LETTER OF INTENT TEMPLATE: PCORnet PATIENT-POWERED RESEARCH NETWORK PHASE II

PART I: NETWORK OVERVIEW

Title of Proposed Network: MoodNetwork

As per the Letter of Intent (LOI) Template, we briefly describe how the MoodNetwork will contribute to PCORnet as a national resource for patient-centered research: The MoodNetwork is the **only psychiatric component** of PCORnet and the only patient powered research collaboration for psychiatric disorders in the nation. National estimates of the frequency of burden of the spectrum of depression and bipolar disorder suggest that, combined, up to 22% of the population will have a mood disorder - about 17.5% with depression at some point in their lives and 4.5% with lifelong bipolar spectrum disorder [1-3], with much higher estimates of mood disorders present with comorbid medical problems [4] and in primary care [5, 6]. The MoodNetwork will contribute to PCORnet by **providing disempowered and stigmatized patients with a voice** to help determine the psychiatric agenda for PCORnet. MoodNetwork will also provide a framework to examine the course and treatment of mood disorders, with or without medical comorbid conditions, and provide a unique platform for comparative effectiveness studies and new technologies to track patients with mobile apps. MoodNetwork will also provide opportunities to examine the critical issue of suicide and suicide prevention [7-9].

As per the LOI template, we include the names of the participating organizations and ensure significant participation by patient organizations: All major patient organizations and advocacy groups for individuals with mood disorders are MoodNetwork stakeholders and serve on the governance board as part of the Executive Committee and Stakeholder Advisory Boards: This includes the President of the Depression and Bipolar Support Alliance (DBSA), Medical Director of National Alliance for Mental Illness (NAMI), the Executive Director of Anxiety and Depression Association of America (ADAA), the Chairman of the International Bipolar Foundation (IBPF), and the Co-Founder, President and Executive Director of the National Organization for People of Color Against Suicide (NOPCAS).

As per the LOI template, we state current and projected size of the network: As we await IRB approval for the MoodNetwork, the projected size of the network remains 50,000 patients. The comprehensive recruitment plan includes social media campaigns by our advocacy group partners (DBSA: 1.75 million hits/month on website, 5 million served, 20,000 on a mailing list; NAMI: 200,000 calls/year, 500,000 brochures distributed annually; ADAA: 900,000 hits/month on website, nearly 12,000 on their mailing list; IBPF: 20,000 hits/month on website, 15,000 on mailing list), CDRNs with nearly 25 departments of psychiatry embedded within PCORnet, and a network of 47,000 clinicians associated with the Massachusetts General Hospital Psychiatry Academy, as well as 200 clinical research sites affiliated with the MGH Clinical Trials Network and Institute.

As per the LOI template, we briefly provide any significant examples of research conducted using the network: We are awaiting the award notice for a National Institute of Mental Health Small Business (SBIR) Phase II grant (1R44MH107065-01) to assess 1000 patients in the MoodNetwork using a sophisticated mobile phone app from Cogito, Inc. This app will use passive monitoring tools (e.g., movement, location, cell phone use, voice recordings) to track and detect warning signs for depression or mania. We also have a PCORI large pragmatic trial application currently under review for a comparative effectiveness study of monotherapy with a second generation antipsychotic vs. combination therapy with a second generation antipsychotic plus a mood stabilizer for bipolar youth.

As per the LOI Template we describe any changes to the composition of our network: We have added two stakeholders to MoodNetwork governance structure, Alies Muskin, the Executive Director of ADAA and Donna Holland Barnes, PhD Co-Founder, President and Executive Director of NOPCAS. We also added another patient stakeholder, Ken Bello.

PART II: ABILITY TO ACHIEVE PCORnet PHASE I GOALS

As per the PFA, we briefly describe the current and expected status of our PPRN with respect to Phase I requirements and relevant capabilities for each of the Phase I goals:

- ***Availability of PPRN governance policies with substantial involvement from patients in leadership:*** We have developed governance and decision-making policies jointly with patients and advocacy groups having authority equal to the academic clinical researchers. All policies have been developed with stakeholder involvement, such as creating our data safety and data sharing policy, and MoodNetwork governance structure. Stakeholder input is solicited at every opportunity to facilitate high patient engagement as well as to foster good communication.

