LETTER OF INTENT (LOI): PATIENT-POWERED RESEARCH NETWORK (PPRN) RESEARCH DEMONSTRATION PROJECT: A CROSS-PPRN OPPORTUNITY TEMPLATE

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LETTER OF INTENT (LOI): CROSS-PPRN RESEARCH DEMONSTRATION PROJECT TEMPLATE

TITLE OF PROPOSED STUDY: Healthy Mind Healthy You: A Dose Finding Study of mindfulness

As per the PFA, we describe the process by which the research question was generated and prioritized.

The research question was generated during the PCORnet PI retreat on 11/3/2015. The PPRN PIs and Co-PIs (including stakeholders) met face-to-face to identify a common theme across PPRNs and to decide how the group would approach the Demonstration Project opportunity. The group identified high rates of stress, anxiety, depression, and low levels of well-being across the more than 100 conditions and populations covered by the network of PPRNs. Once this common set of problems was identified, the group then brainstormed to identify possible interventions including mindfulness meditation, peer support, resiliency training, and supportive smartphone apps. At an additional breakout session during the PI retreat, the group decided that some variation of a mindfulness intervention plus a patient-engagement, PPRN-specific app would be the focus of the demonstration project. The intervention would be scalable, online, inexpensive to deploy, free to participants, and easy to access. The group agreed that simplicity would be the overriding principle to unify the cross-PPRN project with the PPRN's great breadth and depth and complexity of conditions (common disorders, rare disorders, populations of interest, and diversity).

The next step was to determine the research question. After considerable discussion, the group determined that it would be helpful for patients to know the **best dose of mindfulness** that would be effective and feasible. With such a heterogeneous cohort across all of the PPRNs, it was recognized that some people would have a difficult time with extensive mindfulness training while others would not benefit from a small dose of mindfulness; some would be able to adhere to the program while others would not due to medical/life burdens (e.g., cognitive problems, severely ill children). Thus, the question evolved into: what is the comparative effectiveness of evidence based briefer "mindfulness light" to a more extensive intervention of mindfulness-based cognitive behavioral therapy?

We then convened a smaller workgroup by teleconferences to discuss an engagement app from the Community Partnered Participatory Research PPRN that they had developed. After considerable discussion, even with agreeing that the app had great value, we decided jointly that we needed to follow the principle of simplicity and rejected the app option. We also agreed that we would have to solve the challenges of integrating data from each PPRN (using the Common Data Model) so that participants did not have to re-enter data, how the data will flow and be shared, how the IRB issues will be covered including informed consent, and how PPRN specific measures would be part of the flow of assessments. For the primary outcome measure, this smaller working group achieved strong consensus on measuring wellness with the WHO-5 measure with secondary brief measures of stress, anxiety, depression, and baseline mindfulness.

As per the PFA, we detail how the PPRN participant communities were engaged and how consensus was achieved.

Each of the 21 PPRNs engaged their stakeholders through meetings, teleconferences, and email to discuss the common problem across PPRNs (stress, anxiety, depression, and low levels of well-being) and the potential solutions and options discussed. Based on the discussions outlined above, the smaller working group circulated a one page executive summary for each of the PPRNs to share and discuss with their stakeholder groups. The PPRNs reported back the feedback and we continued with several teleconferences and an additional face-to-face session at the PCORnet Council Meeting on 12/16/15 with a final question and answer teleconference on 12/18/15. The near-final version of this letter of intent was sent out on 12/21/15 for final review and feedback. The participant communities had overwhelming consensus around the question, the comparison, and the general design of the proposal. They also had particular ideas about outcomes, and overall, agreed that measuring wellness was a priority.

The particular question, "what is the best dose of mindfulness?", is important to PPRN participants because each PPRN condition or population of interest carries with it a burden of stress. Either the condition or population is the cause of stress or stress exacerbates the underlying condition. Anxiety, depression, and a nagging sense of just not feeling well is common with medical conditions or being in a minority (whether racial or sexual orientation); and each of the conditions have high rates of comorbid depression and even suicidal ideation and behavior. Mindfulness as an evidence-

based method to decrease stress and increase wellness is quite attractive, but its implementation can be challenging. How much mindfulness is enough? How much training is needed? How often should it be done? How much can people actually do? The findings of the proposed research will help patients know the effectiveness of "light" vs. full doses of mindfulness overall as well as the feasibility of each dose for their particular PPRN condition or population.

