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Internet-Delivered Lifestyle Physical Activity Intervention for Cognitive Processing Speed in Multiple Sclerosis

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Abstract

Background: We propose a randomized controlled trial(RCT) of a Social Cognitive Theory-based(SCT), Internet-delivered behavioral intervention targeting lifestyle physical activity(LPA) for yielding improvements in cognitive processing speed(CPS), learning and memory(L/M), symptoms, and quality of life(QOL) among persons with mild multiple sclerosis(MS)-related ambulatory impairment who have impaired CPS.

Methods/design: The study involves a Phase-II, parallel group, RCT design. Participants with MS(N=300) will be randomly assigned on an equal basis(1:1) into behavioral intervention(n=150) or attention and social contact control(n=150) conditions. The conditions will be administered over 6-months by trained behavior coaches who will be uninvolved in screening, recruitment, random assignment, and outcome assessment. We will collect outcome data remotely every 6-months over the 12-month period(baseline, immediate follow-up, and 6-month follow-up) using a treatment blinded assessor. The primary outcome is the raw, oral Symbol Digit Modalities Test as a neuropsychological measure of CPS. The secondary outcomes include the California Verbal Learning Test-II as an objective measure of L/M, and patient-reported outcomes of fatigue, depressive symptoms, anxiety, pain, and QOL. The tertiary outcome is accelerometry as an objective, device-based measure of steps/day for generating a minimal clinically important difference(MCID) value that guides the prescription of LPA for improving CPS in clinical practice. The primary data analyses will involve intent-to-treat principles, and mixed-effects models and logistic regression.

Discussion: If successful, the proposed study will provide Class I evidence for the efficacy of a theory-based, Internet-delivered behavioral intervention focusing on LPA for improving CPS and mitigating its negative impact on other outcomes in persons with MS.

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Background

Multiple sclerosis(MS) is a neurological disease of the central nervous system(CNS) with a prevalence of nearly 1 million adults in the United States(1). MS is initially characterized by inflammatory processes and demyelination of axons, and eventual transection of axons and loss of neurons in the brain, brain stem, and spinal cord(2). This CNS damage manifests in cognitive impairment – one of the most prevalent, impactful, and poorly-managed consequences of MS. Upwards of 67% of patients demonstrate cognitive impairment(3), and cognitive impairment primarily presents as slowed cognitive processing speed(CPS), and secondarily impaired learning and memory(L/M)(3) as a possible by-product of the CPS deficit(4). MS-related CPS impairment further is associated with worse fatigue, depression, anxiety, pain, and quality of life(QOL)(5–8). There are no FDA-approved pharmacological treatments for CPS impairment in MS(9), and few cognitive rehabilitation studies have directly targeted CPS in persons with MS who have objective CPS impairment(10,11). Exercise training has been unsuccessfully applied for treating CPS impairment in MS because of poor quality trials that were (a) not informed by feasibility/pilot data or (b) included small sample sizes of non-CPS impaired persons with MS(12). This underscores the importance of identifying new approaches for managing CPS impairment in MS, particularly those that can result in benefits on secondary outcomes.

Lifestyle physical activity(LPA) involves accumulating 30+ minutes per day of moderate or vigorous physical activity during planned or unplanned leisure, occupation, household, or transportation activities as part of daily life, and represents a new target for health promotion and rehabilitation in MS(13). Persons with MS overall engage in substantially less LPA than adults from the general population(14), and lower levels of LPA have been associated with worse CPS among ambulatory persons with MS(15,16), particularly those who have CPS impairment(17). The association between LPA and CPS in MS has its basis in a mechanistic framework involving underlying brain-systems(18) and cross-sectional research indicating that lower levels of LPA correlated with smaller volumes of brain structures associated with CPS in MS(19). Such data have been buttressed by a pilot, randomized controlled trial(RCT) indicating that a social-cognitive theory-based(SCT), Internet-delivered behavioral intervention targeting LPA resulted in a clinically meaningful improvement in CPS among those with mild MS-related ambulatory disability(20); there were additional improvements in fatigue, depressive symptoms, anxiety, pain, and QOL(21). The aforementioned Class IV and Class II evidence(22) supports the timeliness of a Phase-II, RCT that may provide the first Class I evidence for LPA as a treatment for slowed CPS in MS.

