

Comparative Effectiveness of Two Self-Assessment Tools: KIOS-Bipolar or eMoods: A Randomized, Open 52 Week Study for Persons with Bipolar Disorder

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Abstract/Project Summary

A. Objective: What we propose to do

Bipolar disorder (BD) is a complex chronic illness characterized by recurrent, often dramatic mood changes. Self-management of BD is an important component of treatment, but is likewise complex and can be fraught with difficulties, including misunderstanding of the condition and a lack of self-awareness. Combined with the nationwide shortage of mental healthcare providers and the advent of the Affordable Healthcare Act, patients are assuming an increased role in understanding and managing their chronic conditions. At the same time, the emergence of mobile health and computational tools are engaging patients in self-management by enabling timely access to information and resources.

The goal of this project is to complete the development of a patient-centered software system and mobile app to assist in managing bipolar disorder. In Phase I, we developed a novel computational tool known as KIOS-Bipolar. Based on concepts from nonlinear systems (chaos) theory, KIOS-Bipolar tracks multiple interacting symptoms to determine the precise state of a BD patient. Once the patient's state is identified and the trajectory of the patient is established, KIOS-Bipolar produces advice specific to the patient's condition to help manage the course of the disease. To facilitate user convenience for the software, KIOS-Bipolar was converted to an online tool with mobile access. Twenty bipolar patients evaluated KIOS-Bipolar in a twelve week field trial. No technical problems with the software were observed and results showed that patients had significantly more reductions in symptom severity than increases. The development of this innovative tool to help patients self-manage BD has the potential to profoundly impact public health and achieve significant commercial success.

This Phase II study has the specific aim of evaluation of KIOS-Bipolar in a randomized, open 52 week effectiveness study of 120 bipolar subjects in current treatment at three socioeconomically diverse academic health science centers. Concurrent with this clinical effectiveness study, the research team, funded by the same NIH grant, will refine prototype software and integrate data security and establish quality standards into the KIOS-Bipolar system.

The clinical trial will:

- a. Assess aggregate time spent in seven primary clinical states of BD (remitted; subsyndromal depression, mania or mixed state; and syndromal depression, mania or mixed state).
- b. Assess the weekly completion of KIOS-Bipolar and eMoods.
- c. Determine indices of patient satisfaction with the format, ease of use, time required and patient motivation for continuing use of the patient tools both during the trial and following completion.
- d. Determine patient satisfaction with the clinical information on BD illness trajectory and recommendations to facilitate good health and effective interventions. Note that eMoods does not provide this element of information, therefore no comparative data will be feasible for this one objective.
- e. Assess patient scored life function indices (Life Function Questionnaire (LFQ) over the 52 week period of the study.
- f. Assess the relationship between the 8 symptom items in K-B with relevant items rated both by clinicians and as self-assessments by patients at seven time points (week 0, 8, 16, 24, 32, 40 and 52) in the study. These are times at which clinical care visits will routinely occur, and therefore will not add either to extra burden on the participants, or extra contact time with staff. Subjects randomized to eMoods will be similarly scheduled, with the correlations limited to those feasible with the eMoods product. Self-assessments with the 27 item BISS-Self are routinely obtained as part of regular treatment visits.

Table 1. Schema for Randomized Clinical Trial

Week	0	1-7	8	9-15	16	17-51	24, 32, 40	52	RS
MINI-6.0, Demographics/course of illness	X								
K-TABS/eMoods	X	X	X	X	X	X		X	
Life Functioning Questionnaire	X		X		X			X	
BISS-42,	X		X		X		X	X	
BISS Self-Assessment	X		X		X		X	X	X
KIOS NIH Software Evaluation Form					X			X	

The clinician administered scale will be the 42 item Bipolar Inventory of Symptoms Scale (BISS), however comparisons will be limited to the symptom areas represented in both K-B and eMoods, e.g., depression and mania subscales; depression, mania, irritability and anxiety domains. The BISS Self (BISS-S) is a 27item scale covering similar symptoms to the BISS, but answered as yes/no, rather than the 0-4 range of the BISS. The MINI is a structured diagnostic interview providing current and lifetime psychiatric diagnoses, requiring approximately 20 minutes.

g. Estimate the utility of ancillary features of Kios-Bipolar or eMoods. These features include capability to submit to the investigative staff displays of symptom trajectories for the patient's medical record and visual displays of selected aspects of the patient's illness/wellness. No transmission of data to treating clinical staff will occur as component of this study.

h. Assess sensitivity of K-B assessed improvement or worsening by comparison with assessment by BISS-Self and BISS-42.

