PLOS One

STUDY PROTOCOL

Online mindfulness-based cognitive therapy for people with multiple sclerosis with mild-to-moderate depression– protocol for a type 1 hybrid effectiveness-implementation study

Robert Simpson[1,2], Jillian Scandiffio[1,2]*, Laura Langer[3], Sarah Munce[4,5], Ashvene Sureshkumar[5], Anthony Feinstein[6,7], Mark Bayley[1,3], Caroline Bowman[8], Tania R. Bruno[3], Dawn Ehde[9], Katherine Knox[10], Nanette Lai[11], Penelope Smyth[12], Abhimanyu Sud[13,14], Sarah J. Donkers[15]

1 Rehabilitation Sciences Institute, University of Toronto, Toronto, Canada, **2** St. Michael's Hospital, Unity Health Toronto, Toronto, Canada, **3** Toronto Rehabilitation Institute, University Health Network, Toronto, Canada, **4** Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Canada, **5** Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Canada, **6** Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada, **7** Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada, **8** Department of Family Medicine, McMaster University, Hamilton, Canada, **9** Department of Rehabilitation Medicine, University of Washington, Seattle, United States of America, **10** Department of Physical Medicine and Rehabilitation, College of Medicine, University of Saskatchewan, Saskatoon, Canada, **11** Ontario Veterinary College, University of Guelph, Guelph, Canada, **12** Department of Medicine (Neurology), Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Canada, **13** Department of Family and Community Medicine, University of Toronto, Toronto, Canada, **14** Humber River Health, Toronto, Canada, **15** School of Rehabilitation Science, University of Saskatchewan, Saskatoon, Canada

* jillian.scandiffio@mail.utoronto.ca

Check for updates

OPEN ACCESS

Citation: Simpson R, Scandiffio J, Langer L, Munce S, Sureshkumar A, Feinstein A, et al. (2026) Online mindfulness-based cognitive therapy for people with multiple sclerosis with mild-to-moderate depression– protocol for a type 1 hybrid effectiveness-implementation study. PLoS One 21(11): e0362553. https://doi.org/10.1371/journal.pone.0362553

Editor: Jenna Scaramanga, PLOS: Public Library of Science, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Received: October 20, 2026

Accepted: October 23, 2026

Published: November 13, 2026

Copyright: © 2026 Simpson et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data availability statement: No datasets were generated or analysed during the current study. All relevant data from this study will be made available upon study completion.

Abstract

Background

Mindfulness-based cognitive therapy (MBCT) is an effective treatment for recurrent depression in the general population and is recommended in clinical guidelines for those with mild-moderate depression. However, the effectiveness of MBCT in people with multiple sclerosis (PwMS) with mild to moderate depression is unknown. Further, how best to tailor and implement MBCT for PwMS is largely unstudied. This manuscript describes the study protocol for a hybrid-effectiveness study to evaluate online MBCT tailored for PwMS.

Methods

This type 1 hybrid effectiveness-implementation study will employ an embedded mixed methods experimental design. Quantitative findings will be collected through a powered waitlist randomized controlled trial examining online MBCT in a minimum of 152 PwMS with case-ness of mild-moderate depression (Clinical Trials Gov #NCT07742579). The intervention will consist of an online 8-week MBCT course with weekly sessions conducted by qualified mindfulness instructors experienced int the

Funding: This study is receiving funding from the National MS Society/MS Canada RFA (#1541284). The funder will have no role in the design, conduct, analysis, and reporting of the trial.

Competing interests: RS's research is supported by Physicians Services Incorporated, Associated Medical Services Healthcare, CIHR, and MS Canada. SM is the EIC of JMIR Rehabilitation and Assistive Technologies, PS has received honoraria as a speaker and member on advisory boards for EMD Serono, Novartis Pharmaceuticals, Roche Pharmaceuticals, Eli Lilly Canada, Sanofi Genzyme, and Amgen Pharmaceuticals. She is a co-investigator on research supported by MS Canada and CIHR. The other authors declare no competing interests. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

care of PwMS. Questionnaires will be collected at baseline, post-intervention, and 3 months later. The primary outcome will be depression, measured using the Hospital Anxiety and Depression Score – Depression (HADS-D). An intention-to-treat analysis will be conducted. Qualitative findings will be collected through semi-structured interviews with 30–40 MBCT participants, HCPs, MBCT instructors, and MS decision makers. Thematic analyses will be used to analyze interview data. The RE-AIM PRISM tool will be used to evaluate implementation and mixed data assessed in a joint display.

Conclusion

The results from this study will provide evidence regarding the effectiveness of online MBCT in PwMS with mild to moderate depression, recommendations for intervention tailoring and implementation. Findings will be disseminated through traditional and novel, creative knowledge mobilization methods.

Introduction

Multiple sclerosis (MS) is a highly disabling chronic inflammatory neurodegenerative condition which affects over 2,800,000 worldwide [1]. MS affects females at a higher rate than males, with females diagnosed at approximately a 3:1 ratio to males [2]. People living with multiple sclerosis (PwMS) rarely experience the condition as a stand-alone diagnosis. The most common comorbidity is depression which affects ~23.7–30.5% [3,4] PwMS and is typically chronic. The etiology of depression in PwMS is likely multifactorial, including genetic, immune-inflammatory, and psychosocial [5], however comorbid depression is commoner in those PwMS who are aged 42–57, have a secondary progressive phenotype, and are more physically disabled [6]. Comorbid depression strongly correlates positively with fatigue [7] and self-stigma [8], and negatively with self-efficacy and self-esteem [6]. Of added concern, those PwMS with comorbid depression are less likely to adhere to disease modifying therapies (DMTs) for MS [9], and more likely to engage in adverse health behaviours such as smoking and alcohol use [6]. Although comorbid depression exerts strong negative effects on quality of life (QoL) in PwMS [10], it is treatable. Limited evidence supports the use of pharmacological agents in the treatment of comorbid depression in PwMS; systematic reviews confirm that treatment attrition for antidepressants among PwMS with depression is very high in clinical trials [11,12]. However, in meta-analyses, both cognitive behavioural therapy (CBT) and Mindfulness-based interventions (MBIs) have been found to be effective in treating symptoms of depression and have low attrition in PwMS [13–15]. Furthermore, previous work has shown that PwMS express a preference for behavioural programming for managing mood [16]. Indeed, both CBT and MBIs appear to be acceptable to PwMS. To optimize effects, tailoring is required [17,18]. Despite this, depression in PwMS is undertreated [6].