The current protocol paper describes the design of a Phase-II, RCT that examines the effects of a SCT-based, Internet-delivered behavioral intervention targeting LPA(23) for yielding immediate and sustained improvements in CPS, L/M, symptoms, and QOL outcomes among persons with mild MS-related ambulatory impairment who demonstrate impaired CPS. We will test the hypothesis that the behavioral intervention will yield immediate and sustained improvements in the primary outcome of CPS and secondary outcomes of L/M, symptoms, and QOL compared with an active control condition in persons with mild MS-related ambulatory impairment who have CPS impairment.

Methods

Experimental Design Overview

The study was approved by the University of Illinois Chicago Institutional Review Board(IRB#2022–0084), and the project was registered on clinicaltrials.gov(NCT04518657). The study involves a Phase-II, parallel group, RCT design. Participants(*N*=300) who satisfy inclusion/exclusion criteria will be randomly assigned on an equal basis(1:1) into the behavioral intervention(*n*=150; focusing on LPA) or attention and social contact control(*n*=150; focusing on general wellness) conditions using a random numbers sequence with concealed allocation. The conditions will be administered over 6-months by trained behavior coaches who will be uninvolved in screening, recruitment, random assignment, and outcome assessment; the administration of the conditions will be evaluated using a fidelity monitoring plan(24). We will collect primary, secondary, and tertiary outcome data remotely every 6-months over the 12-month period(i.e., baseline, immediate follow-up, and 6-month follow-up) using a treatment blinded assessor. The primary outcome is the oral Symbol Digit Modalities Test(SDMT; 25) score as a neuropsychological measure of CPS. The secondary outcomes include the total learning score from the California Verbal Learning Test-II(CVLT-II; 26) as an objective measure of L/M, and measures of fatigue, depressive symptoms, anxiety, pain, and QOL. The tertiary outcome is accelerometry as an objective, device-based measure of steps/day for generating a minimal clinically important difference(MCID) value that may guide future prescription of LPA for improving CPS. The primary data analyses will involve intent-to-treat principles, and mixed-effects models and logistic regression. This study does not include a data safety monitoring board as it is (a) not an NIH-defined Phase-III clinical trial, and further (b) is a low risk, behavioral intervention with minimal side effects conducted in a population that is not identified as vulnerable.

Participants

The proposed sample of 300 persons with MS will be recruited from across the United States through electronic advertisements disseminated by the National MS Society(NMSS). The advertisements will describe the study as comparing two different approaches for lifestyle behavior change delivered through the Internet for managing consequences of MS and improving health indicators. Those interested in participation will contact the study project coordinator who will describe the study and its procedures, answer all questions, conduct a screening for inclusion/exclusion criteria, and, if eligible, collect information for remotely obtaining informed consent through AdobeSign®.

Inclusion/Exclusion.—There is a two-stage screening process with the inclusion/exclusion criteria per stage listed in Table 1.

Attrition.—We have experienced low attrition(5–10%) in previous RCTs of this physical activity behavioral intervention(23). We estimate that attrition could be higher in this RCT based on recruiting a sample with CPS impairment, and therefore plan for an attrition rate of 20%.

Power Analysis.—The power analysis for the sample size estimate was based on a pilot RCT(20) of the behavioral intervention compared with a waitlist control condition for improving SDMT scores in persons with MS who had mild ambulatory disability, but not CPS impairment. We observed a difference between the intervention and control conditions of 4.48 units on the oral SDMT and the observed standard deviation was 12.65 units. Based on those findings, a sample size of 127 per condition will yield 80% power for detecting a difference in means of 4.48(i.e., the difference between means of the two treatment groups of 4.48 assuming that the common standard deviation is 12.65 using a two-group *t*-test with a 5% two-sided significance level). Our goal is to recruit 300 participants(150 per condition) as yielding adequate power, even with 20% attrition rate.

Outcomes

Overview.—The primary outcome is the oral SDMT as a measure of CPS, whereas the secondary outcomes are the total learning score from the CVLT-II as a measure of L/M and patient-reported outcomes of fatigue, depressive symptoms, anxiety, pain, and QOL. The tertiary outcome is accelerometry as an objective, device-based measure of LPA. Outcomes will be assessed at baseline, immediate follow-up, and long-term follow-up by a treatment-blinded assessor who has been thoroughly trained based on manualized operating procedures. The same outcome assessor will perform baseline, immediate follow-up, and long-term follow-up assessments, and the assessor will not be involved in random assignment or delivery of the conditions.

