C.2. Research Methods

C.2.1 Overview of Study Design. We propose a 2-arm pragmatic randomized trial comparing MMB (N=230) to the standard Depression Care Pathway at KPCO (DepCare N=230) for patients with PHQ-9 scores $\geq$ 5 and $\leq$9, using efficient EMR-based methods for identifying and recruiting patients, web-based data collection, and a low intensity stepped approach to telephone support for participants who show evidence of not engaging in the MMB program. Patients in MMB will follow the 8-session, online program augmented by email or phone support if they fail to respond to email or online messaging. Patients in DepCare will access a depression care pathway involving referral to specialty behavioral health services or to one of several behavioral medicine specialists working in primary care clinics (see DepCare C.4.2).

C.3. Participant Selection and Recruitment.

C.3.1. Inclusion/Exclusion Criteria: Consistent with a pragmatic trial and with the goal of implementing MMB broadly if it demonstrates effectiveness, inclusion criteria are minimal. Participants will be aged 18 or older with at least one prior episode of MDD or prior PHQ-9 score $\geq$ 15, as indicated by EMR, and a current PHQ-9 score of $\geq$ 5 and $\leq$9. **Randomization to each of the study arms will be stratified by the setting in which treatment was received (primary care or behavioral health)**. Patients should also be planning to continue their membership at KPCO for at least the next 6 months and have internet access. Exclusion criteria are similarly minimal: presence of schizophrenia or current psychosis, organic mental disorder or pervasive developmental delay. We have found that Internet access among KPCO members is high, and KPCO has promoted members' access to their medical records via secure web portals. Based on KP membership data we expect that total minority representation will be between 20 and 25% of the sample, but that no single racial or ethnic minority or ethnic group will comprise more than 15% of the sample. **This seems feasible, as minority enrollment for our R34 study was 19%.** Current estimates cite 18% Hispanic, 7% African American, 4% Asian and 2% Native American KPCO members. **Specifically, we plan to target 7 KPCO clinics where Hispanic membership is > 20% and 3 clinics where African American membership rates are between 12 and 22%. We also will consult with Dr. Muñoz and the KPCO Latino and African American Centers of Excellence to ensure that our contact and study materials maximize recruitment of culturally diverse participants from the KPCO system.**

C.3.2. Performance sites. The study will be implemented over a 4 year period (see Fig.5 for study tasks and timeline). The lead site for this trial will be the University of Toronto - Scarborough (UTSC) and all study activities will be coordinated by Dr. Segal, who will establish study procedures, monitor progress, and lead regular team meetings with project staff. **A coordination plan outlining study roles and responsibilities is described in Appendix 3.** He will work closely with NogginLabs to ensure website functionality is maintained throughout the study and, along with Dr. Dimidjian, will moderate content posted to the MMB virtual community. Drs. Segal and Dimidjian will also complete the finalization of the MMB revisions, in partnership with NogginLabs, specifically the inclusion of a virtual community and mobile application features. Dr. Dimidjian will supervise the telephone website support and, in collaboration with Dr. Segal and consultant Ludman, will operationalize support and troubleshooting functions into a manual suitable for non specialist providers. The recruitment site for this study will be Kaiser Permanente Colorado (KPCO; Dr. Arne Beck Co-PI). KPCO is a mixed-model plan with some portion of general medical and mental health care provided by contracted external providers reimbursed on a fee-for-service basis. KPCO has extensive experience using EMRs for case finding and recruitment into clinical trials. KPCO has served as the implementation site for two clinical trials that our team has conducted, including our open trial of MMB, open trial (N=49) and RCT (N=86) of in-person MBCT for pregnant women (PI: Dimidjian). In addition, KPCO is a member of the NIMH-funded Mental Health Research Network **(MHRN; PI: Dr. Greg Simon)**. Drs. Dimidjian and Beck are collaborating on a study of Behavioral Activation (N=200) for perinatal depression as the demonstration RCT for the MHRN and the proposed study leverages important innovations in conducting pragmatic clinical trials that have been developed in the context of that ongoing work within the MHRN (see Dr. Simon's letter of support).