- ***Network agreement to abide by PCORnet-wide governance policies and ensure readiness to collaborate in PCORnet research:*** MoodNetwork governance has agreed to abide by PCORnet-wide governance policies. With respect to PCORnet research readiness: (1) Starting in February 2015, following successful beta testing of the website/database and IRB approval we will have established the infrastructure (web-portal and database) to accommodate comparative effectiveness trials using patient reported outcome data via the MoodNetwork. We will share data across PCORnet by adhering to the PCORnet common data model and have successfully answered the test query; (3) the MoodNetwork database/website is designed such that we have the capacity to link up with CDRNs and other PPRNs in order to combine MoodNetwork patient reported outcomes with clinical EHR information or other patient reported outcomes collected by other PPRNs. This will be accomplished by a modular database structure that allows us to expand our database and website as needed in order to incorporate EHR data or other patient reported outcomes.

- ***Current and projected (by end of Phase I) number of participants in the PPRN, and the enrollment and retention rates:*** The MoodNetwork awaits IRB approval at the time of this LOI submission. We are maintaining a list of participants who are interested in joining the MoodNetwork. The website is currently being beta tested and IRB approval is expected in late January. We project the proposed 50,000 participants and have planned social media campaigns through the advocacy groups to ensure target enrollment.

- ***Availability and organization of standardized, quality-checked data stored in the PCORnet Common Data Model (CDM) Version 2.1; ability to query this database through PopMedNet:*** Data will be acquired through the MoodNetwork website and stored in a secure MySQL database housed on the Massachusetts General Hospital Research Computing Cloud. The system is designed to constrain the data input and to prevent missing values and conducts comprehensive automatic logic checks. Website and database adhere to the PCORnet Common Data Model 2.1. In agreement with PCORnet, we created an artificial dataset and successfully queried the database using the standardized test query generated by PopMedNet in November 2014.

- ***Ability to collect patient-reported data for at least 80 percent of the cohort and types of data collected*****:** In order to become a MoodNetwork member, participants must provide demographic and clinical information (common data model) therefore, we will meet the requirement for 80% patient-reported data collection. In addition, patients can complete the common measures designed by the PCORnet Common Measures Working Group (Dr. Deckersbach is a member of this group), as well as other clinical measures (e.g. depression or mania symptoms).

- ***Ability to efficiently identify and contact eligible network participants interested in participating in clinical trials and other types of research:*** We will have email addresses to efficiently contact eligible network participants to inform them of clinical trials and other types of MoodNetwork research opportunities (e.g., surveys).

- ***Ability to work with one named clinical data research network (CDRN)***: We have an agreement with the Harvard SCILHS group to link data for patients who are in the SCILHS CDRN by having a collaborator within the SCILHS group run SHRINE queries to identify potential participants and with mood diagnoses along with their providers; then our collaborators can invite their patients to become members of the MoodNetwork. Additionally, we will have the option of participating as a node in SCILHS by placing MoodNetwork data into a SHRINE connected i2b2 node that is hosted by the MoodNetwork.

- ***Ability to confirm the absence of significant barriers to meeting PCORnet Phase I requirements:*** Once we launch the patient portal (MoodNetwork website), our broad recruitment and marketing strategies will gather 50,000 patient partners by September 2015 (see above). We have a solid database infrastructure (see above) and a team ready to respond to and overcome unforeseen barriers that might arise. We are continuing to explore feasible EHR import methods with the Harvard SCILHS group as well as other CDRNs. We have also been working with the other PPRNs at Partners Hospitals (Sleep Apnea PPRN and the ALD PPRN) to streamline IRB submissions to further minimize this barrier and strengthen our clinical trial infrastructure.