Primary Outcome.—The primary outcome for measuring CPS will be the oral version of the SDMT(25). The SDMT requires the examinee to substitute a number for a randomized presentation of a geometric figure. The appropriate number is provided in a key containing the numbers 1 through 9 each paired with a different geometric figure. The total number of correct responses in 90 seconds(i.e., raw score) is the primary outcome of the SDMT. The SDMT is considered a more pure measure of CPS, as it relies less on working memory(i.e., the central executive) than other neuropsychological measures included in MS research(e.g., PASAT)(27). The SDMT is a better predictor of whole-brain atrophy and T2-lesion volume than the PASAT(27), and the SDMT has emerged as the best predictor of future cognitive decline in persons with relapsing-remitting MS(28). The oral SDMT will be administered remotely(29) via Zoom™ videoconferencing. Participants will be sent a link for accessing the videoconference suite via email. Upon entering the videoconferencing suite, the outcome assessor will confirm that the participant is seated alone in a quiet room without distractions. Using the Zoom™ screen-sharing feature, the SDMT will be administered using identical instructions and procedures as the paper-and-pencil version of the oral SDMT(25). We will include alternate forms of the SDMT across the outcome assessment time points(30).

Secondary Outcomes.—L/M will be measured using the CVLT-II(26). The CVLT-II involves the examiner reading a list of 16 words, with four items belonging to four categories (e.g., vegetables, animals, furniture, modes of transportation) that are randomly arranged. The list is read aloud five times in the same order, with each word voiced at a rate of approximately one word per second. Participants are instructed to recall as many items as possible, in any order, following each list reading. The primary outcome

of the CVLT-II is the total number of correct words identified over the five trials (i.e., raw total learning score)(26). The CVLT-II has been established as feasible and valid for remote delivery(31). This will be administered remotely(31) immediately after the SDMT via Zoom™ videoconferencing, and we will include alternate forms of the CVLT-II across the outcome assessment time points(30).

Fatigue, depression, anxiety, pain, and QOL will be measured by the Fatigue Severity Scale(FSS)(32), Modified Fatigue Impact Scale(MFIS)(33), Hospital Anxiety and Depression Scale(HADS)(34), Short-Form McGill Pain Questionnaire(SF-MPQ)(35), and 29-item Multiple Sclerosis Impact Scale(MSIS-29)(36), respectively. Those patient-reported outcomes will be delivered electronically through Qualtrics and have demonstrated strong psychometric properties in representative samples of persons with MS(37–40).

Tertiary Outcome.—The tertiary study outcome is objective, device-measured steps/day by ActiGraph model GT3X+ accelerometers(Actigraph Corporation, FL) over a seven-day period. The accelerometer will be placed on an elastic belt that is worn around the waist over the non-dominant hip during the waking hours of a seven-day period. The data from the accelerometer will be downloaded, processed into one-minute epochs using ActiLife(Actigraph Corporation, FL) software, and then scored for wear time and steps/day(41). Only data from valid days (wear time ≥600 minutes) will be included in the analyses(41). We will average the data over two or more valid days for the outcome of steps/day during the previous week, as this provides a reliable estimate of LPA(42). This treatment of accelerometer data will permit the generation of other measures such as minutes/day spent in light, moderate, and vigorous LPA and sedentary behavior.

Random Assignment.—After obtaining consent and collecting baseline data, participants will be randomly assigned into either the behavioral intervention condition or the attention and social contact control condition using a computerized process based on a random numbers sequence. Group allocation will be concealed(i.e., opaque sealed envelopes), and further verified by a second individual via duplicate copy of the randomization table as a procedure for ensuring no mistakes. Participants will not be informed that the behavioral intervention condition represents the experimental treatment and the overall wellness condition represents the active control. To do this, the study will be advertised and described as comparing two different approaches for lifestyle behavior change delivered through the Internet for managing consequences of MS and improving health indicators among persons with MS.

