Mount Sinai	Protocol Title:	1/2-Pramipexole in Bipolar Disorder: Targeting Cognition (PRAM-BD)
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MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
4. *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

Brief Summary of Research (250-400 words):

1) Objectives:

Converging evidence suggests that patients with bipolar disorder suffer from deficits in neurocognitive functioning that persist, despite remission of acute affective symptoms. These impairments contribute directly to functional disability, highlighting the need for interventions above and beyond standard treatments in order to achieve a full inter-episode recovery. The current study aims to investigate the safety and efficacy of a dopamine agonist (pramipexole), on these persistent cognitive abnormalities in euthymic bipolar patients using a placebo-controlled, adjunctive, 12-week trial design.

Aim 1: Baseline to Week 6

a) To determine the short-term efficacy of pramipexole on neurocognitive functioning in stable BD patients. b) To determine the short-term safety of pramipexole on neurocognitive functioning in stable BD patients.

Aim 2: Week 6 to Week 12

a) To determine the long-term efficacy of pramipexole on neurocognitive functioning in stable BD patients. b) To determine the long-term safety of pramipexole on neurocognitive functioning in stable BD patients.

Exploratory Aim: To integrate results from multiple dopamine-based domains (cognition; affect; reward processing) to evaluate the main and interactive effects of pramipexole on these factors in stable BD patients.

2) Background

Data suggest that, as in schizophrenia (SZ), bipolar disorder (BD) patients' everyday functioning is directly influenced by persistent symptomatology and cognitive dysfunction (Bowie et al. 2010; Burdick et al. 2010). A recent meta-analysis indicated significant correlations (mean r=.27) between cognition and functional measures in BD (Depp et al. 2012), with little evidence for differences across cognitive domains. These data strongly support the role of cognition in quality of life in BD and highlight the need for treatment and prevention efforts targeting this domain (Burdick et al. 2007). There are several ongoing large-scale clinical trials targeting cognition in SZ, with a parallel need existing in BD. We recently completed one of the first controlled trials of cognition as a treatment target in BD (Burdick et al. 2012). We approached the initial question of which agent to test based upon prior evidence that enhancing dopamine may result in improvements in neurocognition in other clinical samples.

Although the neurobiological basis of persistent cognitive impairment in BD is not well-understood, convergent evidence suggests that the enhancement of DA activity may be a useful remediation strategy. Neuroimaging studies highlight structural brain abnormalities in BD in regions rich in DA receptors, including anterior cingulate, dorsolateral, orbital, and subgenual cortex (Drevets et al. 1998; Lopez-Larson et al. 2002) and the basal ganglia (Baumann et al. 2001). Abnormal activation in these regions has been reported in BD during cognitive tasks using fMRI (Blumberg et al. 2000; Gruber et al. 2004). Moreover, in previous studies of healthy subjects increasing levels of DA via agents such as pergolide, a D1 agonist (Kimberg et al. 2003) or bromocriptine, a D2 agonist, (Kimberg et al. 1997; Luciana et al. 1998) improves cognition, particularly in cognitive domains linked to prefrontal cortex (PFC) functions. Finally, molecular genetic studies support the importance of DA in normal cognitive functions. Several cognitive studies have focused on the gene coding for catechol-o-methyl transferase (COMT), an enzyme responsible for the degradation of catecholamines, including DA, in the PFC (Dickinson et al. 2009). Convergent results demonstrate an association between genetic variation within *COMT* and cognitive function in SZ (Bilder et al. 2002; Egan et al. 2001) and healthy controls (Malhotra et al. 2002; Tsai et al. 2003). *COMT* has also been implicated in the susceptibility for BD (Kirov et al. 1998; Papolos et al. 1998), including work by our group (Burdick et al. 2007). In a sample of 52 Caucasian BD probands and 102 Caucasian healthy controls, we detected a modest but significant association between SNP rs165599 and BD, with the g allele being over-represented in cases vs. controls (OR=2.41; genotypic p=0.04; allelic p=0.02). We found a relationship between the risk allele at this SNP and poorer performance on verbal memory tasks (California Verbal Learning Test; CVLT Trials 1-5; p=0.005; eta^2=0.07) particularly with regard to PFC aspects of learning (CVLT semantic cluster; p=0.037; eta^2=0.04) in BD patients and in