- ***As per the PFA, we briefly describe our plans for successful completion of Phase I goals by September 2015 and any key accomplishments related to each of the goals:*** Phase I, Goal 1: Engagement, Governance, and Collaboration: (1) Plans for successful completion: We will continue our successful ongoing governance structure (see above); (2) Key accomplishments: We have formed trusting relationships with co-production and co-learning at the heart of our collaboration with patient stakeholders. Phase I, Goal 2: Data Infrastructure and Analysis-Ready Data Requirements: (1) Plans for successful completion: Data infrastructure is complete along with data security requirements; (2) Key accomplishments: We completed the MoodNetwork database which is able to receive and organize patient reported outcomes and can expand to include additional sources of data including EHRs and clinician entered data. The database is ready for PCORnet queries through PopMednet. Phase I, Goal 3: Clinical Trial Infrastructure: (1) Plans for successful completion: In our application for a PCORI Large Pragmatic Trial, we planned to recruit 500 clinicians to each recruit 10 patients and agree to cluster randomization at the individual clinician level. We also plan to recruit clinical research champions within the 25 academic departments of psychiatry embedded within the CDRNs – those clinical champions will, in turn, recruit clinicians who would be willing to conduct comparative effectiveness trials within PCORnet. (2) Key accomplishments: We had preliminary discussions with 7 of the department chairs of psychiatry and also with Greg Simon, MD the director of the NIMH Mental Health Research Network. All agreed to collaborate on any future clinical trials. We also working with the other Partners' PPRNS to streamline the IRB process and with the Harvard Catalyst CTSA to adopt the Accelerated Clinical Trials Agreement.

PART III: PLAN FOR ACHIEVING PHASE II GOALS

As per the PFA, we describe our PPRN's plans with respect to meeting Phase II goals.

- ***The governance structure that will allow the PPRN to participate in PCORnet studies:*** We plan to continue our current governance structure with advocacy group and patient stakeholders while expanding our structure to include practicing clinicians. We will also be able to participate in PCORnet wide studies by continuing our queriable database and maintaining a database structure that permits us to link data with other CDRNs and PPRNs.

- ***Plans to enhance engagement of patient leadership in governance and research:*** Patient stakeholders will play an even more prominent role in Phase II. Allen Doederlin, the president of the Depression and Bipolar Support Alliance (the largest depression and bipolar advocacy group in the United States) is the Co-Principal Investigator on this proposal. In Phase II, we also plan to create additional sub-committees to enhance explicit stakeholder involvement. For example, stakeholders will oversee the MoodNetwork forum, manage the MoodNetwork blog, and contribute to the MoodNetwork eNewsletter, as well as serve as study staff to have oversight of new projects, and review and vet new studies proposed by other researchers and patients.

- ***Plans to maintain and increase an engaged, representative patient membership interested in participating in research:*** Given the expansion of expected tasks in Phase II, we recognize the need to add new stakeholders to assist the current Stakeholder Advisory Committee. A key avenue for adding new stakeholders has been the National Institute of Mental Health's (NIMH) Alliance for Research Progress Meeting. This is a bi-annual meeting hosted by the NIMH to inform key advocacy groups in mental health on research progress in the field. The Director of NIMH invited Dr. Nierenberg to present at two of these meetings during which we identified potential new stakeholders for Phase II from other advocacy groups.

- ***Plans to maintain and extend the collection of standardized data and quality-checked data transformed into the PCORnet CDM and efficiently respond to queries:*** Once the website is launched by early February 2015, interested participants can sign up for the MoodNetwork PPRN at any time. Website and database (including regular automated data quality control procedures) will be maintained by our IT team. Existing patients will be maintained by engaging them in the design of future studies, message boards, blogs, and free access to tools to help patients manage their disorders. Expansions to the network will adhere to the PCORnet common data model. Our IT team will continue to accommodate all variants of PopMednet queries.

- ***Plans for developing a valid electronic algorithm to identify patients with the condition(s) of interest to the PPRN:*** The Harvard SCILHS group has developed and implemented a validated electronic algorithm to identify patients with depression [10] or bipolar disorder [11]. As confirmed by the SCILHS group, their algorithms will be readily applicable to the EHR data in PCORnet and they are willing and able to share these algorithms with the MoodNetwork.

- ***Plans to collaborate with CDRNs:*** We plan to collaborate with the Harvard SCILHS group to identify and recruit patients for the MoodNetwork. Furthermore, consistent with the approach of many PPRNs with CDRNs, we plan to recruit through "champions" within the 25 academic departments of psychiatry affiliated with the CDRNs. We have also started to plan to collaborate with the Great Plains Collaborative through the University of Texas SouthWestern Medical Center Depression Center and the University of Iowa Medical Center, Mid-South CDRN through the Vanderbilt Health System, PORTAL CDRN through Group Health Cooperative, PATH CDRN through Johns Hopkins University, NYC-CDRN through Mt Sinai Medical Center, and the CAPriCorn CDRN through Rush University Medical Center.

