] For individuals who are on more than one medication, an average TRQ for each medication will be calculated. |
| | SimpleMed Boxes (Vaica) / Compliance log | Daily objective adherence data of BD medications are captured in real |

| | | |
|---|---|---|
| | | time via GMS connectivity. Features to enhance adherence, including reminders and alerts will be activated for those in CAE as part of the Routines module while those in ETAU will use the system as a simple pill box. |
| **SECONDARY OUTCOME** | | |
| Quality of Life | Quality of Life Inventory (PedsQL™)[61, 62] | 23 items representing physical, emotional, social, and school functioning and a total score for Teen (13-18 years) and Young Adult (18-25) versions will be used. Scores range from 0-100 and reliability for scales approach or exceed α= 0.70. |
| Mental Health & Medical Service Utilization | Longitudinal Interval Follow-up Evaluation (LIFE) -modified mental health, medical and crisis service utilization.[63, 64] | A systematic assessment recording week by week use of psychiatric medications. |
| **ADHERENCE BARRIERS** | | |
| Bipolar Knowledge (Module 1) | Oxford Bipolar Knowledge Questionnaire[65] | 40-item self-report questionnaire used to assess knowledge of BD management on a 3-point Likert scale from agree to disagree[131] |
| Communication (Module 2) | Adolescent Patient-Provider Interaction Scale[66] | 9-item self-report measure of adolescent patient-provider interaction which demonstrates good internal consistency (Cronbach's alpha = .75) and construct validity and has been used in 15-21 year olds. |
| Medication Routines (Module 3) | Self-Report Habit Index[67] | 12-item self-report questionnaire on a 5-point Likert Scale from agree to disagree that measures habit strength can be used with both adolescents and emerging adults and will be administered regarding the habit of taking medication |
| | Bipolar Disorder Routines Questionnaire (adapted from Asthma Routines Questionnaire)[68] | Factor analysis identified two distinct dimensions to the original scale, Medication Routines and Routine Burden. Medication Routines is associated with both medication adherence and health care utilization while Routine Burden is associated with quality of life. Alphas are adequate for each scale. |
| Risk Behaviors (Module 4) | Teen-Addiction Severity Index[69] | Semi-structured interview developed as a standardized instrument for periodic evaluation of substance abuse. This is an age-appropriate modification of the Addiction Severity Index. It yields 70 ratings in seven domains: substance use, school status, employment/support status, family relations, peer/social relationships, legal status, and psychiatric status. It has established validity and inter-rater reliability.[78, 69] We will ony be using the chemical use section in this study. |
| | Rule Breaking Subscale of the Antisocial Behavior Questionnaire[70, 71] | Self-report measure used to assess rule-breaking behavior commonly seen in AYA 13 to 21 years of age. Eleven rule-breaking behaviors are assessed on a 5-point Likert Scale with a Cronbach's alpha calculated at .78. |
| **DEMOGRAPHICS** | | |