healthy controls (Burdick et al. 2007). In addition to these lines of evidence supporting the use of a DA agent to enhance cognition, recent evidence suggests that pramipexole, a novel D2/D3 agonist, may be an effective adjunctive anti-depressant in BD. Pramipexole (Mirapex®) is an FDA-approved medication for Parkinson's disease (PD) and restless leg syndrome.

3) Setting of the Human Research

The Icahn School of Medicine at Mount Sinai (ISMMS) site has ideal facilities for the proposed study. The research activities will be conducted in the Clinical Neuroscience Center located at 53-55 E. 96th Street, 1st floor suite. This space, completely renovated in 2014, consists of a seven-room suite with ample space for research staff, interview rooms, and an exam room.

4) Resources Available to Conduct the Human Research

Recruitment for this study will be done across Mount Sinai and will include:

Psychiatry Outpatient Clinic

The Mount Sinai Psychiatry outpatient department (OPD) serves a large catchment area that includes both an affluent neighborhood on the Upper East Side of Manhattan and an economically challenged neighborhood in East Harlem. Mount Sinai is the primary provider of medical care (and mental health care) for many area residents. On a monthly basis, approximately 60 new patients are seen in the adult OPD, of whom 40% have a diagnosis of mood disorder. Approximately 90 subjects with bipolar disorder are currently treated in the OPD; 82 new intakes per year have a diagnosis of bipolar disorder. Any patient referred to the Mount Sinai Psychiatry Outpatient Clinic is presented at intake meetings and research eligible patients are referred to a research psychiatrist in MAP.

Mood and Anxiety Disorders Program (MAP)

The Mood and Anxiety Disorders Program (Director: Dan V. Iosifescu, M.D.; Co-I on this study) is one of the major research and clinical programs of the Department of Psychiatry.

Referrals are anticipated for the proposed study from the following sources: (1) patients with bipolar disorder currently receiving treatment in the MAP program; (2) the Mount Sinai Hospital Adult Outpatient Psychiatry Department; (3) self-referrals from patients who have completed other research protocols in the MAP program; (4) clinicians within

and outside of the Mount Sinai Hospital system, including affiliates with large numbers of underserved patients such as Elmhurst Hospital in Queens; (5) self-referrals from individuals attending presentations on bipolar disorder in the New York State and tri-state area and from media advertisements. In addition, we anticipate the receipt of referrals from consumer advocacy groups specializing in severe, treatment resistant mood disorders, including NAMI and the Mood Disorders Support Group (MDSG) of New York.

5) Study Design

a) Recruitment Methods

Subjects will be recruited from MAP and the OPD as described above. Community advertisements will be placed if needed (none currently attached for review). Potentially eligible patients are identified by the patient's clinical care taker (nurse practitioner and/or physician), who would then ask the patient's permission for our research team to approach and explain the protocol. A research member will approach that individual and explain the study objectives, procedures, risks and benefits, and begin the informed consent process if the patient wishes.

b) Inclusion and Exclusion Criteria

Inclusion criteria: 1. Age 18-65. ***2.*** DSM-IV BD I or II diagnosis. ***3.*** Affective stability, defined by a Young Mania Rating Scale (YMRS) rating of < 8 and a Hamilton Depression Rating Scale (HRSD) rating of ≤ 16 at screening and baseline. We will further require that any subsyndromal depression has not significantly worsened in the 4 weeks prior to randomization so as to avoid enrolling subjects who are on the verge of a full depressive episode. ***4.*** Evidence of clinically-significant neurocognitive impairment at screening. This will be formally assessed using a short battery of tests including Trails B, Wechsler Adult Intelligence Scale (WAIS-IV) Digit Symbol, WAIS-IV Digit Span Forward and Backward, Wisconsin Card Sorting Test (WCST), and California Verbal Learning Test – Second Edition (CVLT-II). Clinically-significant impairment will be defined as scoring ≥ 1 SD below normative means on at least one of these measures. ***5.*** Clinically-acceptable, stably-dosed, mood stabilizing medication regimen for ≥ 1 month prior to enrollment, with no medication changes planned over the 12-week study period.