- ***Plans to enhance capacity to efficiently contact and recruit eligible participants for clinical trials (and other types of studies) with appropriate safeguards in place to protect the participants' privacy:*** After discussing this topic with our Stakeholder Advisory Committee, they agreed that it was appropriate to ask potential MoodNetwork members to give us their names and emails addresses. Thus, we will have these data in our website so that we can link participants' patient-reported outcomes with their contact information to efficiently contact and recruit participants for future clinical trials as well as to keep them updated on other MoodNetwork activities. We have worked with our IT team to ensure that these data will be well protected as described above.

- ***Ability to work with external researchers and funders, including both public and private funding agencies (e.g., the medical products industry and the federal government):*** During Phase I, we applied for a NIMH Phase II Small Business Innovation Grant with Cogito, Inc., received a highly favorable score and are awaiting the award notice. We have discussed funding for a biomarker portion of MoodNetwork with Tom Insel, MD, the Director of NIMH ; we have had similar discussions with Jordan Smoller, MD from the Broad Institute and with Husseini Manji, MD, from Johnson and Johnson who will consider funding a biomarker collection. Also, we discussed possible funding opportunities with Jane Pearson, PhD from NIMH and Philip Satow from the Jed Foundation to study suicide. We have applied for a PCORI Large Pragmatic Trial for a comparative effectiveness study for treatments for bipolar youth – the letter of intent was accepted and this application is currently under review. Additionally, we have discussed potential collaborations with C. Anthony Altar, PhD, from Assurex, Inc. for a specific and targeted biomarker study, and with Antony Lobel, MD, from Sunovion to examine the frequency of mixed manic symptoms in a cohort of patients who do not meet criteria for bipolar disorder. Finally, we have been approached by Greg Simon, MD, from Group Health to collaborate with the NIMH Mental Health Research Network, S. Nassir Ghaemi, MD from Tufts University to collaborate on a grant submission to study an internet-based intervention to enhance recovery for bipolar patients, Eric C. Campbell, PhD, from the Massachusetts General Hospital Institute for Health Policy to collaborate on a study of smoking and bipolar disorder, and Ronald Kessler, PhD from the Harvard Medical School Department of Health Care Policy to collaborate on a study to develop predictors of response to antidepressants.

- ***Ability to participate in PCORnet-wide activities, such as governance and Task Force activities:*** We will continue to participate and contribute to PCORnet-wide task forces including the Clinical Trials Task Force (Andrew A. Nierenberg), DSSNI Task Force (Alex Sherman), Obesity Task Force (Louisa Sylvia), Patient Reported Outcomes Task Force (Thilo Deckersbach), PCORI Governance and Collaboration Task Force (Dan Goodman-stakeholder), Ethics and Regulatory Task Force (Roberta Tovey-stakeholder), and Patient Engagement Task Force (Lucinda Jewel-Stakeholder).

- ***Ability to coordinate with co-located Clinical and Translational Science Awards (CTSAs):*** We will be able to coordinate with the Harvard Catalyst CTSA, specifically through collaborations with Ann Klibanski, MD (Head, Catalyst CTSA Clinical Research Center) and Lee Nadler, MD (Director) – they have agreed to assist with any supporting our Network and can help coordinate with the PPRNs within the Harvard system.

- ***Plans to ensure the PPRN's sustainability beyond the three-year funding period:*** We have pursued multiple pathways to sustainability during Phase I and plan to continue to do so during Phase II. We have explored funding opportunities from public as well as private sources to collaborate using MoodNetwork as a national resource.

- ***Confirm the absence of significant barriers to meeting Phase II requirements:*** We confirm the absence of significant barriers to meeting Phase II requirements.