Intervention and Control Conditions

The behavioral intervention(BIPAMS; 23) focuses on promotion of LPA through walking during ambulatory activities of daily living and accumulating greater steps/day and minutes/day of LPA. The control condition(WellMS; 23) focuses on general wellness(e.g., sleep, diet). Both conditions consist of two primary components, namely a dedicated Internet website and one-on-one video chats with a behavioral coach for parity(Table 2), and the full description of the conditions is provided in the Supplement. We have reported on the effectiveness of the behavioral condition for immediate and sustained increases in LPA in

persons with MS(23). We further note that walking-based LPA, in particular, represents a behavior positively associated with CPS in cognitively-impaired persons with MS(17).

Fidelity Monitoring Plan.—We will include a comprehensive fidelity monitoring plan based on the NIH Behavior Change Consortium treatment fidelity workgroup(43) and a recently completed Phase-III RCT for changing LPA in MS(24).

Procedure.—Interested participants will contact the project coordinator who will describe the study and what it entails, and then conduct the two-level screening for inclusion criteria. The project coordinator will then distribute the informed consent document among participants who satisfy inclusion criteria through AdobeSign®. This will be followed by a phone call to ensure that the participants received the document, understand the study and its procedures, and provide informed consent. Participants will complete enrollment by returning a signed copy of this document through AdobeSign®. Once enrolled, the project coordinator will contact participants and schedule baseline data collection. The project coordinator will send the participant a link for electronic completion of the questionnaires. The battery of questionnaires will be delivered using Qualtrics and will take 30 minutes for completion. The project coordinator will further send the participant a packet containing an accelerometer via certified postal mail. This packet will include instructions for reminding the participants about the importance of wearing the accelerometer as instructed every day during the seven-day period, and provide a pre-stamped and pre-addressed envelope for return postal service. The participants will wear the accelerometer for a seven-day period. The project coordinator will send brief e-mails for reminding participants about wearing the accelerometer daily during the seven-day period. This will be followed by a phone call to make sure the participants wore the accelerometer daily during the seven-day period and returned it through the US postal service. We will then proceed with the remote delivery of the SDMT and CVLT-II for the baseline assessments of CPS and L/M, respectively. Once the baseline assessment is completed, participants will be randomly assigned into either the behavioral intervention(BIPAMS) or the control(WellMS) condition. The intervention/control conditions will be delivered in six waves of approximately 50 participants per wave, and the conditions will be delivered across a 6-month period. Participants will contact the project coordinator via the dedicated toll-free number or e-mail in the occurrence of an adverse event or any other problem; this information will further be collected during video chats with behavioral coaches. The participants will complete the same measurement procedures immediately(i.e., immediate follow-up) and 6-months(i.e., long-term follow-up) after the intervention/control conditions. There will be no website access or chats during the 6-month follow-up period for examining sustainability; this is important for determining the if the behavioral intervention results in relatively permanent and stable improvements in CPS based on the logic of teaching the participants skills, strategies, and approaches based on SCT for initiating and maintaining LPA behavior change over time, as reported in a Phase-III RCT(23). Participants will receive $50 USD remuneration for completing the measures per measurement period for a total of $150 USD.

Data Analyses

Overview.—The data analyses will follow intent-to-treat principles(i.e., include all persons regardless of dropout). We will impute missing data by multiple imputation(e.g., PROC MI in SAS and MI-ANALYZE) and by carrying the last observed value forward. We further will perform exploratory data analyses only among those who complete immediate and long-term follow-up testing(i.e., completer's or per protocol analysis). We will check the data for errors and outliers, and then lock the data set before analyses. The analytic plan will account for potential imbalances that may be considered for adjustment in subsequent analyses, including age, sex, race, MS duration and type, disease-modifying therapy, and relapse occurrence.

The first analysis tests the hypothesis that those who are randomly assigned into the intervention condition will demonstrate (a) improvements from baseline in CPS that (b) are sustained over 6-months of follow-up compared with those in the control condition. The primary analysis will involve a Condition(2 levels: Intervention vs. Control) by Time(3 levels: 0, 6, & 12 months) mixed-effects model on SDMT scores with individual as a random effect and condition and time as fixed effects. We will evaluate key assumptions of the model (i.e., normality, homogeneity, sphericity) and undertake transformations and/or adjustments/corrections, as necessary, including using an AR-1 covariance structure if compound symmetry does not hold. The hypothesized interaction term will be decomposed with follow-up tests and appropriate adjustment of alpha. We will express the overall effect size from the analysis as Cohen's d with standard guidelines for interpretation(44).