Exclusion criteria: 1. History of CNS trauma, neurological disorder, ADHD, or learning disability. ***2.*** Positive urine toxicology or DSM-IV diagnosis of substance abuse/dependence within 3 months. ***3.*** Active, unstable medical problem that may interfere with cognition. ***4.*** Recent history of rapid-cycling. ***5.*** Abnormal lab or ECG result at screen. ***6.*** History of heart failure. ***7.*** Significant suicidal risk (HRSD item 3 > 2 or by clinical judgment). ***8.*** Estimated IQ in MR range as per Wide Range Achievement Test (WRAT) standard score of less than 70. ***9.*** Pregnant women or women of child

bearing potential who are not using a medically accepted means of contraception (including oral contraceptive or implant, condom, diaphragm, spermicide, intrauterine device, tubal ligation, or partner with vasectomy) ***10.*** Women who are breastfeeding. ***11.*** Participation in any other investigational cognitive enhancement study within 30 days.

Concomitant Medications*:* Practical and ethical considerations prevent a focus on medication-free patients. Medications with known adverse cognitive effects will be disallowed (i.e., topiramate, anticholinergics), as will agents that may enhance cognition (e.g., amphetamine, other DA agonists). Benzodiazepines will not be allowed within 6 hours of testing. ECT in the past 12 months will be disallowed, as will any drug known to interact with pramipexole. With regard to antipsychotic medications specifically, only half of the sample will be allowed to be taking any antipsychotics. Recruitment efforts will be adjusted to ensure 50% of the sample is antipsychotic-free at baseline. Further, we will exclude any subject who is taking more than 4 concomitant psychotropic medications. Older generation neuroleptics will be specifically disallowed due to their high binding potential at the D2 receptor (Kapur et al. 1999). Although some of the standard treatments for BD (e.g. lithium) may influence cognition, it is impractical to exclude these medications given their widespread use; therefore, data will be coded for medication classes and dosages to determine a load score (as per Hassel et al. 2008) to be included as a covariate in statistical analyses.

c) Number of Subjects

Up to 50 affectively stable patients with Bipolar Disorder will be randomized via recruitment through MAP, the Mount Sinai OPD, and community advertisements if necessary. Additional subjects will be screened, with an assumption of some not meeting eligibility; therefore, we estimate 70 patients to be consented for 50 to be randomized.

d) Study Timelines

There will be a 2-month start-up, 28 months of recruitment and 6 months of follow-up. The last patient randomized will be mid-way through Year 2 to ensure study completion by end of Year 3. Analyses and manuscript preparation will be completed immediately thereafter. We will screen ~3 patients per month (~1 patient randomized/month), totaling 70 patients screened and 50 patients randomized.

e) Study Endpoints

The primary endpoints related to the safety and efficacy on neurocognitive functioning of pramipexole will be measured. Neurocognitive performance on the MATRICS Consensus Cognitive Battery will be measured at baseline, week 6, and 12 (or end of study). Safety measures will be assessed at each visit throughout the study. Co-primary measures of everyday functioning (described below) will be assessed at baseline and week 12 (or end of study).

f) Procedures Involved in the Human Research

All eligible participants will undergo study visits at screening, baseline (week 0), week 1, week 2, week 3, week 4, week 6, week 8, and week 12, (end of study).