B. Sample Size and Enrollment:

One hundred twenty (120) participants, 50 at UTHSCSA site, and 35 each at The University of Louisville Research Foundation, Inc. and The University of Cincinnati, will be involved in the clinical trial in Aim 2. All study participants will sign informed consent forms prior to being enrolled and will be recruited from the UTHSCSA, the University of Louisville or the University of Cincinnati.

Inclusion Criteria:

1. Male or female outpatients 18 years of age or older
2. Bipolar I or II disorder as assessed by MINI 6.0
3. In psychiatric outpatient treatment at UTHSCSA, University of Louisville, or Lindner Center of Hope, Mason Ohio
4. Currently taking mood stabilizer or second generation antipsychotic for 4 weeks or longer
5. Ability to access Kios-Bipolar or eMoods (via computer, smartphone or tablet)

Exclusion Criteria:

1. Unwilling or unable to comply with study requirements
2. Drug/alcohol dependence within the past 30 days

Early termination:

Participation in the study will be terminated if a patient has a score of 4 on the BISS suicide item, BISS-Depression Scale ≥ 50 , or BISS Mania Scale ≥ 35 for 4 consecutive weeks, or if the treating psychiatrist determines that a patient poses an imminent risk of self-harm.

C. Hypotheses:

a. Patients randomized to KIOS- Bipolar compared with those randomized to eMoods will have a higher proportion of time in remitted status, lower proportion in syndromal status (Manic, depressed, mixed) and higher

LFQ scores.

- b. Persistence with use of KIOS- Bipolar and eMoods will not differ. Persistence is defined as 1) the proportion of subjects who complete weekly scheduled use of the bipolar self-assessment scales and 2) completion of the 52 week self-assessment protocol.
- c. The proportion of on-time completion of assessments will not differ between groups.
- d. Subject satisfaction, assessed by qualitative questionnaires completed by subjects during and principally shortly following completion or discontinuation of the trial, will not differ between groups.
- e. LFQ subscales will be associated with superior outcomes for the KIOS-Bipolar group.
- f. Correlations between scores on items included in KIOS- Bipolar and similar items on the BISS SR and the BISS 42 will be conducted. Strength of association will be higher between KIOS- Bipolar and BISS comparisons than eMoods-BISS comparisons.
- g. Aggregate changes for the KIOS- Bipolar items and corresponding eMoods items will indicate greater proportions of decreased scores for KIOS- Bipolar

D. Measures of clinical status – BISS and K-B

The BISS (Bipolar Inventory of Symptoms Scale) is a 42 item, structured, clinician-administered rating scale that has demonstrated good sensitivity to change across the life span.²¹⁻²⁴ Unlike traditional scales, which focused on inpatient samples, the BISS was developed with a focus on outpatients. The scale yields an overall severity of illness score and five domain scores (for manic, depressive, anxious, irritable, and psychotic elements, with the latter established in exploratory factor analyses).²² The psychometric characteristics of the BISS were established in studies on over 400 patients in all clinical states of BD. Table 2 provides the BISS clinician-rated items from which the KIOS-BIPOLAR items were derived and the KIOS-BIPOLAR questions that the patients will answer. The final design for the user input will be determined in Aim 1.1.