Based on evidence from the general population, an intervention that incorporates elements of both CBT and MBIs is likely to have incremental benefits for PwMS with

comorbid depression. Indeed, Mindfulness-Based Cognitive Therapy (MBCT) was developed and evidenced as a preventative treatment for depressive relapse [19], building on well-established evidence for Mindfulness-Based Stress Reduction (MBSR) as a treatment for stress in people with chronic medical conditions, and CBT. In the general population, MBCT is recommended in best practice guidelines for those with mild-moderate depression, whereas those with severe depression should have individualised treatment [20]. MBCT is typically delivered as a group and includes psychoeducation, cognitive and behavioural tasks designed to raise awareness of and address putative key drivers of depression such as ruminative cognition and negative affect [19].

Besides strong evidence of effectiveness for MBCT in decreasing symptoms and recurrence of depression in the general population [21,22], including self-stigma [23], it also improves positive mental health outcomes such as QoL [24], mindfulness, self-compassion [25], positive affect and spirituality [26]. Indeed, among PwMS, the largest pooled effects in meta-analyses of MBIs are for improving mental health-related QoL [15]. Positive effects from MBCT have been shown to be stable for up to 2 years post treatment in people with depression – this is important because for a self-management intervention for PwMS (a chronic, progressive condition) to have a meaningful impact, effects have to be longitudinal and ideally incremental, meaning that with the right infrastructure and support, skills continue to develop and endure over time [27].

There are well documented inequities related to mental health care access faced by PwMS [28]. Online delivery of self-management resources helps to address some of these inequities by improving access for those PwMS who are more physically disabled, of lower social means, and living rurally, and hybrid (live and asynchronous) digital self-management interventions are more effective for people with chronic neurological disorders than those fully digitized [29]. Indeed, qualitative research synthesis suggests PwMS prefer a hybrid of live (synchronous) and asynchronous MBI offerings, which maximize acceptability and accessibility, respectively [17,18]. Community, camaraderie and common humanity are suggested as key factors which motivate sustained participation in MBIs for PwMS [18]. Those studies which have demonstrated long-term benefits from MBCT have highlighted the importance of ongoing access to learning materials beyond the standard 8-week course [30], and that for those people with depression, learning to use mindfulness is a longitudinal process which involves increased self-awareness, perspective-taking and acceptance, and requires continued practice to exert agency [31]. Taken together, implemented at scale, MBCT has the potential to help a large number of PwMS. However, there is a lack of evidence regarding the effectiveness of MBCT in PwMS with mild-to-moderate depression and there is a lack of understanding as to how to effectively implement this intervention for PwMS.

Objectives

The overall aim of this project is to implement and evaluate online MBCT tailored for PwMS.

Specific objectives include:

1. Conduct a pragmatic, powered waitlist randomised controlled trial (RCT) of effectiveness of tailored online MBCT among PwMS who have case-ness of mild to moderate depression.
2. Evaluate implementation of the tailored online MBCT course for PwMS who have mild to moderate depression using the RE-AIM framework, informed by PRISM, through a parallel process evaluation.

Methods

This type 1 hybrid effectiveness implementation study will employ mixed methods and comprises a powered RCT to evaluate the effectiveness of the tailored MBCT course, embedded qualitative interviews to explore participants' experiences, and a process evaluation of the implementation of the course. Implementation will be examined using the RE-AIM (Reach, Effectiveness, Adoption, Implementation & Maintenance) framework, informed by PRISM (Practical,

Robust Implementation and Sustainability Model), of participants in the course, and explores barriers and facilitators to implementation. This approach was chosen with the rationales of triangulation and expansion to examine convergence between quantitative and qualitative findings and to more comprehensively study the intervention, including factors influencing its use and implementation. This allows us to expand upon not only *whether* it is effective but also *how* the intervention is perceived and should be implemented.

The trial was registered on ClinicalTrials.Gov (Identifier: NCT07742579) on July 31, 2026. The trial will be conducted online through the University of Toronto. This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines for a RCT protocol.

Eligibility

Inclusion criteria will include: 1. Age >/= 18; 2. Neurologist confirmed MS diagnosis (McDonald criteria [32]); 3. Able to understand spoken and written English; 4. A score of 14–28 on the Beck Depression Inventory-II (BDI-II) signifying mild-moderate depression [33]; 5. Registered with a primary care provider (family physician or neurologist), 6. Residing in Canada.

Exclusion criteria will include: 1. Potentially life-threatening comorbidities (suicidal ideation [i.e., score of 2 or 3 on the BDI-Fast Screen (BDI-FS) suicidal ideation question], history of psychosis, terminal/life threatening inter-current illness), or those such conditions expected to significantly limit participation and adherence (pregnancy, cognitive impairment, i.e., score <26 on the Montreal Cognitive Assessment – MoCA) [34], and 2. Receipt of MBCT in the past 2 years (completed at least 4/8 sessions).

Recruitment and trial procedures

Study materials (e.g., study flyer) will be disseminated by NeuroSask Active and Connected, MS Canada, the Canadian Network of MS Clinics, and social media (e.g., MS groups on Facebook). Potential participants can reach out to the study team to indicate their interest and will undergo eligibility screening. Initial contact between participants and the research study team will always be by telephone, or videoconferencing software, where baseline eligibility screening will take place (Fig 1). Outstanding participant questions about the study can also be addressed at this point. Following this call, the research study team will send electronically a Participant Information Leaflet, consent forms, and baseline questionnaires to be completed via REDCap.