| | | |
|---|---|---|
| Participant demographics | Demographics Form | The questionnaire will assess basic demographic data, including age, sex, race/ethnicity, living situation, school status, and socioeconomic status. |
| **DEVELOPMENTAL MECHANISMS** | | |
| Medication Attitudes | Attitudes Towards Mood Stabilizers Questionnaire, a modification of the Lithium Attitudes Questionnaire[72] | 19-item self-report questionnaire grouped into 7 subscales: Opposition to Prophylaxis, Denial of Therapeutic Effectiveness, Fear of Side Effects, Difficulty with Medication Routines, Denial of Illness Severity, Negative Attitudes toward Drugs in General, and Lack of Information about Medications. Test-retest reliability is good to excellent. |
| Self-Management | Transition Readiness Assessment Questionnaire (TRAQ) [73] | The 20-item TRAQ assesses the degree to which AYAs demonstrate the self-management skills necessary to transition from pediatric to adult healthcare across conditions. It has good internal consistency and criterion validity. |
| Decision Making Style | Global Decision-Making Scale [79] | A 25-item questionnaire measuring five decision-making styles: rational, intuitive, dependent, avoidant, and spontaneous. Within an adolescent sample, the scale showed good reliability, factorial stability, and convergent validity [80] |
| Parent-AYA Communication and Conflict | Conflict Behavior Questionnaire - 20[75] | A 20-item self-report questionnaire assessing perceived communication and conflict with a parent during the past 2 weeks. The questionnaire assess both the AYA's evaluation of the parent's behavior and AYA's dissatisfaction with parent's behavior.[75] The scale shows good reliability and has been used in a number of studies evaluating the efficacy of interventions for AYA's with bipolar disorder.[81] |
| Parent and peer supportive communication | Inventory of Parent and Peer Attachment[76] | The parent and peer communication subscales assess the perceived quality of supportive communication with parents and peers when discussing personal problems, issues, or concerns. The 9-item parent subscale and 11-item peer subscale (one of three subscales in the IPPA) has demonstrated reliability and validity with AYA samples. While the IPPA assess relationships with both mother and father, we will only query AYAs about 1 parent. |
| **FEASIBILITY, ACCEPTABILITY, AND SATISFACTION OF TREATMENT** | | |
| Acceptability & Satisfaction | Patient Acceptability & Satisfaction Questionnaire | Participant opinion regarding the format, content, length, and convenience of the intervention |
| Attendance | Attendance Tracking Sheet | Participants will be tracked for their attendance to all intervention and phone sessions |
| Provider perceptions of acceptability and satisfaction with CAE AYA | Clinician Acceptability & Satisfaction Questionnaire | Clinician opinion regarding their impression of the intervention |
| Evaluation of adherence | Mental Health Care Appointments | Participants will be asked how many mental health clinic visits that had |

| | | |
|---|---|---|
| with scheduled routine mental health care appointments/number of routine mental health care appointments in past 6 months | Attendance Tracking Sheet | in the last 6 months at baseline and in the last 3 months at week 12 and week 24, as well as how many mental health visits they scheduled but were unable to attend in the last 6 months at baseline and in the last 3 months at week 12 and week 24,(including those they cancelled and those that they did not cancel, but in the end were unable to attend) |

*** Parents or caregivers will be asked about medication adherence at baseline and at 6 months (V3)
**** Suicidality is clinically assessed by the interventionist during each CAE/EDU session

***Intervention***

**TREATMENT GROUP - Customized Adherence Enhancement for Adolescents and Young Adults (CAE-AYA):** CAE-AYA participants will have 4 core sessions (45-60 minutes each) spaced about 1 week apart over a period of approximately 4 weeks and one "booster" session approximately 4 weeks after completion of the 4 core sessions (total of up to 5 in-person sessions spaced out over 8 weeks). These CAE sessions may take place in person or via a video conferencing platform with optional telephone call-in if needed. There will be one follow-up phone call with a study interventionist, approximately 6 weeks post-baseline (timed half-way between completion of the core sessions and the "booster" session; Figure 4). Given that in the CAE RCT, the majority (63%) of participants were assigned all 4 modules, all AYAs will receive all 4 modules, with the content within each module being customized to developmental stage and behavioral experience. Within each module, there will be a range of material based on relative difficulty with the barrier experienced and developmental stage. Low endorsement of barriers will elicit sessions focused on anticipatory guidance while high-level endorsement of barriers will elicit sessions focused on problem-solving around the immediate barriers with the goals of becoming more independent and engaging in behaviors which encourage adherence and BD self-management. Module customization will be determined based on baseline scores on measures of BD knowledge, communication with providers, family members, and support systems (e.g., peers), difficulties with routines, and risk-taking behaviors (e.g., substance use, unprotected sex or other risk behaviors). Coaching in problem-solving skills will be integrated into all modules.