Randomization will be conducted via a computer generated program and all study staff will be blinded unless un-blinding is required for safety reasons. Subjects will be randomized on a 1:1 ratio with stratification for concomitant antipsychotic status and depression at baseline (HRSD <8 vs ≥ 8). Study drug will be blinded and matched to placebo. Adapting from our previous work in BD and according to package labeling, the dosage titration schedule will be slow and flexible. Dosing will be initiated at 0.25 mg QHS on night one, followed by 0.25 mg BID day two onward, and increased every week to a target of 4.5 mg/day. As compared with our previous maximum 1.5 mg/day (Burdick et al. 2012), we opted to allow up to 4.5 mg/day (the maximum approved dosage in Parkinson's disease) to ensure adequate target engagement. We are familiar with this dose range, as 4.5 mg/day was allowed in our study in BD depression (Goldberg et al. 2004). Dosing will be flexible based on side effects; however, if 1.5 mg/day cannot be tolerated, the subject will be discontinued. Titration will occur up to week 6 and then efforts will be made to maintain the same dose until the completion of the trial (week 12).

Measures are described in detail below:

Safety Outcome Measures

- Side Effects Checklist (SEC; physician administered) – (*all visits*)
- Columbia Suicide Severity Rating Scale – *(all visits)*
- Iowa Gambing Task – (*baseline, week 6, week 12*)
- Vital signs including blood pressure (standing/supine) – (*all visits*)
- Electrocardiogram (ECG) – (*screening, week 6, week 12*)
- Liver function tests; chemistry panel; CBC; urinalysis – (*screening, week 12*)
- Pregnancy test for women of childbearing age – (*screening, week 12*)
- Urine toxicology – (*screening, week 12*)
- Medication log of current medications and all medications administered during previous week – (*all visits*)

Clinical/Symptom Measures

- Structured Clinical Interview for the DSM-IV (SCID–IV) – (*screening*)
- Symptom rating scales: Young Mania Rating Scale (YMRS); Hamilton Rating Scale for Depression (HRSD); Brief Psychiatric Rating Scale (BPRS) – (*all visits*)
- Smoking questionnaire – *(screening, baseline, week 6, week 12)*

Neurocognitive/Functional Measures

- Screening cognitive battery (see inclusion criteria 4.) – (*screening*)
- Cognitive assessment: MATRICS Consensus Cognitive Battery (MCCB- plus; see description below) – (*baseline, week 6, week 12*)
- The Probabilistic Stimulus Selection Task – (*baseline, week 6, week 12*)
- UCSD Performance Skills Assessment (UPSA) – (*baseline,week 12*)
- The World Health Organization Disability Assessment Schedule (WHODAS 2.0) – (*baseline, week 12*)

The MATRICS Consensus Cognitive Battery	**Domain**	**Note/Description**
Category Fluency	Speed of Processing	Total animals in 60 seconds
BACS Symbol Coding	Speed of Processing	Matching numbers to symbols
Trail Making Test Part A	Speed of Processing	Dot-to-dot: Numbers only
CPT-Identical Pairs	Attention/Vigilance	Computerized numeric stimuli
Letter-Number Span	Working Memory	Recoding numbers and letters in order
WMS-III Spatial Span	Working Memory	Visual sequence forward and backward
Hopkins Verbal Learning (HVLT)	Verbal Learning	12 word list x 3
Brief Visuospatial Memory Test (BVMT)	Visual Learning	6 designs to be drawn from recall
NAB Mazes	Reasoning & Problem Solving	Pencil-paper maze solutions
MSCEIT Managing Emotions	Social Cognition	Situational social judgments
Additional Measures ("Plus")	---	---
Affective Go-no-go	Affective Neuroscience	Emotional modulation of inhibition
Emotional Stroop	Affective Neuroscience	Affective Bias/Cognitive Control

g) Specimen Banking

N/A

h) Data Management and Confidentiality

If a participant agrees to be in this study, we will collect health information that identifies them ["Protected Health Information" (PHI)]. We may collect the results of tests, questionnaires and interviews. We may collect information from a patient's medical record. We will only collect information that is needed for the research. This information is described in the consent form. By signing the consent form a participant gives us permission (authorization) to collect, use and share their health information.