Table 2. BISS Item and Corresponding KIOS-BIPOLAR Questionnaire

BISS Item	KIOS-BIPOLAR Question
Affective Lability	Have your emotions shifted fairly suddenly at times?
Sadness	Have you felt depressed, sad or down?
Irritability	Have you felt easily irritated, angry or resentful?
Pessimism	Have you been discouraged, pessimistic or felt hopeless?
Anxiousness	Have you felt tense or anxious?
Less Need for Sleep	Were there nights you needed less sleep than usual?
Psychomotor Slowing	Have you felt slowed down?
Energetic	Have you had more energy than usual to do things?

Software: Subjects assigned to KIOS-Bipolar will have the app loaded onto their preferred device. The program is available for iPhone and Android devices, and accessible on a pc. The research coordinator will demonstrate the KIOS-Bipolar operation with the subject and ask the subject if he/she has any questions about the procedures of the trial. A phone number and email address will be provided to allow the subject to make contact if any question arises after leaving the clinic. The data entry procedure will take less than 5 minutes per session, with most subjects completing their entries in 2 minutes.

For participants who have been randomized to the eMoods App an additional procedure will occur. After each completed weekly entry on eMoods, the participant will have the option to email the results to the Research Coordinator weekly or postpone sending data until their scheduled research visit.

The subject will be told that an email, text, or push notification reminder will be sent one day after a missed scheduled assessment. The participants phone number will be shared with a third-party (Twilio) solely for the purpose of reminding the participant to complete their questionnaire. This information will only be used for the administration of the push notification and will be kept strictly confidential. The participant will not have the option to opt out of the notification. For participants randomized to KIOS-Bipolar, a text message reminder will be sent one day after a missed scheduled assessment. The participant's phone number will be added to New Patient section in KIOS-Bipolar.

It should be noted that the Summary Statement contained a criticism that email reminders prior to expected assessment days would be a direct intervention that confounds weekly reporting adherence. Because the reminder will be sent *after* the scheduled assessment day, we are still able to judge adherence to the study schedule; the response to the notifications will provide a relevant secondary outcome measure. In addition, many subjects in the Field Trial requested this feature, which will almost certainly be included as an option in the commercialized version of KIOS-Bipolar.

Study participants assigned to eMoods will also have the software downloaded on their device (Either Android phone or computer) and the procedure of demonstrating the software and providing contact information described above will be followed. In the case that the IOS version of eMoods is not available by the time the study begins, the randomization of subjects will be stratified by device to ensure equal representation in the treatment groups.

Participation in the study will not impact the patient's routine clinical care for his/her bipolar condition. However, some subjects may want to discuss their KIOS-Bipolar or eMoods experience with their psychiatrist and/or psychologist, and will be permitted to do so.

Participants randomized to their assigned group who are unable to complete their weekly entries based on the following criteria: technical difficulties completing the weekly entry, difficulty emailing data to Research Coordinator (for eMoods group), and any other technical issues that may arise throughout the course of the study will have the option to switch to the other group. The participants who have been switched to the other group will have to complete a BISS self-report form along with a weekly entry from the newly assigned group.

Focus group(s): There will be an addition of one group at approximately Week 8. The group will have 10 participants and the focus of the group will be related to participants experience with mood charting. Recruitment for group 1 will consist of participants who are not currently enrolled in the 52-week comparative study. One half of the group will be participants who have experienced with mood charting and the other half will be participants with no prior mood charting experience. The focus of the first group will consist of the participants experience with mood charts as well as polling the participants on their preferences for logging in, graphs, and other software features.

Additionally, there will be a focus group at approximately Week 16. The focus group will consist of 10 participants who are currently randomized to the KIOS-Bipolar app. The focus of the second group will be related to their experience using the KIOS-Bipolar app along with suggestions for improvements. The participants will be polled on their preferences related to but not limited to logging in, graphs, advice, as well as other KIOS-Bipolar software features.