- **MODULE 1 - Psychoeducation on BD Medications:** Psychoeducation approaches BD as a biological disorder that can be managed by appropriate medication in conjunction with coping strategies.[39] Psychoeducation improves medication adherence.[40,41] This module uses a modified Life Goals Program [30,42-44]. Educational materials will be refined to meet the developmental needs of AYAs. For example, if AYAs have high levels of knowledge, more detailed and extensive knowledge will be provided. If AYAs have low levels of knowledge, more basic skills and education will be provided. Notably, problem-solving skills will also be taught in this initial session as it will serve as the foundation for future modules. The following approach to teach problem-solving skills will be used: 1) Coach the AYA to identify an adherence barrier (Problem Definition), 2) Teach AYA to generate several creative solutions (Generating Alternative Solutions), 3) Systematically evaluate potential solutions by the AYA and support system (Decision-Making), 4) AYA selects one solution for implementation (Implementation of New Solution), and 5) Detailed solution is reviewed with specifics regarding the who, when, where, and how the solution will be attempted.
- **MODULE 2 - Communication with Providers & Caregivers:** This module focuses on improving communication using principles from collaborative care and a patient-focused, patient-directed approach.[45-47] Individuals will explore key components of treatment planning including expectations for medication and feared/experienced side effects. Content will focus on communication with a treatment support team, which may be comprised of family, friends, and other individuals within their network of support. For AYAs engaged in good communication styles, anticipatory guidance will be provided about how to transition from a triadic partnership for care to a dyadic one, with more focus on transition elements. For AYAs with more problematic communication styles, basic communication skills will be emphasized, including optimal ways to communicate with their support network, issues of disclosure, allocation of treatment responsibility, and initial stages of transition. The communication with providers CAE intervention module was also designed to specifically address patient-perceived medication burden. This includes both experienced side effects as well as side effect concerns. A focus of CAE is helping patients learn to communicate with clinicians about medication burden vs. benefit and ideally determine, in collaboration with their clinician, a treatment plan that balances benefit vs. burden in a way that is acceptable to AYA. The CAE intervention uses a detailed manual with forms that are completed in collaboration between patients and interventionists, which will be translated to CAE-AYA. Specifically, this module uses a form to identify care access/delivery problems and ideally empower patients to problem-solve and/or discuss adherence impediments with their providers. These forms will be collected at the end of each CAE-AYA session to identify whether access issues appear to be a main driver of poor adherence.
- **MODULE 3 - Medication Routines:** Complex medication regimens may interfere with adherence.[47] Using principles from interpersonal and social rhythm therapy for BD,[48] a key activity is the focus on daily routine with respect to medication-taking (when, where, and how medications are taken) and problem-solving regarding identified challenges. This module emphasizes the use of prompts/reminders and self-

monitoring/self-regulation to maximize and maintain adherence. Tools to improve routines including pillboxes, alarms or use of other technology available to the participant (e.g., smart phone apps) will be introduced and evaluated. For participants interested in using apps, we will provide a one-page handout providing an overview of 4 apps that are well-utilized and receive positive reviews for medication management (i.e. MyMedSchedule Mobile, Mango Health, MedCoach Medication Reminder, and MediSafe Meds and Pill Reminder). App information will be provided on the handout (see Figure 5 as an example). All participants will be asked, if they want to use an app, which app they will try. Unfortunately, there are no electronic ways to track app usage on phones. As such, we will be relying on self-reported use of apps. Features of the SimpleMed pillbox, such as alarms and visual reminders, can be turned on and off. These features can further reinforce the use of organization tools and will be part of the intervention for the CAE-AYA treatment group only. The SimpleMed pillbox will serve as a passive monitoring tool for the control group but will serve as both a monitoring device and as an active intervention around medication routines for the treatment group. Phase 1 input will inform embedding additional technology elements into this module. The medication routines module includes a form that identifies impediments (e.g. access) to medication-taking, and will allow the study team to identify whether access issues appear to be a main driver of poor adherence.

- **MODULE 4 - Targeting Risky Behavior via Modified Motivational Enhancement Therapy (MET):** MET is adapted from an evidence-based intervention for dual diagnosis.[43, 49-52] We have successfully used this technique in AYA with BD and substance use in prior studies.[53] For AYAs with BD, it is expected that substance use will be considered within the general context of risk behavior and protective factors associated with the occurrence of these behaviors will similarly be addressed. For those using drugs or alcohol, the module will be similar to that in CAE. For those who are not using, anticipatory guidance about patterns of risky behavior that impact BD self-management such as staying out late will be emphasized.