Fig.5 Study Timeline	Month															
	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
4 Month Project Start-up	■															
Finalize virtual community, app features MMB	■															
Recruit, enroll, consent, randomize: MMB or DepCare		■	■	■	■	■	■	■	■	■	■	■				
Longitudinal follow up for 12 months			■	■	■	■	■	■	■	■	■	■	■	■		
Collect health system cost/utilization data			■	■	■	■	■	■	■	■	■	■	■	■	■	
Analyse data, manuscript preparation													■	■	■	■

C.3.3. Recruitment and assessment procedures

EMR-based case finding. An important innovation of the proposed study is the use of EMR for case finding. Through KPCO's participation in building the data infrastructure for the MHRN, we will have access to programming code that can identify more than 25,000 unique patients with one or more PHQ-9 scores in Epic as well as 29,000 depression diagnosis codes (from both primary care and specialty mental health departments) recorded in their respective EMRs in 2011 alone. An additional electronic recruitment method is available at KPCO through an automated outcomes system within Behavioral Health that captures all intake visits starting in January 2011. Real time PHQ-9 scores are available via a software reporting tool that accesses a database that currently contains approximately 15,000 unique patient records. Using these methods, we will identify potentially eligible patients with PHQ-9 scores $\geq$5 and $\leq$9, to whom we will send an electronic recruitment brochure. The e-brochure will explain the study, including the requirement for broadband internet access, and include the study website internet address for interested participants.

Electronic provider referral. A secondary recruitment method will involve electronic referrals from primary care or specialty mental health clinicians at KPCO. We will communicate with leaders in these departments to encourage clinician referrals to the study for those patients who may have completed treatment for depression but who have RDS or for those who, despite long-term antidepressant use, still report RDS.

Online consenting. Interested individuals who obtain the e-brochure or are electronically referred from providers will visit the project website's home page where they will be able to read a brief project description. At this point, individuals can continue with the online consent process or opt out, requesting no further contact from the study team. To proceed, each person will be asked to enter a unique identifier printed on each brochure. This number is not linked to any individual identity, but is used to verify that individuals receiving a brochure are KPCO members. These recruited individuals will then proceed to the electronic consent and HIPAA Authorization forms. Participants will be encouraged to read each section and provide their consent by clicking "I Agree" at the bottom of each page. Individuals who click "I Do Not Agree" will be informed that it is not possible for them to participate in the study and we will provide them with a list of alternate referral options.

Online Assessments. To conduct assessments efficiently, KPCO will use Qualtrics online survey software that allows participants to access assessment instruments via email. These procedures are employed in our ongoing collaborative clinical trials (see above in C.3.2.). Previous research has shown that web-administered assessment of health status is comparable to the telephone or in-person administration formats and is advantageous with respect to anonymity and reduced stigma when topics are sensitive (Ogles et al.,1998). Increased data integrity is also provided via programmed checks and correction routines.

C.3.4. Clinical Monitoring: Patients will be asked to use KPCO's MyChart, which allows members access to portions of their EMR and provides a secured email messaging system for communicating with providers and the study team. We will rely on the PHQ-9 (Kroenke et al., 2001) completed at scheduled monthly assessment points to monitor depressive symptoms throughout the study. If a patient scores > than 13, study investigators will be notified immediately via an algorithm programmed into our online data collection and management system. We then will initiate a clinical response by phone call and will inform the KPCO clinician who will engage in outreach from KPCO. Although a score of 15 is suggested as the threshold for moderate depression (Kroenke et al., 2001), we believe that our more conservative criterion of > 13 (mild depression) is warranted due to the fact that remote access reduces the number of in person assessment opportunities. Additionally, we will monitor responses to the suicide item (#9) on the PHQ-9, 'Thoughts that you would be better off dead or hurting yourself in some way'; if a patient endorses this item with a score of 1 or greater, the study investigators and KPCO crisis teams, available 24/7, will be notified in order to provide immediate outreach and assessment for the patient. Any participant who misses the scheduled assessment point will be contacted immediately by the project coordinator. Throughout the study, all participants will also be encouraged to contact the project coordinator at the first sign of increased depression or prior to initiating any non-study treatment. We will obtain information about any treatment utilization during MMB or DepCare (i.e., type of treatment, primary problem initiating treatment seeking, frequency, and duration of treatment) from Epic. These data will be used to characterize additional care in either study arm. For those patients receiving maintenance pharmacotherapy, we will track medication type, dosage and any switches via EMR.