ASSESS KIOS-BIPOLAR OR eMOODS:

- a. At the beginning of the study subjects will be provided preformatted evaluation sheets and will be encouraged to note observations regarding ease/benefits of use, impediments to use, and suggestions for additional features that would enhance the utility of KIOS-Bipolar or eMoods for sustained health.
- b. We will ask the subjects to estimate how completing the KIOS-Bipolar /eMoods assessments contributed to their self-awareness, attitude, and overall sense of satisfaction with their health status.
- c. We will assess the sensitivity of KIOS-Bipolar to identify improving or worsening by comparing the concordance between subject-assessed items with staff -administered BISS items that address similar symptoms.

Plan of analysis: The primary aims of the analyses are to investigate patterns of adherence and attrition. The term adherence refers to the extent to which participants follow the weekly completion of KIOS-Bipolar's eight pivotal symptoms of bipolar disorder. Adherence will be measured through such usage indicators as the proportion of weeks completed on time, the proportion completed only with follow-up prompts, and the number of weeks not submitted. Proportions of stable trajectories or improving trajectories are of primary interest. With $n=90$ subjects (which allows for as many as 30 of the enrolled 120 subjects to have met some criterion for early termination) in the study we will be able to estimate any proportion within 0.10 with 95% confidence. For proportions larger than 0.9 we will be 95% confident we are within 0.06 of the true proportion. For a trajectory neither improving nor degrading there should be a 0.5 proportion

of each. For any hypothesis test for a proportion improving or degrading, i.e. not 0.5, we have 0.80 power at two tail significance of 0.05 to detect 0.65 different from 0.5 with n=90 subjects. For subgroups of patients with n=45 we can detect 0.71 different from 0.5 and with n=30 we can detect 0.74 different from 0.5. When comparing proportions of two subgroups of subjects, we will be 95% confident that the difference in proportions of the two subgroups is less than 0.25 for subgroups of n=30 and smaller than 0.20 for subgroups of size 40. If the proportions are larger than 0.9 (i.e. less variable), then we will be 95% confident that the difference in proportions of two subgroups with n=30(45) is less than 0.15 (0.12).

Assumptions needed for each analysis will be examined to assure they are reasonably well met and the conclusions are valid. End of study overall improvement or not for each measure can be analyzed with logistic regression using covariates and predictors of interest. By focusing analyses on proportions and changes in trajectories, each subject will serve as their own control and trends in improved scores, symptoms and behavior may be identified.

Initially, we will also assess the effects of site, ethnicity, and bipolar disorder subtype (BD I, BD II), but none of these factors will be retained in the final model if they are not shown to be significant moderating factors.

The rate of dropout at any given time will be modeled through logistic regression models, with health, socioeconomic, and treatment factors as explanatory variables. *The impact of quality of life on dropout will be assessed similarly.*

Outcome Measures from KIOS Analytics: Knowledge Base performance metrics will be computed to measure the effectiveness of the content provided to patients. These metrics take several forms and are based on changes in the symptom scores for all subjects in the field trial (see Phase I Final Report). Changes in the symptom scores provide a global measure of efficacy. Each of these measures can be computed as a function of changes, either over the course of the entire field trial or at each incremental assessment. This latter approach will provide a measure of effectiveness over time. Other KIOS analytic methods will reveal which specific content in the knowledge base needs improvement. Behavioral frequency analysis will show which patient states are entered most frequently. Behavioral transition analysis will show which conditions are precedents to undesirable states.

Implementation of Clinical Trial Results into Final Product: The results of the randomized trial will be used to make further refinements to KIOS-Bipolar. The KIOS-generated results will be used to guide changes to the knowledge base. Suggestions about additional features will be considered in development of the commercialization plans.

RISKS TO HUMAN SUBJECTS

a. Human Subjects Involvement, Characteristics, and Design

The collaborating sites are the UTHSCSA, the University of Louisville and the University of Cincinnati. Under the direction of Dr. Bowden, Biomedical Development Corporation will create an identical set of study binders containing source documents and case report forms for each of the study sites. Each site will have a designated study coordinator who will be responsible for obtaining, managing and protecting the data. All study materials will be kept under lock and key. The study sites will be monitored throughout the project period by BDC for study compliance, including a preliminary monitoring visit prior to the initiation of the trial to ensure that the study site is adequately equipped and staffed to perform the trial.