**Delivery and Fidelity to CAE-AYA:** The CAE-AYA intervention will be delivered by social workers or equivalent with mental health experience and at least some experience in working with AYAs with BD. We will randomly assign social workers to be designated as either the CAE-AYA or ETAU interventionist once interventionist staff are hired and oriented to the project. The format will closely follow the original CAE intervention, although the content will be refined based on Phase 1 and 2 data. All CAE-AYA sessions will be held in outpatient clinical settings. Interventionists will participate in monthly teleconferences supervised by a senior interventionist at the UH/CWRU site to discuss implementation issues. For the CAE-AYA intervention, we will use training and fidelity procedures similar to the adult CAE RCT. A senior interventionist at the UH/CWRU site will lead the interventionists in intensive protocol training with mock intervention sessions using the standardized protocol until 100% protocol fidelity is achieved. Fidelity will be assessed by video or audio-recording all CAE-AYA sessions and 20% of randomly selected sessions will reviewed using a standardized check-list to evaluate that content and format has been administered appropriately. Fidelity evaluations will be done by a senior interventionist at the UH/CWRU site. If there are any omissions/deviations, Dr. Levin will conduct additional training/support to ensure fidelity. This method of assessing fidelity is easily implemented in community practice settings.

**CONTROL GROUP - Enhanced Treatment as Usual (ETAU):** ETAU will consist of usual clinical care with prescribing clinicians and therapists, augmented by written materials specific to BD for AYAs and 6 follow-up telephone calls to briefly review the materials and be available for questions (weekly in the first month, then at Weeks 6 and 8) by social workers with mental health experience and at least some experience in working with AYA with BD. In order to ensure that there is not treatment contamination, different trained interventionists will be used for CAE and eTAU. Therapists will briefly review the materials and be available for questions during the phone calls. Materials will cover general self-management in BD. The calls will be relatively brief (maximum of 20-30 minutes). ETAU sessions will be video or audio-recorded and fidelity evaluations will be the same as for CAE-AYA and will be done by a senior interventionist at the UH/CWRU site. eTAU will not vary across sites. The "enhanced" elements include the use of an electronic monitoring of medication, which may in and of itself increase adherence, written materials specific to BD for AYAs and 6 phone calls to briefly review the written materials and be available for questions about the materials. Thus, participants in both arms will have a similar number of sessions.

***Data Analysis:***

Study data will be collected and managed at each site using REDCap,[77] a secure, web-based application

designed to support data capture for research studies. Each site (CWRU and UC) will use their own institutions' REDCap. When the study is over, UC will send their de-identified data to the CWRU site where it will be combined with CWRU data and analyzed as outlined below. Consistent with the developmental nature of the R34 mechanism, we will evaluate feasibility, acceptability and satisfaction of the interventions using the feasibility evaluation noted in section C.3 e. and C.3f., attendance tracking, and an exit interview that includes Likert scales to evaluate perceived benefit vs. burden as well as open-ended/write-in suggestions. PIs at each of the proposed study sites will be responsible for overseeing data input and quality and, working with Dr. Tatsuoka, will oversee the data analytic procedures. For the primary RCT outcome, we will adopt Type I error level of 0.05. Multiple comparisons adjustment will be applied for barrier variable analyses. We propose to enroll 40 AYAs with BD who are randomized to either CAE-AYA (N=20) or to ETAU (N=20). Based on our prior studies,[28, 29] we expect up to 30% of participants will discontinue study participation during the 24-week study period.

As outlined in Aim 2, the primary statistical outcome measure will be change in adherence behavior as measured by past month TRQ. Adherence rates will be calculated for TRQ as well as the SimpleMed as follows: the number of days with a missed dose will be divided by the number of days in the time period and then multiplied by 100 with higher number indicating worse adherence.