C.3.5. Data Security. The MMB website will be hosted by NogginLabs and will be secured using a firewall and password access, with a 128-bit level of SSL encryption. User passwords will be distributed to participants via email. Passwords and their associated web access will be terminated at the close of this study. The study team and the NogginLabs development team will have administrative access to the website. A business associate agreement with KPCO will be executed with NogglinLabs for this project. NogglinLabs is experienced in managing confidential data using encryption and passwords and has successfully hosted MMB in our pilot work to date. Email communication between patients, the study team and providers will be done through KPCO's secured email, which has a firewall, requires passwords, and uses 128-bit SSL encryption.

C.4. Treatment Protocols

C.4.1. Mindful Mood Balance. MMB is an individually tailored, web-based version of Mindfulness-Based Cognitive Therapy, a manualized, group skills training program (Segal et al., 2002) that is based on an integration of aspects of cognitive therapy for depression (Beck, 1979) with components of the mindfulness-based stress reduction program (Kabat-Zinn, 1990). MMB was developed by PI Segal and co-PI Dimidjian to replicate the core components of the in-person MBCT program in an online, self-administered platform. It teaches patients how to disengage from habitual ("automatic") dysfunctional cognitive routines, in particular depression-related ruminative thought patterns, as a way to reduce RDS and vulnerability to relapse (Table 2).

#	Session Topic	Table 2: MMB Session Objectives
1	*Finding Your Place Beyond Blue*	Enhancing motivation for online learning; recognizing automatic patterns of reactivity associated with perpetuation of dysphoric moods; committing to mindfulness practice as a means of stepping out of automatic pilot.
2	*The Body Scan*	Practice in moving attention to specific foci in the body, contrasting intentional versus automatic deployment of attention; cognitive interpretations of interpersonal events.
3	*The Breath*	Increasing awareness of how often the mind is busy/scattered; introducing key formal practices including mindfulness of breathing, walking, and yoga.
4	*Exploring the Landscape of Depression*	Increasing awareness of the ways avoidance or clinging to particular experiences can be associated with depression; practicing a new mode of responding that stays present and attentive in the face of difficulty; identifying symptoms and cognitions characteristic of depression as early warning signs.
5	*Facing Difficulties*	Increasing use of mindful attention at the first step in responding effectively to difficulties, including difficult internal experience such as sadness; decreasing judgmental thoughts and avoidant responses to difficulties.
6	*Thoughts Are Not Facts*	Decreasing affective reactivity to thoughts previously associated with depression; learning to "de-center" from difficult thoughts, recognizing one's personal patterns of recurring thoughts.
7	*Building Your Plan of Action*	Identifying unique 'signatures' of mood worsening; identifying activities that improve or deteriorate mood; developing action plans to implement during periods of high risk; using mindfulness practice explicitly to guide action plan steps.
8	*Supporting Your Practice in the World*	Emphasizing the importance of regular self-care routines, identifying 'your daily routine of mindfulness practice'; reinforcing links between mindfulness practices, well-being and maintenance of mood balance; continued connection to the community of MMB users.

Each MMB session incorporates a sequential tripartite learning cycle (Experiential Practice, Video-Based Vicarious Learning, and Didactic Information) that is core to the in-person MBCT program and that is designed for the integrated learning and application of mindfulness and CBT exercises (see Appendix 2). This provides patients with the opportunity for threefold presentation of content, but accessed through unique and overlapping receptive learning modes (Eastmond, 1998; Dirkx, 2008). For example, one of the core MBCT practices is a "Body Scan" meditation practice in which participants are asked to direct their attention systematically to regions of their body. In MMB, patients are asked to: 1) perform the Body Scan by listening to guided instructions led by PI Segal or co-PI Dimidjian provided on the website (or by downloading the file onto an MP3 player), 2) watch a video-clip of the interaction between PI Segal and co-PI Dimidjian as the MBCT instructors and participants in an MBCT class as they probe their reactions to and difficulties with this practice, and finally, 3) answer questions in an interactive learning module designed to permit them to describe their own experience with the Body Scan and how it might be relevant to managing RDS. Accompanying materials are also provided for each MMB session via online access to forms, handouts and audio guides

identical to those used in standard MBCT, but modified for the web (e.g., presented in a more interactive format, shortened to accommodate the typical amount of text presented on screen).