Randomization will be generated using a random computer-generated scheduler (e.g., SAS PROC PLAN) by a biostatistician who is unaware of participant identity and uploaded to REDCap software for the research coordinator to assign treatment allocation to recruited participants. As the design is a waitlist-controlled trial, randomization will be performed in clusters of 30 participants and will be allocated to Intervention or Waitlist Control arms in a 1:1 allocation in blocks of 2 (Fig 2). A waitlist control was selected as the comparator because there is currently no standard of care intervention for PwMS who have mild-moderate depression. Our pragmatic study design will thus compare MBCT to the care PwMS in Canada actually receive and will thus allow assessment of incremental benefit rather than efficacy.

Participant blinding in MBI research is challenging [35]. Pragmatic mitigation strategies in this study include [35]: 1) randomization will be generated via computerized randomization schedule generation and only the PI and statistician will have access to the schedule; 2) assessors and statistician blinded to group allocation for data entry, analysis, participant questionnaire data identifiable only by random study ID, group allocation concealed until final analysis; 3) publicly accessible study information kept general, no suggestion of intervention superiority; 4) participants advised only that they are allocated to an intervention ‘to improve emotional wellbeing’; 5) participants asked to not discuss group assignment with healthcare providers (HCPs) or study assessors for study duration.

TRIAL PERIOD						
	Enrollment		Post-randomization			Close-out
TIMEPOINT[b]	$-t_1$ to 0	0	t_1	t_2	t_3	t_4
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTION/ COMPARATOR:						
MBCT		X				X
Usual Care					X →	X
ASSESSMENTS:						
Sociodemographic factors (i.e. PROGRESS+)	X	X				
Primary outcome		X	X	X	X	X
Secondary outcomes		X	X	X		X

Fig 1. Participant timeline: schedule of enrollment, interventions, and assessments.

https://doi.org/10.1371/journal.pone.0362553.g001

Intervention

The intervention will comprise online group MBCT, tailored for PwMS, delivered live, via secure video conferencing software, by trained MBCT instructors, with up to 15 PwMS per group, weekly 2.5 hour sessions (with comfort breaks) for 8 weeks, including core meditation practices (mindful-breath, -body, -movement awareness), psychoeducation on depression, reflective group discussion ('enquiry'), and home practices of up to 45 minutes/day [36].

Outcomes

The primary outcome is change in depression, as measured by HADS-D as a continuous measure. Between and within group differences in HADS-D will be evaluated. Clinically significant reductions in HADS-D will also be examined as an exploratory outcome (a reduction of 20% considered a 'minimally important difference' [MID] [37].

Secondary outcomes will be collected for exploratory analysis and can be found in Table 1. In all trial participants, trial outcomes will be collected remotely online using REDcap™, at baseline (T0), immediately post MBCT (T1), and 3 months later (T2) to assess magnitude and stability of treatment effects and/or hazards.

Implementation outcomes will be collected throughout the study and formally assessed and reported following 12 months completion of the trial. These outcomes are described in Table 2.

Data collection

Participants will be asked to fill out an online questionnaire at baseline (0 weeks), post-intervention (8 weeks) and follow-up (21 weeks). Online questionnaires will be used to collect data on the outcomes noted above and

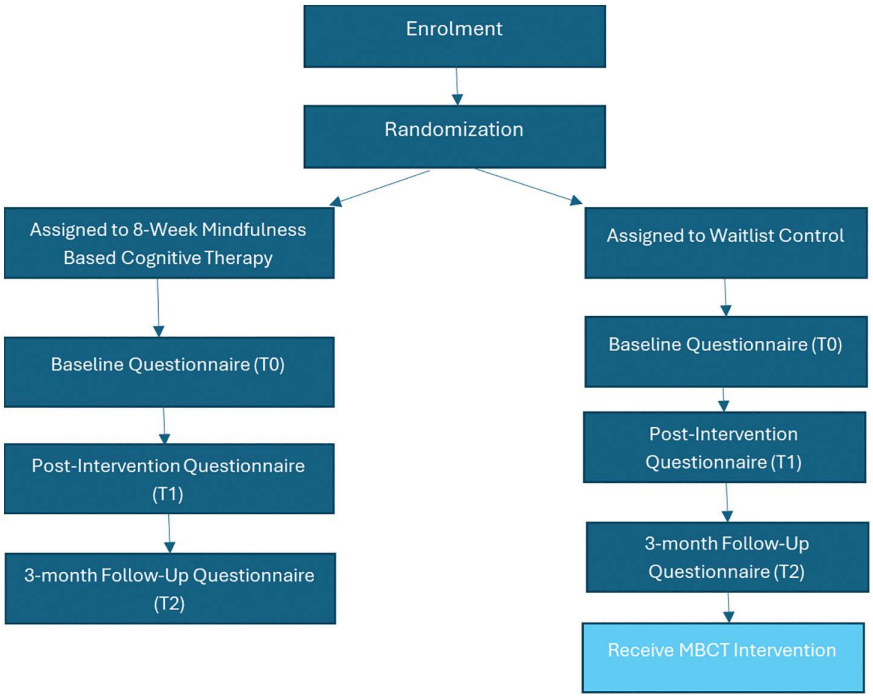


Fig 2. Participant Flow Chart.

https://doi.org/10.1371/journal.pone.0362553.g002

socio-demographic variables including age, sex, gender identity, race/ethnicity, current living situation, marital status, household income bracket, educational attainment, disease duration, disability level, number/type comorbid conditions, disease modifying therapy (DMT) and/or psychotropic use/type/dose.

Further, a subset of participants (n = 30–40) will be invited to participate in one semi-structured interview via video-conferencing software examining motivations for participation, acceptability, accessibility, perceived effects of the MBCT program, as well as explore barriers and facilitators to implementation. HCPs, MBCT instructors and MS decision makers (e.g., clinic directors) will also be invited to participate in one semi-structured interview regarding their thoughts on the barriers and facilitators to implementation of MBCT for PwMS. Interview data will be digitally recorded and transcribed verbatim.