For the primary intent-to-treat analysis in Aim 2, we will use longitudinal mixed-effects modeling to evaluate the treatment-by-time interaction of adherence levels between CAE-AYA and ETAU. Significant interaction would indicate that the treatments (i.e., CAE-AYA vs. ETAU) have different trajectories of adherence. We will adjust for site and consider covariates such as age, gender, SES, *psychiatric comorbidity (e.g. ADHD), mood state (e.g. (hypo) manic vs. euthymic vs. depressed) and symptom ratings (e.g. HAM-D and YMRS scores), and/or family history*. We will consider representing scores as binary outcomes, indicating whether or not an adherence threshold has been met (e.g., 80% adherent), particularly if adherence levels are highly skewed. We will thus consider generalized linear mixed models for binary outcomes (SAS PROC GLIMMIX). Adherence barriers, symptom rating scales and HRQoL scores will also be modeled by through longitudinal mixed models. In addition, we will compare corresponding TRQ and SimpleMed pillbox adherence levels. Correlation between the measures will be estimated and Bland-Altman plots will be generated[82].

In Aim 3, it is hypothesized that reductions in adherence barriers (e.g. BD knowledge, medication routines, communication with clinicians and parents/guardians, and substance use/risk behaviors) will be associated with changes in adherence. We will regress respective changes in adherence levels upon changes in barrier variable values. We will also compare difference values in barriers by treatment arm, and include treatment indicator variables in regression models. Modeling assumptions will be thoroughly assessed, and transformations will be considered. In a similar manner, we will also examine whether improvements in adherence behaviors correlate with improvements in symptoms and HRQoL. These analyses will support the clinical interpretability of effect sizes in adherence change for future studies. Barrier variables with change values that appear to be associated with change in adherence levels and that appear to differ by treatment will be considered further as mediator variables, following as in MacKinnon (2008)[83] and Preacher and Hayes (2008).[84] This will involve single mediator analyses as well as exploring multiple mediator models. These analyses will involve the treatment variable and change in adherence values. Associated standard errors of estimated indirect effects will be derived through bootstrapping, using the M-Plus software.

**Missing Data:**

Data that remain missing despite our retention efforts will be accommodated in our analyses and their impact evaluated through sensitivity analyses. The models we propose can be estimated without bias under the missing at random (MAR) assumption[85] and provide valid analysis as long as auxiliary covariates associated with missingness (if any) are included in the analysis model. To assess which covariates may be associated with missing outcome data, we will create binary indicators of whether the outcome was missing (=1) or not (=0). If a covariate is correlated with missingness at $r > 0.40$ and is correlated at $r > 0.40$ with the original response variable, it will be included in the analysis as an auxiliary correlate.[86] We will conduct preliminary assessment of the missing at random (MAR) assumption by pattern mixture models that relax the missing at random assumption. We will also consider selection models to assess sensitivity to MAR in a Bayesian Markov Chain Monte Carlo framework,[87].

**Power:**

As a reference, for the projected sample size of 40 subjects with up to 30% attrition, given two-sided Type I error of 0.05, two-sample t-tests will have power of 0.70 for effect sizes of at least 0.975. Tests for non-zero correlation will have power of 0.70 for correlations with magnitude of at least 0.438. Note that we are associating change in adherence with change in clinical outcomes, to better calibrate clinical significance in adherence effect sizes related to the target population for future studies.

***Confidentiality of Data***

To maintain the confidentiality of the data, a unique study identifier to code individual's identifiable data and will store the master list separate from the study data. The key will be stored in a password protected document that only the study staff will have access to. When the study is closed with the IRB (after primary outcomes data has been analyzed), we will delete the file that contains identifiable information and will be securely shred any paper documents containing identifiable information. Electronic data will be stored in CWRU Redcap, CWRU Box, and UH Secure Network Drive. University Hospital PHI will only be stored on the UH Secure Network not on CWRU REDCap or CWRU Box. Paper research data and documents will be stored in a double-locked secure environment in the PI's research offices in the Psychiatry Department at the W.O. Walker Center.