As per the PFA, we document that the existing evidence is insufficient.

The efficacy of mindfulness treatments has been well-documented for a wide variety of problems (e.g., pain, depression, anxiety, and stress) [1-5]. Most empirically tested variants such as mindfulness-based stress reduction [MBSR], or mindfulness-based cognitive therapy [MBCT] include a curriculum of guided meditation exercises that are taught in sequence over the course of 2-3 months in weekly sessions (8-12 sessions as well as regular homework practice) coupled with treatment elements devoted to developing alternate ways to cope with stress and disengaging from negative ruminative thoughts associated with stress, depression and anxiety. More recently, shorter mindfulness-based interventions with fewer sessions (range 1-6) have been tested and also received support in terms of their efficacy in increasing mindfulness and decreasing anxiety, depression, negative thoughts, headaches and pain [6-11].

THE GAP: Standard (8-12 session) and briefer ("light") mindfulness based treatment have never been compared directly, head-to-head in terms of their efficacy and acceptability. Given the substantial time and effort associated with the standard (8-12 session) treatments, it is of interest whether standard mindfulness treatment is indeed superior to shorter mindfulness treatment across a wide range of populations (adults, children, patients and caregivers) as well as to investigate who responds better to which treatment (i.e. standard vs. light). The importance of this topic has also been recognized as evidenced by its inclusion in the 100 initial priority topics for comparative effectiveness research by the Institute of Medicine ("Compare the effectiveness of mindfulness-based interventions (e.g., yoga, meditation, deep breathing training) and usual care in treating anxiety and depression, pain, cardiovascular risk factors, and chronic diseases"). The proposed dose finding study can help patients, parents, and caregivers (as well as clinicians) know the best dose of mindfulness to manage stress and increase wellness with a substantial impact on care.

OBJECTIVES: As per the PFA, we state the specific aims of this study.

Specific Aim 1: **To determine if standard (8-session) mindfulness-based cognitive therapy (MBCT) or a brief 3-session mindfulness intervention, improve well-being in PPRN participants.** Specifically, we plan to conduct a randomized trial comparing the impact of standard 8 session/weeks of MBCT or a brief, 3 session mindfulness intervention ("mindfulness-light") for participants in all PCORnet PPRNs including participating adults, children and caregivers and explore the impact on (1) self-reported well-being (WHO-5 well-being index, primary outcome), (2) stress, (3) anxiety, (4) depression, (5) quality of life, and (6) psychosocial functioning (secondary outcomes).

Hypothesis 1: Because MBCT is the longer and more comprehensive intervention, we hypothesize that standard MBCT will be superior to mindfulness-light in increasing well-being, quality of life and functioning as well as decreasing stress, anxiety and depression.

Specific Aim 2: **Explore the heterogeneity of treatment effects (HTE) to both interventions.** This aim will allow us to *explore* who will benefit from either standard MBCT or mindfulness-light (predictors) and to determine the factors that can help match patients to either intervention (moderators or who will have better outcomes with standard MBCT versus mindfulness-light). Moderators include (1) PPRN site, (2) age, (3) role (patient, caregiver), (4) levels of well-being, stress, quality of life, anxiety, and depression.

Specific Aim 3: **Contribute to the PCORnet Commons** by (1) conducting an analysis of the factors contributing to successful collaboration between multiple PPRNs including the data infrastructure and co-registration; 2) providing access to the library questionnaires/surveys and online screening procedures and therapeutic material, 3) making the code available that allows other networks to implement the online resources, 4) providing guidance for future online interventions.