Analysis

The sample size was based on 3-month follow up data from Bogosian et al.[53] whereby, assuming the HADS-D scores are normally distributed, we expect to see a difference between the tailored online MBCT group and the usual care group of 2 units on average, with a standard deviation (SD) of 3.5, or a difference of 0.57 per SD. A minimum sample of 152 will provide a linear regression model with 3 time points (T0-T2) spaced at baseline (0 weeks), post-intervention (8 weeks) and follow-up (21 weeks) with 80% power. Sample size is adjusted for an assumed intracluster correlation of 0.2 of the repeated measures and assumed moderate baseline adjustment correction of 0.4 and 16% loss to follow-up for the analysis of our primary outcome, HADS-D based upon previous trial attrition rates. Sample size was calculated using SAS 9.4 for Windows (SAS Institute, North Carolina, USA).

All statistical analyses will be undertaken by blinded staff (biostatistician). A statistical analysis plan will be completed and signed off prior to database lock. Demographic baseline characteristics will be summarized by allocated group

Table 1. Secondary outcomes analyzed.

Outcome	Measure
Trial Outcomes	
Self-efficacy	Generalized Self-Efficacy Scale (GSES) [38], which assesses self-beliefs around coping with a range of demanding life situations, and has strong internal consistency in PwMS
Self-management	Multiple-Sclerosis Self-Management Scale-Revised (MSSM-R), a multi-dimensional assessment of self-management knowledge and behaviour, which has strong internal consistency in PwMS [39]
Stigma	Stigma Scale for Chronic Illness-8 (SSCI-8), which measures enacted and internalized stigma, and has strong internal consistency in PwMS [40]
Fatigue	Modified Fatigue Impact Scale (MFIS), measuring how much cognitive, physical, and psychosocial aspects of fatigue impact on daily activities, higher scores indicating a greater impact. A 4-point reduction has been established as the MID in PwMS [41]. The MFIS has strong reliability, internal consistency and precision
Sleep	Insomnia Severity Index (ISI), measuring seven domains of sleep: difficulties initiating and staying asleep, early morning wakening, satisfaction, interference with daily function, noticeability, and distress. The ISI is recommended for use in PwMS [42], is reliable and valid [43], with suggested clinical cut-offs and MIDs [44]
Pain	Pain Effects Scale (PES), a 6-item measure which assesses the ways in which pain and unpleasant sensations interfere with mood, movement, sleep, work, recreation, and enjoyment of life. Higher scores indicate greater impact of pain on mood and behavior. The PES has good face validity and reliability [45]
Quality of life	Multiple Sclerosis Impact Scale-29 (MSIS-29) assesses the physical and psychological impact of MS on QoL. Based on the preferences of PwMS and common MS symptoms, it has good psychometric properties with high internal consistency and good test-retest reliability [46]
Anxiety	HADS-A, with a score > / = 8 demonstrating 'clinically significant' anxiety [47]. The HADS-A has high criterion-related validity and internal consistency reliability, with MID established in PwMS [48]
Mindfulness	The Five-facet Mindfulness Questionnaire (FFMQ) has good internal consistency, structural validity, and hypothesis testing ability [49]
Self-compassion	The Self-Compassion Scale-short form (SCS-sf), a 12-item, six-factor scale that assesses the ability to 'hold one's feelings of suffering with a sense of warmth, connection and concern' [50]. It has adequate internal consistency, and correlates highly with the full-length Self-Compassion Scale
Emotion regulation	The Difficulties with Emotional Regulation Scale short-form (DERS-sf) assesses emotion regulation over six domains: awareness, clarity, goals, non-acceptance, impulse control during negative affect, ability to access effective emotion regulation strategies [51]. It has strong internal consistency, overall and individual (goals) factors predictive of clinical severity and treatment outcome post-CBT
Depressive symptoms	Beck Depression Inventory II (BDI-II), which has been shown to be valid in PwMS [52] and with scores falling between 14–28 indicating mild-moderate depression [33]
Group processes (only those allocated to tailored online MBCT)	Group attendance, climate (Climate Questionnaire-Engage Scale), and therapeutic alliance (Working Alliance Inventory)

https://doi.org/10.1371/journal.pone.0362553.t001

Table 2. Implementation outcomes analyzed.

RE-AIM Domain	Quantitative Metrics	Qualitative Data
Reach	Number eligible, approached, enrolled, participation rate, representativeness, equity indicators	Participant and non-participant experiences with recruitment and access
Effectiveness	Primary and secondary clinical outcomes, PROMs/PREMs, adverse events, quality of life	Participant experiences, perceived benefits and challenges, mechanisms of change
Adoption	Number and proportion of clinicians/sites participating, provider characteristics, intervention adherence	Perceived fit, acceptability, organizational readiness, leadership support
Implementation	Fidelity, dose delivered and received, intervention adaptations, attendance, completion, feasibility, implementation costs	Experiences delivering and receiving the intervention, workflow integration, barriers and facilitators, adaptations
Maintenance	Sustained participant outcomes, continued intervention use, intention to continue delivery	Perceived sustainability, organizational support, recommendations for future implementation