***Data Sharing Plan***

The deidentified transcriptions will be shared with the study personnel at UC, CCHMC, and UF. The UC site will also send deidentified quantitative data from Phase 3 to CWRU for analysis. Deidentified qualitative and quantitative data will be shared via CWRU Box or email.

The ability for research communities to share data as soon as it is available adds to the ability for discovery to translate into useable innovation and adds value to the research. Therefore, we will adhere to the NIH Grants Policy on Availability of Research Results: Publications, Intellectual Property Rights, and Sharing Biomedical Research Resources. Sharing of data generated by the RCT portion of this project (Phase 3) will be carried out in several different ways. In addition to the report we will submit to NIMH, we intend to make emerging results available both to the community of scientists interested in understanding our research, but especially to those in the community who can use these behavioral techniques to possibly assist their patients.

**Data entered into the NIMH National Database:** If this proposal is funded we will collaborate with our project office to determine the best mechanism to ensure that our Phase 3 data is entered into the common informatics platform by NIMH, called the National Database for Clinical Trials Related to Mental Illness (http://ndct.nimh.nih.gov, NDCT). We will work with NIMH to transform the data we collect into relevant information using the suggested consent form language, NIMH software that will create global unique identifiers and a useful data dictionary as much as we are able in order to deposit data into the National Database allowing other researchers and NIMH to use available data. NIMH can use its substantial resources for dissemination of the "go or no-go" results via its website, e-newsletters, internal government communications to other agencies and more.

**Department and University, CTSA websites and newsletters:** As our academic health centers are two of many Centers of Clinical and Translational Science around the country, our findings and strategies may be disseminated quickly through the network of CTSA's.

**Peer-reviewed presentations:** at national scientific meetings. From the project, we expect to submit presentations to regional, national and international meetings.

**Peer-reviewed publications:** We anticipate that the project will result in several peer-reviewed publications each year.

In addition to the above, we will also post study results on www.clinicaltrials.gov and will make de-identified data available to other qualified investigators in the research community. In all cases, data will be shared as soon as it is available and for as long as the format allows. Publications and presentations will use de-identified data in order to preserve confidentiality. In line with accepted data sharing practices and ethical principles, we will share de-identified raw data with other researchers attempting to replicate our findings or including our findings in subsequent projects. Researchers will be able to contact us by telephone or email to request these data, which we will provide in a timely manner. We will not release any data that are considered identifying or protected by IRB, HIPAA, or federal regulations unless that researcher and the PI of the current project have obtained proper administrative agreements or participation in the NIMH national database.

***Risks to Research Participants***

The CAE-AYA intervention is an adjunct to standard clinical care that participants receive, and is not expected to impact ongoing clinical care beyond the fact that some individuals may become more adherent to their prescribed medication regimen and some participants may become more engaged in their own care as a result of CAE-AYA or ETAU. Patients will not be compelled to participate in any way in the activities of the project. Participants will be free to withdraw from any phase of the study at any time without penalty. This study involves either participating in focus groups, advisory board meetings, and possible cognitive interviews or participating in the pilot study of up to 5 therapy sessions, using SimpleMed Pillboxes, and completing a set of self-report instruments. All instruments have been utilized in outpatient research settings by the PIs and are not associated with risks to patients. The behavioral intervention is intended to enhance adherence attitudes, remove adherence barriers, and ultimately, improve adherence behaviors, mood symptoms and HRQoL, and will be adapted from an existing therapy that is not generally known to increase risk to individuals. The participants are not at increased risk from participating in this study, other than finding that talking about some matters may be uncomfortable. However, AYA with BD are at risk for other medical and psychiatric complications because of their underlying condition.

Participants may exhibit worsening of their mood symptoms (depression or mania) during the study. They may also exhibit worsening or the onset of suicidal ideation or homicidal ideation.

Because of the nature of group interactions in Phase 1, participant confidentiality cannot be guaranteed for this phase; however, the importance of respecting other group members' privacy will be stressed to all participants. There is also a risk of loss of confidentiality for participants in Phases 2 and 3, however, precautions against this risk will be taken as described below.