Patients will be asked to logon to MMB on a weekly basis until program completion and to set a regular routine for session and homework practice. Ongoing support for engagement with MMB will be provided through the use of Interactive Voice Response (IVR), email reminder, and telephone outreach. In our planned revision of MMB for the proposed study, users also will be able to access support from an asynchronous virtual group throughout the full study period. Once patients are enrolled in MMB, they will be invited to join a moderated online community where they can exchange information on a listserve of active users, join a discussion group of active users and past graduates, and if they wish, write a web-log (Blog) about their own experiences going through the program. Drs. Segal and Dimidjian will moderate these forums and will ensure that all posted content is anonymized and appropriate to MMB's mission. **In order to build a critical mass of forum participants, Drs. Segal and Dimidjian will seed the forum with 10 FAQ intended to stimulate interaction around relevant topics and themes (Resnick et al., 2010).** Patients will also receive weekly email reminders regarding homework tasks and, if they choose, can contribute to these MMB components while they progress through the MMB sessions or during the 12-month follow up.

We also plan to provide outreach and coaching to enhance participant retention and engagement. An Interactive Voice Response (IVR) system will be used as the first layer of outreach to remind patients to complete MMB sessions and daily home practice. Patients can choose their preferred communication method (text and/or email and/or call) and frequency (daily for home practice, weekly prior to their scheduled "appointment", or only if they miss weekly and/or daily tasks). Participants will have the option to discontinue the IVR reminders at any time. In addition, we will use live telephone outreach for participants who do not respond to email or online messaging and fail to logon to planned MMB sessions, signaling possible disengagement or clinical deterioration. Telephone support and troubleshooting functions will be based on Mohr et al.'s (2010; see Appendix 1) interview protocol that features motivational assessment strategies to enhance retention in online treatments. Drs. Segal and Dimidjian will operationalize adaptations of this manual for specific MMB components that are not presently included, e.g. mindfulness training, barriers to practice, rationale for managing RDS. Once finalized the manual will be available for use in training non specialist providers in KPCO and similar settings.

C.4.2. Depression Care Pathways at KPCO (DepCare)

Treatment as usual follows the *Kaiser Permanente Adult Depression National Guidelines* comprised of an adaptation of STAR*D (Rush et al., 2006) for antidepressant management and the IMPACT (Unitzer et al., 2002; 2008) model for therapy. Specific depression care pathways are determined by PHQ-9 scores (0-4, no depression; 5-9 mild, 10-14, moderate,15-19 moderately severe; $\geq$20 severe) and include treatment with antidepressants and/or psychotherapy. The pathways take into consideration suicidal ideation, prior lifetime MDD episodes, chronicity/dysthymia, and patient treatment preferences. The majority of KPCO primary care clinics have co-located Behavioral Medicine Specialists (licensed clinical psychologists), who may provide brief therapy and/or refer patients to a specialty mental health clinic for additional sessions of psychotherapy and/or initiation of an antidepressant. DepCare will be augmented by ongoing study assessments and the provision of both feedback to participants (e.g."Your answers to our survey suggest that you are having significant symptoms of depression. We recommend that you talk with your primary care provider or behavioral medicine specialist about whether treatment might help") and direct referrals to the Behavioral Health department and/or to a behavioral medicine specialist, depending on their treatment preferences. Care will not be constrained for participants randomized to DepCare, and protocols will be in place in order to provide assessment and intervention for any participant who expresses suicidal ideation or clinical deterioration. As a preliminary indicator of DepCare health care service use, we collected data for 94 MMB users in the year prior to enrollment in our open trial. **Results point to a substantial amount of services use, including an average of 4 mental health visits (1 of which was psychotherapy), 5 antidepressant prescriptions (average 60 day supply), 7 primary care visits, and 8 medical specialty visits. This study will evaluate whether the addition of an accessible psychological treatment to DepCare can further reduce RDS.**

C.5. Clinical Measures

Baseline Measures. The *Demographic Form* is a project designed measure that gathers descriptive information about basic demographic variables. It also assesses previous treatment history, history and current

practices with meditation and yoga, and internet usage, familiarity, and comfort; these variables will be used in exploratory analyses of potential predictors and moderators of treatment outcomes.