https://doi.org/10.1371/journal.pone.0362553.t002

using means and SDs for continuous variables if normally distributed and counts and percentages for categorical ones. Primary outcome of HADS-D will be analyzed comparing baseline, post-intervention and follow-up between study arms using a linear mixed effects model (LMM) with a group, time, and group by time interaction term. Secondary linear mixed models will be run adjusting for demographic baseline covariates following variable selection and shrinkage algorithm (i.e., LASSO) and compared to the unadjusted models. All covariates will be assessed for multicollinearity (tolerance statistic <0.4) and the most clinically relevant variable of correlated covariates will be included in the model. As there will be multiple iterations of tailored online group MBCT, within group dependencies may influence observed effects [54]. As such, subjects will be clustered within groups as random effect in LMM. Potential cluster effects [55] will be explored by examining between group means, and baseline-follow-up measures using one-way ANCOVA. Exploratory subgroup analyses on factors such as age, sex, gender identity, ethnicity will be undertaken and will also explore differential impact of MBCT between those with depression and those with depression plus anxiety (HADS-A>/=8). An intention to treat (ITT) analysis will be followed with all randomized participants included in analysis. No interim analyses will be undertaken. Missing outcome data and nature of missingness will be assessed. If less than 5% missing data and missing completely at random (MCAR), whole case analysis will be conducted. Assumed baseline data missingness will be < 5% and MCAR due to REDCap data collection and as such whole case analysis will be appropriate. Should baseline data to be included in ANCOVA models exceed 5% missing, missing baseline data will be imputed using multiple imputation methods [56] via five imputed datasets and model results averaged across the five iterations. A clinical prediction model will identify those PwMS with depression most likely to benefit from tailored online MBCT in which the binary outcome is considered a 20% reduction in HADS-D. This will involve a logistic regression model on the group receiving online MBCT to examine the impact of potential predictors (e.g., sex, gender, race, ethnicity, MS phenotype, disability level, DMTs, psychotropics) following variable selection and shrinkage algorithm. Predictors will be assessed for multicollinearity and sparsity. Bootstrap validation will be used to internally validate the prediction model's performance. This will involve 10,000 samples of the same size as the original dataset chosen with replacement. The results over the 10,000 simulations will be examined for which predictors remain statistically significant and sufficiently meaningful (in > 50% of simulations). Adherence and attrition rates will be compared between treatment arms. False discovery rate will control for multiplicity of testing.

An inductive thematic analysis, as described by Braun and Clarke [57], will be employed initially to interview transcripts, but we will also subsequently perform deductive analyses using the Consolidated Framework for Implementation Research to explore barriers and facilitators to delivering and implementing tailored online group MBCT to PwMS with comorbid depression.

Qualitative and quantitative results will first be analyzed individually and then will be merged for the generation of meta-inferences. Findings will be merged using a joint display to examine fit of integration in terms of explanation, discordance, and concordance. Meta-inferences will be generated through examination of the joint display regarding effectiveness and assessment of the implementation of the intervention [58].

Monitoring

No adverse events are anticipated from online MBCT, with participants expected to benefit [59]. Online MBCT is considered safe [60]. Participant safety will be monitored continuously by the trial steering committee (TSC) and an independent data safety monitoring committee (IDMC). The trial steering committee will include a neuropsychiatrist, neurologist, physiatrist, neuropsychologist, biostatistician, and PwMS knowledge users. Trial stopping criteria will be any overt evidence of harm arising from online MBCT. A suicidality standard operating procedure was developed and approved by the sponsor, whereby any participant expressing suicidal ideation will be referred for urgent assessment by their primary care physician (family physician or neurologist) and/or in their local emergency department.

Ethics

This study has received ethics approval from the University of Toronto Research Ethics Board (#49655) on February 26, 2026. Informed written consent will be obtained from all participants by study personnel prior to trial procedures and participants will be alerted if any protocol changes occur. Only pooled de-identified quantitative results will be presented/qualitative results reported using study IDs only.

Dissemination

Study results will be disseminated through traditional knowledge mobilization strategies, including publication in peer-reviewed journals (e.g., Multiple Sclerosis and Related Disorders) and presentations at appropriate conferences and scientific meetings (e.g., Americas Committee for Treatment and Research in Multiple Sclerosis [ACTRIMS] Forum). Further, findings will be disseminated through the Canadian MS Rehabilitation Knowledge Mobilization Network and other MS organizational networks (e.g., NeuroSask Active and Connected). Less traditional, novel and creative strategies, including an integrated knowledge translation (iKT) approach, will also be employed to maximize uptake by people and organizations serving minority and marginalized PwMS. IKT, per the Canadian Institute of Health Research, is "a way of doing research that involves decision makers/knowledge-users in all stages of the research process" [61].

Study Timeline

Participant recruitment has not yet begun but is expected to begin November 1, 2026. Participant recruitment is expected to be completed in October 2027. Data collection is expected to be completed in March 2028. Results are expected in spring 2028.

Discussion/Conclusion

Depression is the most common comorbidity affecting PwMS. Currently, access to effective treatment is limited. Evidence for pharmacological treatment strategies is limited and PwMS express a preference for behavioural programming in this context. Research on the effectiveness and implementability of non-pharmacological interventions for the treatment of PwMS with comorbid depression is thus urgently needed. The primary purpose for this study is to implement and evaluate a tailored online MBCT programme for PwMS with depression. This will be done through a powered type 1 hybrid effectiveness-implementation RCT examining MBCT compared with a waitlist control group. This study will involve both qualitative and quantitative methods to examine whether MBCT is effective in improving depression in PwMS, whether it is acceptable to PwMS, how to implement and scale up the intervention. By using mixed methods, our study will provide novel insights into not only the effectiveness of MBCT in PwMS with depression but also how to tailor and implement it, providing a practical solution to a glaring gap in care. Using qualitative methods provides a meaningful platform for participants to share their own unique experiences with tailored online group MBCT, can help in the interpretation of trial findings (i.e., reasons for adherence, attrition), provides explanations for any change in health behaviors [62] during and following tailored online group MBCT, informs any further required intervention tailoring for future iterations, and provides much-needed insight into how an MBI is received by diverse PwMS. Guided by implementation theories, models, and frameworks (i.e., RE-AIM, PRISM) and integrating qualitative and quantitative findings, our study will comprehensively examine the effectiveness and implementation of MBCT for PwMS.

This study will provide valuable outputs for the treatment of depression in PwMS. Currently, there is a lack of information in whether MBCT is effective in PwMS with comorbid depression. Further, providing information on how to iterate and implement these interventions online can ensure a treatment that is not only effective but practical in a real-world setting where PwMS increasingly access care virtually and where effective self-management complements high-quality clinical care programming.