METHODS:

1a. Study Design. We will prospectively randomize at least 4,000 and as many as 20,000 adult and children participants or their caregivers across all PPRNs to internet-based (1) standard 8-week MBCT or (2) 3-sessions of mindfulness-light. Patients (children and adults) and caregivers (spouses, parents, etc.) will be recruited via each of their PPRNs. Study

recruitment, eligibility assessments and ongoing bi-weekly outcome assessments will be done locally at each PPRN. The coordinating center and delivery network for the two interventions will be the MoodNetwork PPRN.
1b. Study population: ***Inclusion***: (1) Age between 10 and 65 years, (2) being a participant or joining in one of the PCORnet PPRNs (i.e. being an adult and child patient participant or caregiver). ***Exclusion:*** Inability to participate in mindfulness training as determined by the PPRN, patients, clinicians, parents, or caregivers.

1c. COMPARATORS:
(1) Standard, 8-session Mindfulness-based Cognitive Therapy (MBCT): MBCT will be based on Segal et al.[12, 13]. It is the most widely used MBCT program to date and has been adapted as an online (web-based) version with good efficacy[14]. Participants complete an 8-session (2-months) structured curriculum of guided meditation exercises (e.g. mindfulness of the breath, mindfulness of breath and body, mindfulness to thoughts and feelings, open or choiceless awareness, etc.). These meditation exercises are practiced with the instructor and during regular homework practice. Over the course of these exercises, participants learn to adopt an observing, accepting stance (mindfulness) towards difficult thoughts, feelings, and bodily sensations. In addition, participants learn to bring mindfulness to everyday situations and practice to recognize and disengage from negative, ruminative thoughts.
(2) Mindfulness-light 3-sessions: Mindfulness light will be based on Zeidan et al[6, 15, 16]. It includes one single breath-awareness meditation exercise during which participants focus on the flow of their breath. If a random thought arises, they acknowledge the thought and simply let ''it" go by bringing the attention back to the sensations of the breath. With as little as 3, 20-minute sessions and with no additional practice, this intervention has been more effective than sham meditation in reducing negative mood, depression, and fatigue[17].

1d. STUDY OUTCOMES. Note that this set of outcomes is preliminary and will be further refined by collaborating with stakeholders if the letter of intent is approved.
Primary Outcome: Overall Well-Being and Stress**:** The World Health Organization-5 Well-Being Index (WHO-5 Well-Being Index[18]) is a brief self-report (5-item) of positively-worded statements related to positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested), and general interests (being interested in things) over the prior two weeks.
Secondary Outcomes: The Perceived Stress Scale (PSS[19]) is the most widely used psychological instrument for assessing perception of stress. This scale measures the extent to which situations in one's life are labeled as stressful. The Patient Reported Outcomes Measurement Information System (PROMIS) assesses patient self-reports of physical and mental health in both pediatric and adult populations. For the proposed study, we will administer the pediatric and adult versions of the PROMIS "Emotional Distress-Depression" and "Emotional Distress-Anxiety" short forms[20-23]. These measures have been developed and validated broadly such that they are recommended for use by the National Institute of Mental Health. The PROMIS anxiety and depression assessments will be administered to participants in both treatment conditions. The Five Facet Mindfulness Questionnaire (FFMQ)[24] is a 39-item self-report measure that examines mindfulness and is comprised of five subscales (observing, acting with awareness, describing, non-reactivity, non-judging). The FFMQ will allow us to determine changes in participants' baseline levels of mindfulness.
PPRN Specific Outcomes: Several PPRNs requested to include outcomes of interest to their patient population, e.g. the Alzheimer's PPRN is interested in measuring cognition. This project will develop tools to have PPRN specific modules integrated with the other measures, either on the PPRN websites or a simple link between the study website and the PPRN.

1e. SAMPLE SIZE AND POWER. Rationale for sample size: Since the PPRNs vary widely in their populations, including rare diseases, we will recruit as many participants as will be feasible and informative. For those large PPRNs, we will try to recruit at least 215 per group (total of 430) to detect a moderate effect size between two active treatments. For small rare disease PPRNs, the overriding principle will be feasibility. With all active PPRNs plus the Sleep Apnea PPRN as adjunct (with permission from PCORnet), we estimate that no fewer than 4,000 and as many as 20,000 participants will join the study. To illustrate the power of our sample, we computed power with PASS 14 for two alpha levels (.05, .01) and a range of standardized mean differences (SMDs) between our mindfulness and mindfulness-light groups. We chose SMDs to be consistent with what was reported by Hoffman et al.[25] and to allow for some reduction in the SMDs because our mindfulness- light group will probably receive some benefit beyond the usual placebo effect. The alpha

level of .05 corresponds to the test of our one primary outcome. The alpha level of .01 corresponds to our Bonferroni protected test of secondary outcomes. For alpha .05, power will be greater than 80% for SMDs greater than .12; it will be greater than 90% for SMDs greater than .14. For alpha .01, power will be greater than 80% for SMDs greater than .14; it will be greater than 90% for SMDs greater than .16.