Data collected will include questionnaires and assessments as described above in section (5f). Labs and tests will be performed at the MSMC laboratory and information sent to the PI. These data will be stored in a binder which will be secured in a double locked fashion. Blood samples will be labeled with de-identified codes, which cannot be associated with individual subjects. PHI, such as patient name and DOB, will only be included in a separate file including the consent documents. The file linking de-identified data with participant PHI will be stored on an encrypted drive. PHI data will be stored indefinitely, as well as for potential future research. All other data collected for the study will be de-identified and stored apart from PHI, identified by a study number linked to PHI in a secure file. This data will be stored indefinitely.

The PI will be responsible for receipt and transmission of study data and specimens. Quality control of the data collected will include double data entry and data quality checks by investigators after each 5 subjects completed.

Study staff will have access to data and records and these may be reviewed by the Mount Sinai School of Medicine Institutional Review or government agencies (i.e. NIH) in order to meet federal or state research regulations. Participants will be made aware in the consent process that once private information is disclosed, it is subject to re-disclosure by the recipient and can no longer be considered protected. If research records are used for decisions related to clinical care, then a participant has the right to review this information and to request changes. This is limited to information about their treatment, and does not include information related to procedures or tests that are for research purposes only. Participants may access this information only after the study analysis is complete.

Data from this study may be used in medical publications or presentations. The information will be de-identified so that individual subjects cannot be recognized and the information will no longer be considered PHI. The information that is collected for research will be analyzed for many years and it is not possible to know how long this

analysis and follow-up will take. Therefore, participants are allowing access to this information indefinitely.

Participants will only be identified with a numerical code in compliance with HIPAA regulations. Raw subject data will be secured in double locked physical control. Digitized raw data will be similarly de-identified using coding and will be secured on an MS SQL server with Windows-integrated security.

Statistical Methods: *Preliminary analyses*: Groups will be compared on demographics, baseline symptom ratings, and concomitant medication load; if necessary, covariates will be included in subsequent models. MCCB data are standardized using the MCCB program, scores are age- and sex- corrected and reported on a t-score scale (Mean=50, SD=10). Any study focusing on improving cognition must consider practice effects (Goldberg et al. 2008). The placebo arm will provide estimates of expected practice so that we are able to calculate a reliable change index (RCI) to determine the meaningfulness of change (Goldberg et al. 2009).
Primary hypothesis testing: 100 participants will be randomized in a 1:1 allocation to treatment with pramipexole or placebo. The primary assessment of safety will be based on the incident of adverse event rates and standardized mood ratings at each visit. Differences in the incidence of individual adverse events will be compared between randomization arms using Poisson regression. Exact 95% confidence intervals (based on the Poisson distribution) for the risk ratios for individual adverse events for treatment with pramipexole versus placebo will be computed and may incorporate an estimated overdispersion parameter if observed variability exceeds that determined by the Poisson distribution. Performance on the IGT will also be used to track potential changes in impulse-control (baseline, weeks 6 and 12). We will test for correlations between IGT performance and mania symptoms at the times of testing (simultaneous measurements). Moreover, we will use IGT change scores as predictors in regression models to evaluate changes in mania ratings at concurrent time points as well as future time points. This will directly address the question of whether or not changes in IGT strategy serve as markers of current mania and/or impending affective destabilization.

The relative specificity of pramipexole in binding to D2/D3 receptors allows for a unique opportunity to enhance DA in neural networks associated with specific aspects of cognition as well a reward processing, which will be carefully assayed in this study so that exploratory analyses will be able to test questions related to the role for these receptors across several interacting domains in BD, at least at the level of behavior. Exploratory analyses will include specific domains and individual tasks which will be modeled to account for main effects and interactions (as described in primary analyses below).