The Federal Wide Assurance number for the UTHSCSA is FWA00005928. The Assurance of Compliance number for the UTHSCSA is IRB00000553. The Federal Wide Assurance number for the University of Louisville is FWA00002211. The Federal Wide Assurance number for the University of Cincinnati is 00003152. The Federal Wide Assurance number for Biomedical Development Corporation is FWA0000749.

b. Sources of Materials

- Individuals enrolled into the study will be assigned study password-protected ID numbers.
- All information obtained from human volunteers will be utilized strictly for research purposes.

Information to be collected includes: demographic data, MINI-6.0, self-reported symptoms via the KTABS or eMoods (i.e., online questionnaire), Life Functioning Questionnaire, BISS and subjective information regarding the user experience with the software.

- Information will be collected, handled and stored according to the HIPPA regulations and study participants will be asked to read a Privacy Notice and sign a Research Authorization (HIPPA consent). Study participants will be given a copy of the signed consent form for his/her records.

c. Potential Risks

- There are only minimal risks associated with participation in this study. There is no intervention component in the trial. None of the planned activities are likely to be stressful to the subjects. However, it is possible that a subject could worsen in a time frame between clinic treatment visits. We will convey the evidence of the person's worsening to his/her psychiatrist or other therapist.

d. Adequacy of Protection Against Risks

Recruitment and Informed Consent

- Participants will be individually recruited from the respective study sites. The methods of this research as well as the Informed Consent Document and all recruiting materials will be approved by the Institutional Review Boards at the UTHSCSA, University of Louisville, and the University of Cincinnati, respectively.
- Study volunteers will have a detailed discussion of the study requirements and procedures with Drs. Bowden, McElroy, El-Mallakh or the study coordinator at the respective sites. All information regarding the study procedures will be provided to the subjects in understandable layman terms on an IRB approved informed consent form. Participants will receive up to \$600 for participation (Baseline visit, Weeks 8, 16, 24, 32, 40, and 52 at \$10/appointment plus the 52 weekly activities at \$10/self-assessment) for a total of up to \$600. Focus group participants will be compensated for their participation with a \$20 local state voucher.

At the UT Health Science Center, payment for study related procedures will be paid through use of the Mastercard. Compensation will be automatically credited after completion of each study visit. Name, address and date of birth will be shared with a third-party solely for the purposes of compensation processing. This information will only be used for the administration of the compensation (ClinCard) and will be kept strictly confidential.

In addition to the compensation on the card, the participant may also elect to receive study-related messages (text and/or email).

e. Protections Against Risk

Minimal risk to subjects or subject's privacy is anticipated. Nonetheless, we recognize the need for strict protection of confidentiality in this study. To address this, records of patients will be retained as required by statute in locked files. All computer files will be password protected. Subjects will be identified in common-use computer files by ID number only. Research reports and publications will report only group data and not individual names. Identities of subjects will not be revealed in the publication or presentation of any results from this project. All investigators and research staff at the respective institutions have completed the requirements for human research subjects' protection. All investigators and research staff at BDC have completed the requirements for human subjects' protection. The study will be performed in accordance with HIPPA regulations and approved by the IRBs at the UTHSCSA, the University of Louisville and the University of Cincinnati.

Participation in the study will be terminated if a patient has a score of 4 on the BISS suicide item, BISS Depression Scale ≥ 50 , or BISS Mania Scale ≥ 35 , or if the treating psychiatrist determines that a patient poses an imminent risk of self-harm.

All subjects enrolled in the trial will have been under care of a psychiatrist at their respective institutions prior to enrolling in the study. All subjects will continue to receive evidence-based care provided by outstanding psychiatrists at the three sites. Participation in the study will not impact the patient's routine clinical care for his/her bipolar condition. The study's planned visits will generally be scheduled to coincide with the patient's regularly scheduled clinic visits both for convenience and in order to not interfere with regular care.

f. Potential Benefits of the Proposed Research to Human Subjects and Others

Study participants may benefit by becoming more aware of their changing symptoms and improving their ability to manage and track their bipolar disorder.