ENGAGEMENT: As per the PFA, we briefly state how stakeholders are engaged.

As part of the development of the research questions (see Research Question Development) the participating PPRNs already have active and engaged patient and other stakeholder partners throughout their governance structure. The idea of this proposed project was generated and initially vetted by the patient participants of all of the PPRN networks. Once the project is funded we will establish a **cross-PPRN Steering Committee** (led by the MoodNetwork PI Andrew Nierenberg) that governs the proceedings of the study. There will be an in-person "Kick-off" meeting or teleconference with the patient participant and stakeholders of all Networks to review and finalize the study procedures. Specifically, the cross-PPRN Steering Committee will be the governing body guiding the decision making processes such as the monthly reporting requirements and review the monthly data reports and any safety concerns. The cross-PPRN Steering Committee will give input, feedback and propose changes on all aspect of the study development, progress and completion phases to a smaller, operations **cross-PPRN Project Research Team**, which is composed of the two PIs (Dr. Nierenberg and another Co-PI to be determined by the entire PPRN group), a project manager (Dr. Sylvia from MoodNetwork), an expert in mindfulness (Dr. Deckersbach from MoodNetwork) and an additional member from at least 5 other PPRNs (patient stakeholder or researcher) who will implement the suggestions of the oversight Committee.

COLLABORATION: Describe how to use, develop, and contribute to PCORnet's shared tools and resources.

This project will (1) **use** the privacy and governance policies established by PCORnet as well as the common data model and lessons learned from other PPRNs in regards to co-enrollment, data management/sharing between multiple Network infrastructures, and recruitment strategies; (2) **develop** for PCORnet comprehensive online libraries of two evidence-based treatments (a brief and standard mindfulness-based intervention), training materials for both treatments, co-enrollment procedures, cross-Network randomization, a library of well-established and vetted assessments that can be used across diagnostic categories and conditions for adults and pediatrics, procedures for data sharing between Networks and for assessing and ensuring the safety of participants; and (3) **contribute** all of these developed tools to the PCORnet's shared resources, especially, and most noteworthy, all of the materials developed for the interventions. This project would serve as the first cross-PPRN study and the knowledge to be gained will undoubtedly contribute to PCORnet and serve as an excellent demonstration of cross-PPRN collaboration as all 21 PPRNs have agreed to participate in this important and meaningful study.

EVALUATION PLAN: Identify key areas that need to be refined through targeted assessments.

As per Aim 3 we plan on contributing to the PCORnet Commons as described above. First we will establish milestones to ensure that these goals are met in a timely manner. Many of these milestones have already been standardized and developed for previous PCORNet projects which we will use as well as add study-specific milestones (e.g., programming of the interventions, assessing safety, on boarding of each site to the Pan-PPRN network, data checks on data streaming with each node of the Pan-PPRN network, or each PPRN). Secondly, each PPRN will conduct a survey of their teams to identify resources that should/could come out of this project and that could then be contributed to PCORnet Commons. This is important as we may not be able to include all resources already created by each PPRN, but we can begin a comprehensive library of these resources for future studies and collaborations. We will also track requests for material and code them by each PPRN to document the extent to which material, guidelines, and code produced by this project are being utilized and implemented by other networks. This is particularly important as the tools that come out of *this project can be used across a wide range of disorders for adults, children and caregivers **in all PPRNs**. By providing these tools, this project will add to PCORnet's capacity for pan-PPRN studies across multiple disorders.* Finally, each PPRN will survey their participants to determine which aspects of the study they found helpful or unhelpful. This will help to refine future pan-PPRN studies and collaborations.

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