As per the PFA, we describe our plans for successful completion of Phase II goals: We will: (1) have highly engaged patients, caregivers, and researchers who participate in network governance and research topic generation; (2) continue our successful level of engagement of stakeholders in governance and plan to expand this to include clinicians; (3) have analysis ready standardized data, use the PCORnet Common Data Model, and preserve strong privacy and data-security protections; (4) have an infrastructure for supporting clinical trials embedded within patient communities; (5) continue to provide education about clinical trials to the patient community and encourage feedback and topic generation through our patient portal; (6) continue to work with our advocacy groups who will have oversight of MoodNetwork and leverage their broad and deep outreach to foster public trust; (7) continue a collaborative community that attracts a diverse set of researchers, funders, and other networks; (8) continue our already successful strategy to collaborate and obtain external funding so that we are a self-sustainable, patient-centered research network.

PART IV: STAFFING PLAN

***Personnel Qualifications: We briefly state the qualifications of the Principal Investigators (PIs) and key personnel who will perform the described project*:** (1) The PI, Dr. Nierenberg has over 30 years of experience in leading clinical trials and comparative effectiveness research; (2) The Co-PI, Allen Doederlein, the president of the DBSA has extensive experience in patient engagement, large scale web strategies, and dissemination; (3) Dr. Sylvia as Director of Operations has over 12 years of experience in this role for two large, multi-site collaborative clinical trials; (4) Dr. Deckersbach as Director of PRO Assessments has 15 years of experience in assessing mood disorders; (5) Alex Sherman as the Director of Data Management has over 20 years of experience in privacy and security issues and manipulation of large data sets; (6) Dr. Schoenfeld as our statistician has over 30 years of experience conducting statistical analysis plans for large, clinical trials.

As per the PFA, we describe the PI's experience with leading patient-powered network, FTEs; team management experience, qualified women and minorities on the team, etc.: Dr. Nierenberg has been the PI of Phase I of MoodNetwork. He will commit to about 40% effort and Allen Doederlein, Co-PI will commit to about 15% effort. In aggregate, the management team has managed four major comparative effectiveness studies with a total federal investment of $87 million since 1999. In particular, the team completed the NIMH LiTMUS and AHRQ Bipolar CHOICE studies, both of which had to be started and completed within 36 months. Recruitment exceeded the planned targets and both studies were completed within budget. Dr. Deckersbach has 15 years of experience in implementing PROs for multi-site clinical trials. Dr. Sylvia as project manager and Roberta Tovey as Director of Communications are highly qualified women; Dr. Donna Holland Barnes as a stakeholder is a highly qualified African American woman on the team.

References:

1. Kessler RC, Avenevoli S, McLaughlin KA, et al. Lifetime co-morbidity of DSM-IV disorders in the US national comorbidity survey replication adolescent supplement (NCS-A). Psychological Medicine 2012;42:1997-2010.
2. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2007;64:543-52.
3. Bromet E, Andrade LH, Hwang I, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC medicine 2011;9:90.
4. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. The Lancet 2012;380:37-43.
5. Barrett JE, Barrett JA, Oxman TE, Gerber PD. The prevalence of psychiatric disorders in a primary care practice. Am J Psychiatry 1988;45:1100-6.
6. Shim RS, Baltrus P, Ye J, Rust G. Prevalence, treatment, and control of depressive symptoms in the United States: results from the National Health and Nutrition Examination Survey (NHANES), 2005â€“2008. The Journal of the American Board of Family Medicine 2011;24:33-8.
7. Bridge JA, Greenhouse JB, Weldon AH, Campo JV, Kelleher KJ. Suicide Trends Among Youths Aged 10 to 19 Years in the United States, 1996-2005. JAMA 2008;300:1025-6.
8. Kessing LV. Severity of depressive episodes according to ICD-10: prediction of risk of relapse and suicide. The British Journal of Psychiatry 2004;184:153-6.
9. Nierenberg AA, Gray SM, Grandin LD. Mood disorders and suicide. Journal of Clinical Psychiatry 2001;62:27-30.
10. Perlis RH, Iosifescu DV, Castro VM, et al. Using electronic medical records to enable large-scale studies in psychiatry: treatment resistant depression as a model. Psychological Medicine 2012;42:41-50.
11. Castro VM, Minnier J, Murphy SN, et al. Validation of Electronic Health Record Phenotyping of Bipolar Disorder Cases and Controls. American Journal of Psychiatry 2014.