Depression Severity. Participants will complete the PHQ-9 monthly over the 14 month study period to assess depressive symptom severity during MMB (Kroenke et al., 2001). This brief 9 item scale has a sensitivity of 88% and a specificity of 88% for detecting major depressive disorders based on a cut-off score of 10 and is frequently employed in primary care for clinical monitoring of RDS (Meana et al., 2012).

*End State Functioning: SF-12, **PDSQ** and Depression Free Days*: The SF-12 (Ware, 2006) is a brief self-report measure of mental and physical functioning and overall health-related-quality of life; it will be administered at baseline, two months, and at the completion of the 12 month follow up. Test-retest reliability has been reported as 0.890 and validity, based on correlations was .67 (range 0.43 to 0.93). **The PDSQ (Zimmerman & Mattia, 2001) will be used to screen for co-morbid anxiety disorders and has high subscale sensitivity (80-90%) and specificity (66-78%).** Depression Free Days will be calculated via linear interpolation to estimate daily depression severity across PHQ-9 assessment points, as suggested by Vannoy et al. (2010) for evaluating treatment efficacy.

Proximal Markers of Relapse Risk: The *Five Factor Mindfulness Questionnaire* (FFMQ; Baer et al., 2006) is a 39-item self-report measure that is designed to assess five domains of mindfulness, including observing, describing, acting with awareness, accepting without judgment, and non-reactivity. We also will use the *Ruminative Response Scale* (RRS; Treynor et al., 2003), which measures an individual's likelihood to engage in ruminative and distracting responses to negative affect. The *Experiences Questionnaire* (Fresco et al., 2007b) is a self-report measure assessing decentering, or the ability to observe thoughts without identifying with the particular cognitive content. These measures will be administered at the following assessment time points: baseline, 1 month, 2 month, and the completion of the 12 month follow up.

Intervention Acceptance. We will use the 8-item *Client Satisfaction Questionnaire* (Larsen et al., 1979) to measure participant satisfaction with services; the CSQ-8 is designed to yield a homogeneous estimate of general satisfaction with services. This will be administered at the completion of the 14 month study period.

Intervention Adherence. Using *The Weekly Home Practice Record (Segal et al., 2013)*, patients assigned to MMB will be asked to monitor completion of both formal and informal mindfulness practices, weekly during MMB, and monthly during the the 12 month follow up.

Administrative Databases: KPCO has assembled a large mental health data set from its virtual data warehouse (VDW) that is populated from its electronic medical records (EMR) system and will provide data on relevant participant variables such as; demographics, diagnostic status, treatment received, services use, and clinical outcomes.

C.6. Data Analysis Plan

Preliminary Analyses. Descriptive statistics and exploratory graphing such as frequencies, means, standard deviations, box and whisker plots, stem and leaf diagrams, and scatter plots will be used to assess the normality of the data in terms of the presence of skew and/or outliers for all outcome domains. The continuous outcome data will be transformed if necessary by using an appropriate transformation such as the log transform for skewed long-tailed data. To test for possible baseline differences, we will test for differences between the MMB and DepCare groups in key demographic characteristics (e.g., age, gender, ethnicity, SES) and clinical characteristics (depression symptom severity, psychiatric comorbidity, past # depressive episodes, past antidepressant use) will be assessed using t-tests (for continuous variables) or chi-square (for nominal variables) tests. In the event that some continuous variables show evidence of being significantly skewed, nonparametric methods will be used to analyze group differences. Variables that show significant group differences (at $p < .05$) and predict outcome will be entered in all subsequent analyses as covariates.

Aim 1 - Test the effectiveness of Depression Care + Mindful Mood Balance as compared to Depression Care alone, for patients with residual depressive symptoms.

To examine treatment differences in depressive symptoms measured by the PHQ-9 over time, we propose to use mixed effects modeling (MEM) as our primary analytical approach, as it will address the nature of the outcome data, accommodate the within-subject variability, and allow us to inspect the results for bias due to drop out or missing data. Clustered data due to repeated measures of depression status will be handled by the mixed effects approach which accounts for the clustered structure of the data by modeling the correlation between repeated assessments within an individual (Hedeker and Gibbons, 2006). One specific form of MEM will be implemented: Hierarchical Linear models (HLM). HLM assumes change over time for the outcome measure is linear or, dependent on the complexity of the model, can be written in polynomial form with respect to time, resulting in a growth curve model. Under linearity, for each individual the within-subject level (level 1 equation) is:

$$y_{ij} = \beta_{0i} + \beta_{1i}(\text{time}_{ij}) + e_{ij},$$

and the between-subject level (level 2 equation) is:

$$\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Intake}_i + \gamma_{02}(\text{condition}) + u_{0i}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11}\text{Intake}_i + \gamma_{12}(\text{condition}) + u_{1i}, \text{ where } e_{ij} \sim N(0, \sigma^2) \text{ and}$$

$$\begin{bmatrix} u_{0i} \\ u_{1i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \tau_{00} & \tau_{01} \\ \tau_{01} & \tau_{11} \end{bmatrix}\right).$$

In the level 2 equations, the subject-specific parameters from level 1 equation are our outcomes, where our main interest is γ_{12} parameter, which represents, the on-average difference in the rate of change per unit time between the interventions, adjusted for intake.

Analysis of the secondary outcomes of functional status (SF-12) and Depression Free Days will be conducted in the same way, using HLM, as described above.

Attrition. The pattern-mixture procedure described in chapter 14 of Hedeker and Gibbons (2006) will be used to determine if dropouts are influencing the mixed-effects model results, as well as outlining a procedure to create a weighted average of the intervention effect over the patterns of attrition. Sensitivity analyses will be done using local influence, random effects pattern mixture models (Guo, Ratcliffe & Ten Have, 2004) and multiple imputations.

Power Analysis. For this study design, the repeated observations within subjects are correlated. When this within subject correlation is properly incorporated, the repeated measures analysis takes full advantage of all information obtained from each subject, thereby greatly increasing statistical power over methods that compare treatments cross-sectionally (Gibbons et al., 1993). Using the method described by Ahn et al. (2001) to derive formulas for power estimation of linear mixed models, power calculations can be made for repeated measures designs under specified assumptions. Based on a sample size of 135 per group, corresponding to a 60% retention rate and assuming 20% attrition over the 12 months for a total of 230 per arm randomized, with an alpha-level at 0.05 based on a 2-tailed test, and assuming a within correlation of 0.5, we have power of 77.9% to detect an effect size of .35. Varying the effect size we have 87.3%, 93.6%, and 97.1% power for effect sizes of 0.4, 0.45, and 0.5, respectively. Parameters for the power derivation were based on our pilot-study sample where we had a within-subject correlation of 0.5 and a median sessions attended of 4 out of 8. Within our pilot data, we saw a within group effect size of 0.77. This value is based on the full sample of our pilot study, which provides a more conservative estimate to inform our power analysis as compared to the ES (d=1.09) for the RDS subgroup. Assuming a small effect size (d=0.2; Clarke et al., 2005; 2009) within the control arm, we anticipate an effect size for the difference exceeding 0.36, which is the minimal difference to yield 80% power. Kraemer and colleagues' (2006) outline the problems inherent in using pilot data to guide power calculations for larger-scale RCTs, but unlike the issues highlighted in that article (differences between the pilot data and the planned RCT with respect to the sample, study protocol, and study goals), our proposed study has few differences with respect to the previously conducted pilot study; therefore, the inferences from the analyses conducted on the pilot study findings should be accurate.

Aim 2 - To examine intervention differences in the rate of relapse/clinical deterioration compared to DepCare, we will investigate time to relapse (defined as a PHQ-9 score of >13 over the 12 month follow up) using survival analysis. Survival rates will be compared using Cox proportional hazard regression and illustrated in Kaplan-Meier curves (Collett ,1994). In PI Segal's recent study of in person MBCT (Segal et al., 2010), patients with RDS evidenced a 44% difference in relapse rates favoring MBCT over placebo and clinical monitoring. More conservative estimates of relapse prevention effects are provided by prior studies of MBCT, which report approximately 35% difference in relapse rates favoring the intervention over usual care (Goodfrin & van Heering, 2010; Teasdale et al., 2000). Using this as an estimate, Rosenthal (1996) provides comparable thresholds for small-medium-large effect sizes for Odds ratios/Hazard ratio. Based on our proposed sample size, the study has 78.4% power to detect a small effect size (HR=.70) for a two-sided test, which corresponds to detecting a difference of 30% in the relapse rates between the intervention arms.