Consistent with the Federal guidelines, participants will be informed of the federally mandated reporting laws for child abuse and neglect, verbally and in the written consent form. Therefore, if abuse or neglect is suspected the Department of Human Services will be called. Risks associated with this include embarrassment, legal consequences, and removal of the child from the parents'/legal guardians' home.

In summary, based on the previously described considerations, we believe the risks are minimal for participants who are involved in this study.

To maximize safety, at any time during study participation, if it is the opinion of the participant/legal guardian, any of the investigators, or their non-study related clinician, that because of exacerbation of mood or other psychiatric symptoms (defined either by clinical assessment or a CGI-I $\geq$ 5) or a lack of improvement in any mood or behavioral symptoms, it is not in the best interest of the participant to continue treatment, then the participant will be discontinued from study participation and all endpoint procedures will be performed. If at any time during study participation mood or any psychiatric symptoms worsen for any study participant, a study clinician will immediately assess the participant to evaluate whether they are safe to continue in the study and/or whether an immediate referral to the psychiatric emergency department is necessary. Additionally, at Screening, participants (or legal guardians if participants are < 18 years old) will be asked to provide a release of information so that study staff are permitted to communicate with their non-study clinicians. If at any point during study participation an AYA experiences worsening of symptoms or is felt to be a risk to themselves or others, their legal guardian (if < 18 years old) and their non-study clinician will be contacted to discuss a treatment plan. The informed consent/assent will describe that for participants < 18 years old, legal guardians will be informed of worsening of psychiatric symptoms and/or suicidal or homicidal ideation during a participant's study participation and study clinicians will discuss any necessary clinical follow-up with participants and their legal guardians. For participants $\geq$ 18 years old, their non-study clinician will be informed of any worsening of symptoms or suicidal or homicidal ideation if a release of information to contact that clinician was obtained.

For any phase of the study, if an individual who is suicidal or homicidal is identified during the screening process or at any time during the study, the study staff interacting with the individual will immediately notify 1) the participant's non-study clinician (if a release of information has been obtained), 2) the site PI, who is a practicing licensed psychiatrist, and 3) if the participant is < 18 years old, their legal guardian, so that all available and appropriate measures may be taken to ensure the prompt safety and most appropriate care setting for the participant. If at any point during the study a patient has active suicidal behavior on the C-SSRS; an increase from baseline in suicidality, as measured by the C-SSRS, or appears to the investigator to pose a risk of self-harm or a harm to others, guardians will be informed and the participant will be referred to appropriate clinical

care. Individuals who are at immediate risk of harm to themselves or others will be taken to the psychiatric emergency department located in close proximity to where the proposed study will be conducted at both sites.

Additionally, participants/legal guardians will be informed during the informed consent/assent process that if the participant/legal guardian experiences any suicidal ideation, intent, or plan (as measured by the C-SSRS or clinical assessment) during a focus group, advisory board meeting, cognitive interview, a CAE-AYA or ETAU session, or a rating scale interview they will be evaluated immediately by a study clinician and referred to the appropriate clinical follow-up. Specifically, if a participant is judged to be a danger to themselves or others, the participant will be taken to the psychiatric emergency department for further evaluation. As described, If the participant is < 18 years old, their legal guardian will be informed of any suicidal or homicidal ideation and of any necessary treatment referrals or further evaluation (e.g., assessment at the psychiatric emergency room).

***Provisions to Protect the Privacy Interests of Research Participants***

Complete confidentiality cannot be assured due to the nature of group interactions in the focus groups and advisory board, although we will request that participants in these groups maintain other participants' confidentiality. Confidentiality of the research data will be protected in several ways. Paper assessment forms and other study records will be stored in the locked research offices of the site PIs and/or study staff. Participants will be identified by a separate study ID number on all study records. The lists that link study ID codes with participant names, and all electronic study records will be stored on password-protected, encrypted computers or secure servers. Only aggregate data will be presented or published, and will be presented such that individual patients cannot be identified. The proposed project's research personnel who will have access to participant identities are the study PIs, co-investigators, and the study research assistants, interventionists and data analyst. All study personnel will be required to be certified in the protection of human subjects throughout the study. The focus groups, advisory board, and therapy sessions will be recorded and reviewed by study staff for fidelity. The recorded sessions will be stored on a secure server, and will be destroyed at the end of the study, after all data analyses have been completed.