Trial Registration: This trial was registered on ClinicalTrials.gov (NCT07742579) on July 31, 2026 (https://clinicaltrials.gov/study/NCT07742579?term=NCT07742579&viewType=Card&rank=1).

Author contributions

Conceptualization: Robert Simpson, Jillian Scandiffio, Laura Langer, Sarah Munce, Ashvene Sureshkumar, Anthony Feinstein, Mark Bayley, Caroline Bowman, Tania R Bruno, Dawn Ehde, Katherine Knox, Nanette Lai, Penelope Smyth, Abhimanyu Sud, Sarah J Donkers.

Formal analysis: Laura Langer.

Funding acquisition: Robert Simpson.

Investigation: Robert Simpson, Jillian Scandiffio, Sarah J Donkers.

Methodology: Robert Simpson, Jillian Scandiffio, Laura Langer, Sarah Munce, Ashvene Sureshkumar, Anthony Feinstein, Sarah J Donkers.

Project administration: Jillian Scandiffio.

Supervision: Robert Simpson.

Validation: Robert Simpson.

Writing – original draft: Robert Simpson, Jillian Scandiffio.

Writing – review & editing: Laura Langer, Sarah Munce, Ashvene Sureshkumar, Anthony Feinstein, Mark Bayley, Caroline Bowman, Tania R Bruno, Dawn Ehde, Katherine Knox, Nanette Lai, Penelope Smyth, Abhimanyu Sud, Sarah J Donkers.

References

1. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler. 2020;26(14):1816–21. https://doi.org/10.1177/1352458520970841 PMID: 33174475
2. Coyle PK. What can we learn from sex differences in MS?. J Pers Med. 2021;11(10):1006. https://doi.org/10.3390/jpm11101006 PMID: 34683148
3. Marrie RA, Reingold S, Cohen J, Stuve O, Trojano M, Sorensen PS, et al. The incidence and prevalence of psychiatric disorders in multiple sclerosis: A systematic review. Mult Scler. 2015;21(3):305–17. https://doi.org/10.1177/1352458514564487 PMID: 25583845
4. Boeschoten RE, Braamse AMJ, Beekman ATF, Cuijpers P, van Oppen P, Dekker J, et al. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. J Neurol Sci. 2017;372:331–41. https://doi.org/10.1016/j.jns.2016.11.067 PMID: 28017241
5. Solaro C, Trabucco E, Messmer Uccelli M. Pain and multiple sclerosis: Pathophysiology and treatment. Curr Neurol Neurosci Rep. 2013;13(1):320. https://doi.org/10.1007/s11910-012-0320-5
6. Young CA, Langdon D, Rog D, Chhetri SK, Tanasescu R, Kalra S, et al. Prevalence, treatment and correlates of depression in multiple sclerosis. Mult Scler Relat Disord. 2024;87:105648. https://doi.org/10.1016/j.msard.2024.105648 PMID: 38713965
7. Kampaite A, Gustafsson R, York EN, Foley P, MacDougall NJJ, Bastin ME, et al. Brain connectivity changes underlying depression and fatigue in relapsing-remitting multiple sclerosis: A systematic review. PLoS One. 2024;19(3):e0299634. https://doi.org/10.1371/journal.pone.0299634 PMID: 38551913
8. Powell B, Mills R, Tennant A, Young CA, Langdon D. Stigma and health outcomes in multiple sclerosis: A systematic review. BMC Neurol. 2024;24(1):346. https://doi.org/10.1186/s12883-024-03853-3 PMID: 39271990
9. Washington F, Langdon D. Factors affecting adherence to disease-modifying therapies in multiple sclerosis: Systematic review. J Neurol. 2022;269(4):1861–72. https://doi.org/10.1007/s00415-021-10850-w PMID: 34676448
10. Gil-González I, Martín-Rodríguez A, Conrad R, Pérez-San-Gregorio MÁ. Quality of life in adults with multiple sclerosis: A systematic review. BMJ Open. 2020;10(11):e041249. https://doi.org/10.1136/bmjopen-2020-041249 PMID: 33257490
11. Fiest KM, Walker JR, Bernstein CN, Graff LA, Zarychanski R, Abou-Setta AM, et al. Systematic review and meta-analysis of interventions for depression and anxiety in persons with multiple sclerosis. Mult Scler Relat Disord. 2016;5:12–26. https://doi.org/10.1016/j.msard.2015.10.004 PMID: 26856938
12. Koch MW, Glazenborg A, Uyttenboogaart M, Mostert J, De Keyser J. Pharmacologic treatment of depression in multiple sclerosis. Cochrane Database Syst Rev. 2011;2011(2):CD007295. https://doi.org/10.1002/14651858.CD007295.pub2 PMID: 21328292