The second set of analyses test the hypotheses that those who are randomly assigned into the intervention condition will have (a) improvements from baseline in L/M, fatigue, depressive symptoms, anxiety, pain, and QOL that (b) are sustained over 6-months of follow-up compared with those in the control condition. Those hypotheses will be tested with the same modeling approach described for the SDMT. The overall Type I error will be controlled using a step-down procedure testing first L/M, followed by fatigue, depressive symptoms, anxiety, pain, and then QOL(45).

The third aim will identify the MCID for change in steps/day measured by the accelerometer that is associated with a clinically meaningful increase in the SDMT within the BIPAMS or behavioral intervention condition. The mean increase of 4 points on the SDMT has been a clinically meaningful improvement in CPS(46), and we will use this criterion to define CPS responders and non-responders; we will repeat the analysis with larger SDMT change values for examining the robustness of the MCID for steps/day. Logistic regression analyses will be conducted and the MCID for change in steps/day measured by the accelerometer that maximizes sensitivity and specificity will be identified as the MCID. We will accept this as the MCID if the sensitivity of the results are ≥70% for both sensitivity and specificity. The value of 70% is chosen arbitrarily and we would hope to do better, but we felt stating an a priori target was important for guiding our MCID development.

Conclusion

The proposed research on LPA for improving CPS in ambulatory persons with MS who have CPS impairment is highly innovative based on several study features. The proposed research prescreens persons with MS who have slowed (i.e., impaired) CPS, rather than the traditional approach of including any-and-all persons with MS regardless of cognitive status(12), and this permits an innovative assessment of LPA behavior change as a *treatment* for cognitive impairment. The proposed research is innovative as it examines the efficacy of a remotely-delivered behavioral intervention that targets LPA(23) as a new and highly-accessible approach for treating slowed CPS. The proposed research is further innovative as it administers the neuropsychological assessment of CPS using a remote-delivery mechanism rather than in-person assessment in a research laboratory or neuropsychology clinic. This has recently been highlighted as a priority for cognition research in MS(30,47). The inclusion of remotely-delivered interventions and outcomes is particularly innovative as this approach accounts for specific consequences of CPS dysfunction that restrict access among persons with MS. Indeed, CPS deficits are linked with barriers to travel, transportation, and participation (i.e., loss of driving ability, social isolation, lack of community integration) in this population(48,49). This entirely remotely delivered intervention allows for direct translation among large populations of persons with MS without the usual tailoring and cost issues within each clinic's idiosyncrasies.

There are two additional innovative features of the proposed research, namely the focus on sustainability of improvements in CPS over time and identification of MCID values for LPA change that yield clinically meaningful improvements in CPS. The notion of sustainability is based on the coach clarifying, elaborating, and personalizing the SCT content on the website for maximizing its application for immediate and long-term behavior change. Indeed, the intervention is designed on teaching participants the skills, techniques, and strategies based on SCT for sustained LPA behavior change, and we noted the occurrence of sustained change in LPA over a six-month follow-up period in our published data(23). The proposed research may lay the groundwork for the development and dissemination of "real-world" guidelines for LPA change that can be implemented for the treatment of CPS impairment among MS patients. Such an opportunity for rehabilitation of cognitive functioning using an approach with broad reach and scalability is paramount considering the prevalent, disabling, and poorly-managed nature of CPS impairment in MS and limited resources for its treatment.

We may experience problems with the participants understanding the intervention and control conditions based on the presence of L/M problems as part of a fundamental deficit in CPS. We are minimizing this by screening for severe cognitive impairment and anomia using the TICS-M(50) and COWAT(51), respectively. We further are managing this by enrolling a smaller number of persons(n=50) over 6, non-overlapping recruitment waves, and further having 4 behavior coaches who can devote a greater amount of time with the participants during the one-on-one chat sessions. There may be problems with the remote assessment of CPS and L/M using the planned administration of the SDMT and CVLT-II, respectively. Such problems might include distractions and interruptions in the home environment, and we will minimize this through clear and standardized