Aim 3 – Examine whether reductions in RDS are mediated by decreases in rumination and increases in mindfulness, a key premise of our intervention theory, and investigate factors that predict or moderate treatment effects. Mediating effects will be tested using the strategies outlined by Preacher and Hayes (2008). In brief, if an intervention effect obtained under primary aims becomes non-significant or significantly reduced after controlling for the hypothesized mediating variable, this indicates support for mediation. In addition, we will assess the joint significance of the indirect pathways (i.e., the joint significance of the pathways from the

predictor to the mediating variable and from the mediating variable to the outcome) using the bias-corrected bootstrap test as recommended by Fritz and MacKinnon (2007). Bauer et al. (2006) provide the methodology to extend this mediation to the multilevel models, which we will implement to the MEM models discussed in Aim 1. We will apply the bootstrapping technique to testing multiple simultaneous mediators as proposed by Preacher and Hayes (2008). The analysis team has experience implementing these models (Gallop et al., 2009; Lynch, Cary, Gallop & Ten Have, 2008). **Fritz and MacKinnon (2007) documented sample size requirements to guarantee 80% power under the sequential regression framework (i.e., Baron & Kenny, 1986). Under the assumption of a medium effect for intervention with the mediator and a medium effect for intervention on outcome, covarying the mediator, a sample size of 110 is required. Therefore our design consisting of a sample size of 135 completers per arm is sufficiently powered to detect mediation**. To explore potential predictors or moderators that may interfere with or enhance intervention effects (Kraemer et al., 2002), we will employ the same HLM approach as was used to test the primary outcomes (AIM 1) in the analysis of this aim. Variables of interest include: demographic characteristics, internet use history, chronicity and severity of prior episodes, concurrent antidepressant use, medical history, and medical services use.

Aim 4 - To investigate whether the incremental cost of providing MMB will result in a significantly greater number of depression free days than DepCare over the 12 months following the intervention.
Our economic analysis will be based on the perspective of managed care organizations, especially those comprising the 10 Mental Health Research Network members that would be potential adopters of MMB. We will estimate total costs associated with MMB relative to DepCare, costs per participant, and the marginal costs per incremental number of depression free days (DFDs; Lave et al. 1998; Vannoy et al., 2010), a measure used in previous cost effectiveness analyses of depression treatment which is particularly relevant to clinical leaders in deciding whether to adopt the MMB program. Using longitudinal PHQ-9 scores, we will identify periods of remission and periods of residual depression symptoms and sum the days across the periods to estimate DFD over the 12 month follow up.
Intervention implementation cost analysis. We will capture all expenses attributable to implementation and recruitment, including the following cost categories: Fixed costs – server maintenance and data storage, salary and fringe benefits for labor inputs (e.g., behavioral health clinicians, receptionists, IT staff time for updating website content, data collection and analysis, and website hosting); screening and assessment instruments, and other supplies; and indirect costs. Labor inputs will be tracked via time estimates by the project staff. Variable costs – personnel hiring and training, and expert staff time used for: participant recruitment, moderation of interactive Q&A forums, answering participant questions submitted to the MMB website, coaching participants to increase engagement in the MMB homework, website promotion (demos to clinical staff), and enhancements to improve website functionality. Using KPCO administrative data derived from the electronic medical record and claims, we will extract utilization and cost data for the entire cohort (MMB and DepCare) for the 12 months pre and post randomization to the trial. Health care costs will be estimated using KPCO's internal cost management Decision Support Systems (DSS) (Sukhanova et al., 2011).

C.7 Strengths and Limitations

Strengths include efficient methods of recruiting, enrolling and assessing outcomes; first online mindfulness based program to target RDS; capacity to enroll large N with broad inclusion criteria allowing exploration of moderators of outcome and addressing generalizability by examining differences in demographics and clinical severity between participants and KPCO members; strong findings for both reduced RDS and program engagement from our R34; and track record of collaboration among investigators and expertise in conducting large RCTs. Limitations include lack of an active control condition, precluding inferences about specific active ingredients of MMB; however, DepCare provides a stringent comparison, given the careful attention to depression management within that system and the data on care utilization and treatment received (see C.4.2). Therefore, we believe this provides a particularly optimal comparison group in terms of generalizability of benefit and cost effectiveness to other clinical settings.