13. Simpson R, Simpson S, Ramparsad N, Lawrence M, Booth J, Mercer SW. Mindfulness-based interventions for mental well-being among people with multiple sclerosis: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. 2019;90(9):1051–8. https://doi.org/10.1136/jnnp-2018-320165 PMID: 31196913
14. Lucien A, Francis H, Wu W, Woldhuis T, Gandy M. The efficacy of cognitive behavioural therapy for depression and anxiety in multiple sclerosis: A systematic review and meta-analysis. Mult Scler Relat Disord. 2024;91:105858. https://doi.org/10.1016/j.msard.2024.105858 PMID: 39276596
15. Simpson R, Posa S, Langer L, Bruno T, Simpson S, Lawrence M, et al. A systematic review and meta-analysis exploring the efficacy of mindfulness-based interventions on quality of life in people with multiple sclerosis. J Neurol. 2023;270(2):726–45. https://doi.org/10.1007/s00415-022-11451-x PMID: 36348069
16. Senders A, Sando K, Wahbeh H, Peterson Hiller A, Shinto L. Managing psychological stress in the multiple sclerosis medical visit: Patient perspectives and unmet needs. J Health Psychol. 2016;21(8):1676–87. https://doi.org/10.1177/1359105314562084 PMID: 25527612
17. Feng G, Posa S, Sureshkumar A, Simpson S, Bruno T, Morrow SA, et al. Experiences of people with multiple sclerosis and clinicians in using cognitive behavioural therapies for hidden symptoms: A systematic review and meta-aggregation. J Neurol. 2024;271(3):1084–107. https://doi.org/10.1007/s00415-023-12116-z PMID: 38219252
18. Simpson R, Simpson S, Wasilewski M, Mercer S, Lawrence M. Mindfulness-based interventions for people with multiple sclerosis: A systematic review and meta-aggregation of qualitative research studies. Disabil Rehabil. 2022;44(21):6179–93. https://doi.org/10.1080/09638288.2021.1964622 PMID: 34498997
19. Segal Z, Williams J, Teasdale J. Mindfulness-Based Cognitive Therapy for Depression: A New Approach to Relapse Prevention. Guilford Press. 2002.
20. National Institute for Health and Care Excellence. Depression in adults: treatment and management. National Institute for Health and Care Excellence. 2022. https://www.nice.org.uk/guidance/ng222
21. Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. Clin Psychol Rev. 2011;31(6):1032–40. https://doi.org/10.1016/j.cpr.2011.05.002 PMID: 21802618
22. Goldberg SB, Tucker RP, Greene PA, Davidson RJ, Wampold BE, Kearney DJ, et al. Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. Clin Psychol Rev. 2018;59:52–60. https://doi.org/10.1016/j.cpr.2017.10.011 PMID: 29126747
23. Stynes G, Leão CS, McHugh L. Exploring the effectiveness of mindfulness-based and third wave interventions in addressing self-stigma, shame and their impacts on psychosocial functioning: A systematic review. J Contextual Behav Sci. 2022;23:174–89. https://doi.org/10.1016/j.jcbs.2022.01.006
24. Querstret D, Morison L, Dickinson S, Cropley M, John M. Mindfulness-based stress reduction and mindfulness-based cognitive therapy for psychological health and well-being in nonclinical samples: A systematic review and meta-analysis. Int J Stress Manag. 2020;27(4):394–411. https://doi.org/10.1037/str0000165
25. Mistretta EG, Davis MC. Meta-analysis of Self-compassion interventions for pain and psychological symptoms among adults with chronic illness. Mindfulness. 2021;13(2):267–84. https://doi.org/10.1007/s12671-021-01766-7
26. Badaghi N, Buskbjerg C, Kwakkenbos L, Bosman S, Zachariae R, Speckens A. Positive health outcomes of mindfulness-based interventions for cancer patients and survivors: A systematic review and meta-analysis. Clin Psychol Rev. 2024;114:102505. https://doi.org/10.1016/j.cpr.2024.102505 PMID: 39316940
27. Duggal HS. Self-management of depression: Beyond the medical model. Perm J. 2019;23:18–295. https://doi.org/10.7812/TPP/18-295 PMID: 31167709
28. Roddam H, Rog D, Janssen J, Wilson N, Cross L, Olajide O, et al. Inequalities in access to health and social care among adults with multiple sclerosis: A scoping review of the literature. Mult Scler Relat Disord. 2019;28:290–304. https://doi.org/10.1016/j.msard.2018.12.043 PMID: 30641354
29. Lau SC, Bhattacharjya S, Fong MW, Nicol GE, Lenze EJ, Baum C, et al. Effectiveness of theory-based digital self-management interventions for improving depression, anxiety, fatigue and self-efficacy in people with neurological disorders: A systematic review and meta-analysis. J Telemed Telecare. 2022;28(8):547–58. https://doi.org/10.1177/1357633X20955122 PMID: 32954920
30. Mathew KL, Whitford HS, Kenny MA, Denson LA. The long-term effects of mindfulness-based cognitive therapy as a relapse prevention treatment for major depressive disorder. Behav Cogn Psychother. 2010;38(5):561–76. https://doi.org/10.1017/S135246581000010X PMID: 20374671
31. Williams K, Hartley S, Langer S, Manandhar-Richardson M, Sinha M, Taylor P. A systematic review and meta-ethnographic synthesis of Mindfulness-based Cognitive Therapy for people with major depression. Clin Psychol Psychother. 2022;29(5):1494–514. https://doi.org/10.1002/cpp.2773 PMID: 35912665
32. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292–302. https://doi.org/10.1002/ana.22366 PMID: 21387374
33. Gaynes B, Asher G, Gartlehner G. Definition of Treatment-Resistant Depression in the Medicare Population. Agency for Healthcare Research and Quality. 2018. https://www.ncbi.nlm.nih.gov/books/NBK526366/
34. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–9. https://doi.org/10.1111/j.1532-5415.2005.53221.x PMID: 15817019
35. Friedberg JP, Lipsitz SR, Natarajan S. Challenges and recommendations for blinding in behavioral interventions illustrated using a case study of a behavioral intervention to lower blood pressure. Patient Educ Couns. 2010;78(1):5–11. https://doi.org/10.1016/j.pec.2009.04.009 PMID: 19525084