instructions regarding the environment(i.e., quiet and free of distractions) and extraneous devices(e.g., TVs and cellular phones). There further may be participant frustration with the remote-delivery of the SDMT and CVLT-II. We note, however, that previous research has reported participants strongly endorse the home-based, remote delivery of SDMT and CVLT-II through telehealth for cognitive assessment, and examiners have strong confidence in the veracity of this methodology(29,31). The SDMT and CVLT-II further have a long history of administration in MS and this makes those measures readily accessible for remote delivery using screen sharing software. Of note, we have successfully administered these neuropsychological tests remotely in cognitively-impaired persons with MS(52). The power analysis was based on preliminary data for the effect of the behavioral intervention on SDMT in a sample that was not prescreened for CPS impairment, and the preliminary data might not represent the treatment effect for those with CPS impairment. Of note, our preliminary cross-sectional data suggest that the association between LPA and SDMT is stronger in those with CPS impairment(17), and we would, by extension, expect a larger effect of the LPA intervention on change in CPS than in our pilot RCT. There may be some attrition during the 6-month follow-up period wherein there is no Internet access or coaching, but this has been minimal in our previous(23) trials using the same approach; this is expected as the intervention condition, in particular, teaches skills, techniques, and strategies for sustaining behavior change.

Collectively, we propose a Phase-II, RCT that examines the effects of a SCT-based, Internet-delivered LPA intervention for yielding immediate and sustained improvements in CPS, L/M, symptoms, and QOL outcomes among persons with mild MS-related ambulatory impairment who demonstrate impaired CPS. If successful, the proposed study will provide Class I evidence(22) for the efficacy of a theory-based, Internet-delivered behavioral intervention focusing on LPA for improving CPS and mitigating its secondary, negative impacts among persons with MS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Inclusion and exclusion criteria for the two-stage screening process.

First Level Inclusion/ Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
	1. Diagnosis of MS	1. Moderate or high risk for contraindications of possible injury or death when undertaking strenuous or maximal exercise using the Physical Activity Readiness Questionnaire (53)
	2. Relapse free in the past 30 days	
	3. Internet and email access	
	4. Willingness to complete the Symbol Digit Modalities Test (SDMT)(25), California Verbal Learning Test-II (CVLT-II)(26), and questionnaires, wear the accelerometer, and undergo randomization	
	5. Insufficient physical activity (i.e., not meeting current physical activity guidelines) based on a health contribution score of less than 14 units from the Godin Leisure-Time Exercise Questionnaire (54)	
	6. Ability to ambulate without assistance and Patient-Determined Disease Steps (PDDS) score between 0 and 2 (i.e., mild ambulatory disability)(55)	
	7. Age of 18 years or older	
	8. English as a primary language	
	9. Modified Telephone Interview for Cognitive Status (TICS-M)(50) over the phone, and participants must have a TICS-M score of 18 or higher(53)	
Second Level Inclusion/ Exclusion Criteria	1. Initial SDMT scores at least 1.5 *SD* below the regression-based normative score for healthy controls (i.e., 7th percentile).	1. Inability to count between 1 and 9 as this is required for the SDMT.
		1. Anomia based on the Controlled Oral Word Association Test (*z*-score of –2.5 or worse) (51)
		2. Poor visual acuity (20/80 or worse indicating moderate visual impairment) based on a remotely-presented vision chart.

Table 2.

Description of intervention components and elements for the BIPAMS and WellMS interventions.

Intervention Components	Elements within Component	BIPAMS	WellMS
Internet Website	***Target***	***Physical Activity***	***General Wellness***
	Source of intervention content	***Social Cognitive Theory***	***National Multiple Sclerosis Society***
	Interactive video courses (#)	10	10
	Resource section	Yes	Yes
	Learn more section	Yes	Yes
	Tracker	***Yes***	***No***
	Forum	Yes	Yes
	Patient voices (#)	***24***	***10***
	Weekly email announcements	Yes	Yes
	Weekly updates announcements	Yes	Yes
	Tips of the week	Yes	Yes
	News and events section	Yes	Yes
One-on-One Video Chats	***Occurrence (#)***	***13***	***9***
	Semi-scripted guide	Yes	Yes
	Adverse event reporting	Yes	Yes
Other	***Pedometer***	***Yes***	***No***
	Goal-setting	Yes	Yes
	Log books/self-monitoring	Yes	Yes

Note. This table is reproduced from a previously published paper of a Phase-III randomized controlled trial targeting lifestyle physical activity (23), and differences between conditions are noted in bold, italicized text within the table. BIPAMS, Behavioral Intervention for Physical Activity in Multiple Sclerosis. WellMS, Wellness for Multiple Sclerosis.