The primary outcome for efficacy is change in cognition from baseline to week 6 (MCCB Composite). The null hypothesis is that there is no difference in this change between

patients on pramipexole vs. patients on placebo. This will be tested in an intent-to-treat analysis using a 0.05 level two-tailed test based on a mixed effects regression model, with patients considered to be a random effect, and randomization group a fixed effect. In order to preserve statistical power, change in MCCB Composite will be used as the dependent variable; however, secondary analyses will be conducted for MCCB domain scores and measure of reward processing. The use of two post baseline evaluations (weeks 6 and 12) and the ability of the model to incorporate all available data, also improves efficiency (i.e., power). This approach will also be employed in subsequent comparisons of specific domains and for measures of reward processing. These additional analyses will be conducted at a nominal 0.05 level and will focus on enhancing interpretation of the primary analysis by highlighting the specific domains most affected by pramipexole. Since randomization is stratified by concomitant antipsychotic use and baseline depression status, indicators of stratification will be included in the model as fixed effects.

Missing data: Although the mixed effects modeling approach allows patients with evaluations at week 4 but missing at week 8 to be included, bias may be introduced if missing data are related to patient response. For example, it may be that patients responding poorly are less likely to have a week 8 evaluation than those patients with better response. The mixed effects analysis would weigh the results of these poorly performing patients less (as they provide fewer data) and in the presence of a positive effect of pramipexole, decrease power. To assess the extent that any bias has been introduced by missing data, we will impute missing week 8 values. Note that if no bias is produced by the missing data, analyses with and without imputation should provide virtually identical results. If the analyses produce different results, we will work to identify the causes by comparing patients with and without missing data. Based on our prior trial experience we expect relatively few patients (< 10) to be missing the week-8 visit due to attrition. Patients with missing data will have their 8 week MCCB score imputed via multiple imputation assuming that the data are MAR, i.e., the missing nature of the variable is independent of the value of the variable given the observed data. The specific imputation model to be used will be determined prior to examination of any outcome data, but will include MCCB score at baseline and at 4 weeks. Separate imputations will be done for each randomization group.

Due to the 12 week course of the study, mixed models will still be utilized for variables collected with sufficient frequency; however, when incorporating missing data, we will only be able to do so when at least two time points are included. Subjects with only baseline data will be included in descriptive analyses but will be dropped for analyses where necessary.

***Sample size/Power*:** A total of one hundred patients will be randomized 1:1(50 from ISMMS, 50 from ZHH). The adequacy of this sample size is based on the ability to reject the null hypotheses of no difference between treatment groups with respect to the MCCB composite score with sufficient power (80%). Ideally, sample size would be determined to ensure adequate power to detect the minimal clinically important difference. No specific guidelines exist to establish such a threshold in this setting but cognitive change of at least a moderate effect would likely be necessary to allow for clinical meaningfulness. Our sample size provides approximately 80% power to detect a standardized difference (e.g., Cohen's d) of approximately 0.55 with a two-tailed 0.05 level test. For the pre-specified subgroup analysis based on concomitant use at baseline, the detectable standardized difference is about 0.80.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

A formal Data Safety and Monitoring Board (DSMB) will be utilized. The DSMB is already established and is operating through the NIH-funded ACISR center grant at Zucker Hillside Hospital (ZHH).

The membership includes 2 physician researchers who are not involved with the current trial but have experience in clinical trials in psychiatric samples, as well as other senior faculty in the Division of Psychiatry Research at ZHH. In collaboration with the primary statistician for this trial (Michael Parides; ISMMS Co-I), the DSMB will be asked to review data on this trial at any time that there is a serious adverse event, reportable to the Institutional Review Board (IRB) and every 6 months following study start up (regardless of site). In addition to the DSMB, the PI at each site will review safety data in real time to address any concerning adverse events.