36. MacCoon DG, Imel ZE, Rosenkranz MA, Sheftel JG, Weng HY, Sullivan JC, et al. The validation of an active control intervention for mindfulness based stress reduction (MBSR). Behav Res Ther. 2012;50(1):3–12. https://doi.org/10.1016/j.brat.2011.10.011 PMID: 22137364
37. Puhan MA, Frey M, Büchi S, Schünemann HJ. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. Health Qual Life Outcomes. 2008;6:46. https://doi.org/10.1186/1477-7525-6-46 PMID: 18597689
38. Schwarzer R, Jerusalem M. General Self-Efficacy Scale. 2012. https://doi.org/10.1037/t00393-000
39. Saadat S, Kajbaf MB, Kalantari M, Hosseininezhad M. The Multiple Sclerosis Self-Management Scale–Revised (MSSM-R). Int J MS Care. 2020;22(1):37–42. https://doi.org/10.7224/1537-2073.2018-090
40. Molina Y, Choi SW, Cella D, Rao D. The stigma scale for chronic illnesses 8-item version (SSCI-8): Development, validation and use across neurological conditions. Int J Behav Med. 2013;20(3):450–60. https://doi.org/10.1007/s12529-012-9243-4 PMID: 22639392
41. Rooney S, McFadyen DA, Wood DL, Moffat DF, Paul PL. Minimally important difference of the fatigue severity scale and modified fatigue impact scale in people with multiple sclerosis. Mult Scler Relat Disord. 2019;35:158–63. https://doi.org/10.1016/j.msard.2019.07.028 PMID: 31400557
42. Zeng X, Dorstyn DS, Edwards G, Kneebone I. The prevalence of insomnia in multiple sclerosis: A meta-analysis. Sleep Med Rev. 2023;72:101842. https://doi.org/10.1016/j.smrv.2023.101842 PMID: 37660580
43. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297–307. https://doi.org/10.1016/s1389-9457(00)00065-4 PMID: 11438246
44. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34(5):601–8. https://doi.org/10.1093/sleep/34.5.601 PMID: 21532953
45. Jain D, Bernstein CN, Graff LA, Patten SB, Bolton JM, Fisk JD, et al. Pain and participation in social activities in people with relapsing remitting and progressive multiple sclerosis. Mult Scler J Exp Transl Clin. 2023;9(3):20552173231188469. https://doi.org/10.1177/20552173231188469 PMID: 37483527
46. Hobart J. The multiple sclerosis impact scale (MSIS-29): A new patient-based outcome measure. Brain. 2001;124(5):962–73. https://doi.org/10.1093/brain/124.5.962
47. Fomenko A, Dümmler D, Aktürk Z, Eck S, Teusen C, Karapetyan S, et al. Hospital anxiety and depression scale anxiety subscale (HADS-A) for detecting anxiety disorders in adults. Cochrane Database Syst Rev. 2025;7(7):CD015456. https://doi.org/10.1002/14651858.CD015456 PMID: 40600405
48. Honarmand K, Feinstein A. Validation of the hospital anxiety and depression scale for use with multiple sclerosis patients. Mult Scler. 2009;15(12):1518–24. https://doi.org/10.1177/1352458509347150 PMID: 19965520
49. Baer RA, Smith GT, Lykins E, Button D, Krietemeyer J, Sauer S, et al. Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. Assessment. 2008;15(3):329–42. https://doi.org/10.1177/1073191107313003 PMID: 18310597
50. Raes F, Pommier E, Neff KD, Van Gucht D. Construction and factorial validation of a short form of the Self-Compassion Scale. Clin Psychol Psychother. 2011;18(3):250–5. https://doi.org/10.1002/cpp.702 PMID: 21584907
51. Kaufman EA, Xia M, Fosco G, Yaptangco M, Skidmore CR, Crowell SE. The Difficulties in Emotion Regulation Scale Short Form (DERS-SF): Validation and Replication in Adolescent and Adult Samples. J Psychopathol Behav Assess. 2016;38(3):443–55. https://doi.org/10.1007/s10862-015-9529-3 PMID: 41522882
52. Watson TM, Ford E, Worthington E, Lincoln NB. Validation of mood measures for people with multiple sclerosis. Int J MS Care. 2014;16(2):105–9. https://doi.org/10.7224/1537-2073.2013-013 PMID: 25061435
53. Bogosian A, Chadwick P, Windgassen S, Norton S, McCrone P, Mosweu I, et al. Distress improves after mindfulness training for progressive MS: A pilot randomised trial. Mult Scler. 2015;21(9):1184–94. https://doi.org/10.1177/1352458515576261 PMID: 25767124
54. Baldwin SA, Stice E, Rohde P. Statistical analysis of group-administered intervention data: reanalysis of two randomized trials. Psychother Res. 2008;18(4):365–76. https://doi.org/10.1080/10503300701796992 PMID: 18815989
55. Moerbeek M, Wong WK. Sample size formulae for trials comparing group and individual treatments in a multilevel model. Stat Med. 2008;27(15):2850–64. https://doi.org/10.1002/sim.3115 PMID: 17960589
56. Murray JS. Multiple imputation: A review of practical and theoretical findings. 2018. https://doi.org/10.48550/ARXIV.1801.04058
57. Braun V, Clarke V, Hayfield N, Davey L, Jenkinson E. Doing Reflexive Thematic Analysis. Supporting Research in Counselling and Psychotherapy. Springer International Publishing. 2022. p. 19–38. https://doi.org/10.1007/978-3-031-13942-0_2
58. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. Health Serv Res. 2013;48(6 Pt 2):2134–56. https://doi.org/10.1111/1475-6773.12117 PMID: 24279835
59. Simpson R, Simpson S, Ramparsad N, Lawrence M, Booth J, Mercer SW. Effects of Mindfulness-based interventions on physical symptoms in people with multiple sclerosis - a systematic review and meta-analysis. Mult Scler Relat Disord. 2020;38:101493. https://doi.org/10.1016/j.msard.2019.101493 PMID: 31835209
60. Wong SYS, Chan JYC, Zhang D, Lee EKP, Tsoi KKF. The safety of mindfulness-based interventions: A systematic review of randomized controlled trials. Mindfulness. 2018;9(5):1344–57. https://doi.org/10.1007/s12671-018-0897-0
61. Canadian Institute of Health Research. Knowledge mobilization at CIHR. https://cihr-irsc.gc.ca/e/29529.html. 2026.
62. Renjith V, Yesodharan R, Noronha JA, Ladd E, George A. Qualitative methods in health care research. Int J Prev Med. 2021;12:20. https://doi.org/10.4103/ijpvm.IJPVM_321_19 PMID: 34084317