The identifiable information will not be reused or disclosed to any other person or entity outside UHC other than those identified in the protocol, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

***Potential Benefit to Research Participants***

Potential benefits include a thorough psychiatric evaluation performed by study staff with expertise in the diagnosis and treatment of bipolar disorder, and the chance to contribute to a scientific investigation, which may be of benefit to patients with similar illnesses in the future. Participants may also benefit from participating in the sessions and may find it helpful to talk about their conditions and challenges in adherence. There is no guarantee of benefits to any participant. However, the goal of this project to develop a contribution to knowledge, which can be useful in improving the understanding and management of poor adherence in AYA with BD. It will be explained to participants and legal guardians that participation in the study may not benefit them in any way but may be of benefit to other patients in the future. Overall, the risks associated with this study are minimal to the participants and they may receive direct benefit from their study participation as previously described. Therefore, in the opinion of the investigators, the benefits associated with this study outweigh the risks.

***Withdrawal of Research Participants***

Individuals will be discontinued from the protocol prior to 24 weeks if they wish to withdraw for any reason at any time. Since the intervention is an addition to their regular treatment and does not include medication, there is no need for follow-up with the research team.

Should the need arise to discontinue a patient from the study because of symptom worsening (as defined previously) or for any other reason, including patient/legal guardian withdrawal of consent, we will collaborate with the patient/legal guardian, and their non-study related clinician to determine treatment options for that patient following study discontinuation.

***Cost to participants***

Participants and their insurance will not be charged for any study visits. Subjects may incur costs such as travel, parking, and meals. These are reasonable costs that a subject will incur as a result of going to study visits. Subjects are compensated for these costs as outlined below.

***Research Participant Compensation***

Phase 1 focus group and advisory board participants will each receive for $20 for each meeting they attend.

Phase 2 participants will receive $30 for each usability session they attend.

Phase 3 RCT participants ages 13-21 will receive $25 per assessment visit for attending the 5 assessment visits and an additional $10 at the V3 visit for returning the SimpleMed box. Throughout the CAE-AYA intervention sessions, small token items of insignificant value (e.g., $5 gift card, pens, notebooks, key tags, lanyards, mini calendars, etc.) may be given and will not be used as a contingency for study participation.

At the UH/CWRU site stipends will be paid by check mailed to the participant's home or in some cases, in cash at the visit if cashing a check would be burdensome on the participant, or via gift card/e-gift card. At the UC site, subjects will be paid in the form of a prepaid debit card or gift card.

Participants in all 3 phases will be offered a bus pass or parking pass for any meetings, sessions, and assessment visits. In some circumstances other transportation (i.e., taxi or Uber/Lyft) will be arranged and the cost will be covered by the study if necessary.

***Provisions to Monitor the Data to Ensure the Safety of Research Participants***

The study PIs, Drs. Sajatovic and DelBello, will monitor the study to ensure data integrity and the safety of the participants. The CWRU site Data Coordinator, will review the data for discrepancies on a regular basis and will review the study records for compliance with IRB requirements and verification of source documents. The PIs will hold regular weekly meetings across sites via teleconference with all study staff to review study progress and any issues that may come up regarding data integrity and completeness.

***Data and Safety Monitoring Board or Committee***

For Phase 3, we are proposing that a DSMB be comprised of experts in the following fields: a behavioral psychiatrist/psychologist, expert in BD, and biostatistician. These experts, from outside the departments of either PI, will review and evaluate the accumulated data for participant safety, adverse events, study conduct and progress every 6 months. The DSMB will make recommendations to the appropriate regulatory agencies (IRB, NIH) concerning continuation, modification or termination of the study. DSMB members will be identified before the start of the clinical trial in Phase 3 of the project.

***Alternatives to Participation***

The alternative is for research subjects not to participate.

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