Part I: Elements of a Data and Safety Monitoring Plan

1. ***MSSM Principal Monitor:***
Indicate whether this person is the PI, a Team Member, or is Independent: PI

Last Name: Burdick
First Name: Katherine
Academic Title: Professor
Department: Psychiatry
Mailing Address: One Gustave L. Levy Place, Box 1230, New York, NY 10029
Phone: 212-659-8841
Fax: 212-996-8931
E-mail: katherine.burdick@mssm.edu

MSSM Additional Monitor:
Indicate whether this person is the PI, a Team Member, or is Independent: Team Member (co-investigator)

Last Name: Iosifescu
First Name: Dan
Academic Title: Associate Professor
Department: Psychiatry
Mailing Address: One Gustave L. Levy Place, Box 1230, New York, NY 10029
Phone: 212-241-4480
Fax: 212-241-3354
E-mail: dan.iosifescu@mssm.edu

2. Dr. Burdick has been responsible for running two previous studies using this agent in bipolar disorder (Goldberg et al 2004; Burdick et al 2012).

3. Adverse events, subject compliance with the protocol, and drop outs will be monitored for safety.

4. ***ACCUMULATED*** *safety and data information (items listed in number 3 above and interim analysis of efficacy outcomes) will be reviewed by the monitors or the Data Monitoring Committee (DMC) twice a year.*

5. Alteration of the study design is not expected; however, SAEs will be considered for unblinding and relatedness to drug will be assessed.

6. In order to minimize toxicity we are only allowing up to a max of the FDA recommended dose – dosing is flexible based on AEs and tolerability.

7. There will be no specialized grading system used to evaluate adverse events.

8. Procedures that will be used to assure data accuracy and completeness include double data entry and frequent queries of database.

9. Should a temporary or permanent suspension of your study occur, in addition to the PPHS, we will report the occurrence to NIH as well as ZHH, the other site conducting study.

j) Withdrawal of Subjects

Participants with an exacerbation of mania/depression (YMRS $\geq$ 15 or HRSD $\geq$ 18) will be discontinued and treated by the study physician. Suicidal ideation will be assessed at each visit with the Columbia Suicide Severity Rating Scale (C-SSRS). Significant suicidal ideation will be addressed immediately using the standard clinical response at ISMMS (evaluation at the walk-in clinic for potential need for hospitalization). Participants at risk for suicidal behavior will be discontinued. Side effects will be rated by a study physician at each visit. Any side effect deemed to be a serious adverse event or an unanticipated follow up will be reported to the PI, and the ISSMS Institutional Review Board (IRB) and appropriate follow up will be conducted. In addition, participants who exhibit an inability to follow the protocol will be discontinued and withdrawn from the study.

To ensure orderly termination from the study, the study physician would meet with the participant to discuss termination and discontinuation of medication. Safety measures would be collected and a follow-up visit by phone would be scheduled to further ensure safe discontinuation. Pramipexole should be tapered off at a rate of 0.75mg per day until the daily dose has been reduced to 0.75mg. Thereafter, the dose should be reduced by 0.375mg per day. We will schedule an in-person follow-up visit by phone to address any remaining concerns the participant may have.

Participants may withdraw from the study for any reason at any time by contacting the principle investigator or any of the research staff. It is also possible to withdraw permission for the use and disclosure of any protected information for research but it must be done in writing to the principle investigator. In the event permission is withdrawn, information that was already collected may still be used if that information is necessary to complete the research study.

6) Risks to Subjects

During the informed consent process, participants will be informed of the potential risks associated with the study. At each weekly visit the study physician will meet with participants and conduct a thorough review of symptoms including mood, and suicidal ideation. If there is an acute worsening of symptoms the study clinicians will review the case with the PI (or will make an emergency decision as needed) to ensure that the participant receives emergency care or hospitalization. Participation in the study will be discontinued in any case of clear symptom worsening. Between weekly visits, the participants will have emergency contact information.

Along with closely monitoring for symptom exacerbation, each visit with the study physician will entail a detailed side effect evaluation, which will include vital signs and a

side effect checklist. The most common side effects of pramipexole are nausea, headache, dizziness, insomnia, constipation, muscle weakness, abnormal dreams, confusion, memory problems, urinary frequency. Participants will be educated about the potential for these side effects. Rare side effects have also been reported including sedating effects, impulse control symptoms (e.g. gambling), hallucinations, and orthostatic hypotension. The informed consent process will alert participants to these potential risks and close monitoring will ensure prompt response to any adverse effects with appropriate treatment and/or study discontinuation, as indicated.