The results of the research may yield benefits to the class of persons with bipolar disorders, whose treatment interventions, both in research studies and in routine clinical settings, may be optimized and made more effective consequent to the utilization of the K-B recommended interventions.

IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

- Psychiatric investigators, health care providers and government officials have all recognized that current guideline based treatments are limited in minimally personalizing interventions based on mediating variables that dynamically occur during treatment. The potential application of more personalized and evidence based intervention strategies could reduce the functional and morbidity burdens of bipolar disorders, which are a significant U.S. public health problem.
- Subjects will be subject to only minimal risk, as the study contains no intervention component. The minimal risks of the study seem reasonable in consideration of the potential that K-TABS has to improve care of bipolar disorder and reduce healthcare utilization and costs.

DATA AND SAFETY MONITORING PLAN

This Data and Safety Monitoring Plan is intended to ensure the safety of participants in the Clinical Trial and the validity and integrity of the data and reporting. Biomedical Development Corporation (BDC) maintains a chartered Independent Data and Safety Monitoring Board (DSMB) that will review the study prior to initiation. BDC is the sponsor for the Clinical Trial and also serves the role of data coordinator. The Clinical Trial is to be performed in compliance within the guidelines of the National Institutes of Health (NIH) and the IRBs of the UTHSCSA, University of Louisville, and the University of Cincinnati. The Principal Investigator of the Clinical Trial (PI) is Charles Bowden, M.D.

Monitoring the progress of the Clinical Trial

Responsibilities for Monitoring the Clinical Trial follow:

1. The PI is responsible for continuously monitoring the conduct of the trial and is the primary individual charged with identification and reporting of all AE and SAE occurrences.

2. On site monitoring is also conducted by the Regulatory Manager at BDC who provides systematic monitoring for the following central elements: protocol eligibility (direct source documentation of eligibility as defined in the protocol), appropriateness of consent documentation, and timeliness and accuracy of data, including the timeliness of reporting adverse events and serious adverse events. Monitoring for central elements will be performed on all subjects. Reports to BDC documenting the central elements are generated at six month intervals. Other monitoring reports are generated as needed or requested.
3. Assuring Compliance with Requirements for Reporting Adverse Events: All adverse events (AE) and serious adverse event (SAE) forms are submitted by the PI directly to the IRB and BDC. BDC is responsible for submitting AE and SAE reports as required to the DSMB and NIH including OHRP.

Monitoring by the Data and Safety Monitoring Board (DSMB)

The DSMB includes a minimum of four recognized clinical investigators and two or more representatives from the Sponsor including Gregg Siegel, President of BDC. The Board convenes every six months to review materials. The validity of the data is based upon the Clinical Trial infrastructure and the requirements for primary monitoring by the PI and the Regulatory Manager as summarized above. Reports of the DSMB are submitted independently to BDC and subsequently forwarded to the IRB, with a copy to the Principal Investigator.

We will endeavor to ensure that both sexes are adequately represented in the study. Based on epidemiologic studies (e.g. the Epidemiologic Catchment Area Program) and the composition of the patient population of the proposed sites, we anticipate that approximately 50% of the participants will be women.

We plan to include representatives of all minority groups in the proposed research. We have specifically included sites with demonstrated ability to recruit underrepresented minority groups and will review recruitment and enrollment efforts periodically to ensure that we are making every effort possible to enroll a representative sample. We expect to maintain or exceed 30% minority representation in the study. In particular, we expect that at least 15 % of subjects enrolled will be Hispanic and that at least 15 % will be African American.

We are including children ages 18-21. We will include only individuals 18 or older because we are not targeting a pediatric population (ages younger than 18). Additionally, the proposed sites are adult outpatient clinics and thus, the principal investigators and study staff have expertise in treating adults. We anticipate that children ages 18-21 will constitute approximately 5% of the sample.