7) Provisions for Research Related Injury

In accordance with Federal Regulations, if anyone is injured from being in the study, they will receive medical care and treatment as needed from Mount Sinai Medical Center. However, participants are responsible for the costs of such medical treatment, directly or through their medical insurance and/or other forms of medical coverage. No money shall be given to them.

8) Potential Benefits to Subjects

There may be no immediate potential benefit to the participant from participation in this research study; however, the investigational use of the medication for treating neurocognitive functioning may result in an improvement in these symptoms in some of the subjects. In addition, data from this study may lead to subsequent larger scale studies aimed at treating cognitive impairment in patients with BD.

9) Provisions to Protect the Privacy Interests of Subjects

Participants are free to refuse to answer any of the questions that are being asked of them in the study. If the withheld information is critical to study eligibility the participant may not be enrolled. While enrolled in the study, all tests and procedures will be done in a research office at ISMMS ensuring privacy. All research staff will be open to answering any questions and will address any concerns of the participants throughout the duration of the study.

10) Economic Impact on Subjects

There is no cost to participants for participating in the study.

11) Payment to Subjects

Participants will be informed during the consent process of the study compensation. Participants will be paid $100 for the screening visit; $50 for baseline and week 6; $20 for week 1, 2, 3, 4, 8; $100 for week 12. Total possible payment of $400 for study completion.. Screen failures will receive the screening rate ($100) provided they undergo study procedures at that visit.

12) Consent Process

A potential participant will be approached by a member of the study team after she/he has been given permission to do so by the patient's clinician. We will be following SOP HRP-090. Only English speaking subjects will be consented into the study. The research team member will explain the study objectives, procedures, risks and benefits, and answer all the questions the potential participant may have. Participants are advised that they can withdraw from the study at any time. Participants will receive a copy of the consent form for the study. Informed consent will be documented when the subject signs the consent form that has been approved by ISMMS PPHS.

13) Process to Document Consent in Writing

All participants must provide written informed consent. The consent form will be documented in writing. The consent form has been derived from the standard PPHS template.

14) Vulnerable Populations

The following population types will be excluded from the study: adults unable to consent, individuals who are not yet adults, wards of the state, pregnant women, and prisoners.

15) Multi-Site Human Research (Coordinating Center)

The overall organization of this project is provided by the PIs, Drs. Burdick and Malhotra. Each site [Icahn School of Medicine at Mount Sinai (ISMMS) and the Zucker Hillside Hospital (ZHH)] will be responsible for managing the activities of their site. Overall organization and management of sites will be provided by ISMMS. All PIs and Co-Is will participate in monthly conference calls over the first 2.5 years of the study. During the data analytic phase, the frequency of conference calls will be increased to weekly.

Mount Sinai will serve as the coordinating site for this trial; therefore, Dr. Burdick will be the contact PI and responsible for all interactions between sites and with NIH. All procedures specific to the clinical trial will be identical at the two sites. Rater training will be initiated with an in-person, on-site meeting to ensure adequate reliability for clinical and neurocognitive assessments. We are uniquely situated to ensure reliability, as Dr. Burdick was formerly the Director of the Neurocognitive Assessment Unit at the second site (ZHH) and she conducted training with staff at both sites. All statistical analyses will be led by the statistician (Co-I) Michael Parides from ISMMS. This will include intermittent safety data analyses for the Data Safety and Monitoring Committee (DSMB) review and all analyses at the conclusion of the trial.

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

If any preliminary results arise from this study or any related studies are published that change the risks associated with this protocol, we will notify all participants who have participated. Otherwise, results from the analyses will be published in peer reviewed journal articles but will not be transmitted directly to the participants involved in the research.

18) IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

The study drug will be stored and distributed by the research pharmacy.