Randomized trial of a teleconference-delivered fatigue management program for people with multiple sclerosis

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ABSTRACT

Background. Previous studies support the efficacy and effectiveness of face-to-face group-based fatigue management education for people with multiple sclerosis (MS). Nevertheless, many people are unable to access these programs due to environmental barriers.

Objectives. To test the efficacy and effectiveness of a group-based, teleconference-delivered fatigue management program for people with MS.

Methods. A randomly allocated two-group time series design with a wait-list control group was used. One hundred and ninety participants were allocated (94 intervention, 96 wait list control). Primary outcomes (fatigue impact, fatigue severity, health-related quality of life [HRQoL]) were measured before, immediately after, at 6 weeks, 3 months, and 6 months post. Secondary outcome (self-efficacy) was measured at the same points.   Effectiveness (intent-to-treat) and efficacy (per protocol) analyses were conducted.

Results. The program was more effective and efficacious than control for reducing fatigue impact but not fatigue severity. Before and after comparisons with the pooled sample demonstrated efficacy and effectiveness for fatigue impact, fatigue severity, and 6 of 8 HRQoL dimensions. Changes were maintained for 6 months with small to moderate effect sizes.

Conclusion. The results offer strong support for the viability of teleconference delivered fatigue management education for enabling people with MS to manage this disabling symptom.

INTRODUCTION

Seventy to ninety percent of people with multiple sclerosis (MS) experience fatigue as part of their disease (1;2). This common symptom can have a profound, negative impact on everyday life. Fatigue disrupts the ability to find and maintain employment, engage in everyday activities, and participate in leisure activities (3). Although several pharmaceutical treatments for fatigue have been studied in people with MS, findings have been modest and questions have been raised about methodological quality (4). Several rehabilitation strategies have also been examined, all with some degree of success in reducing the impact and severity of fatigue (5-8). One strategy that has a growing body of supportive evidence is fatigue management education delivered in a face-to-face format in community settings by occupational therapists.

One specific published program - *Managing Fatigue* (9)– has been tested in several studies and in multiple countries (5;10-14). A group of Canadian occupational therapists developed this community-based intervention for adults experiencing fatigue secondary to several chronic illnesses, including MS. The six week course involves weekly two-hour sessions during which an occupational therapist uses mini-lectures, facilitated discussions, activities, goal setting, and homework to convey basic principles of energy management and how to apply concepts in everyday life. Over the past 10 years, evidence supporting the efficacy and effectiveness of the program has been building. The most rigorous evaluation to date involved a randomized control trial involving 169 individuals (5). Results indicated that the program lead to significant reductions in the impact of fatigue on participants' daily life (Fatigue Impact Scale (15)), improved health-related quality of life [HRQOL] (SF-36 Quality of Life Scale (16)), and increased self-efficacy for managing fatigue (Self-Efficacy for Managing Fatigue Scale (17)).

Participants made behavioral changes and experienced the benefits of the course for up to a year after its completion (18).

Despite the findings supporting the *Managing Fatigue* program, its major limitation to date has been its inaccessibility to individuals who cannot travel to the community sites where the program is offered. In response to this problem and requests from people with MS, the program was modified in 2003-2004 to permit telephone teleconference delivery (19). This delivery method is easily accessible, does not require specialized technical support, and therefore has the potential for wide dissemination. In a pilot feasibility study (N=29) using a simple before and after design, all of the primary outcome measures changed in the expected direction (fatigue severity, fatigue impact, HRQOL). Effect sizes ranged from 0.03 (SF-36 Role Emotional subscale) to 0.52 (Fatigue Severity Scale). These results suggested that the teleconference program merited further evaluation. The purpose of this paper is to report the findings of a randomized control trial (RCT) that tested the effectiveness and efficacy of the teleconference fatigue management program for people with MS. Three primary hypotheses were tested:

(1) Individuals who participate in the program will report significantly reduced fatigue impact, reduced fatigue severity, and improved HRQOL immediately post-intervention compared to individuals allocated to the wait-list control group.

(2) Participants will report significantly reduced fatigue impact, reduced fatigue severity, and improved HRQOL after the intervention compared to beforehand.

(3) Any improvements in fatigue impact, fatigue severity, and HRQOL will be maintained six months after the intervention.

METHODS

Trial Design

This study employed a randomly allocated two group time series design with a wait-list control group (see Figure 1). This design was selected because current practice guidelines point to the importance of fatigue management education for people with MS and therefore it would have been unethical to withhold treatment for a pure control group (20). Second, this design replicates the one used for the evaluation of the face-to-face version of this program, therefore maximizing opportunities for comparison. No changes were made to the design after the commencement of the study.

<Insert Figure 1 here>

Participants

Recruitment occurred between November 2007 and April 2009 and involved the distribution of advertising through the MS Society and to Illinois residents participating in the NARCOMS volunteer MS patient registry. Individuals interested in participating in the study contacted the study office. A trained research assistant administered a telephone screening procedure to determine eligibility. Inclusion criteria included: living within the state of Illinois; self-reported diagnosis of MS; 18 years of age or older; functional English literacy (i.e., able to read course materials and carry on telephone conversations in English); a Fatigue Severity Scale score of 4 or greater (i.e., moderate to severe fatigue) (21); and weighted score of at least 12 on the short version of the Blessed Orientation Memory Concentration test (22). Individuals meeting these criteria were mailed a study information sheet, the informed consent documents, and a demographics form. Once they returned a signed consent to the office, they were recontacted by research assistant for allocation.

Intervention

The 6-week, group-based intervention involved weekly 70-minute teleconference calls facilitated by a licensed occupational therapist who had received training from the principal investigator. Table 1 provides a summary of the session contents. The facilitator promoted sharing and discussion by calling on individual participants during the calls. Group size was kept small (5-7 participants) in order to maximize participants' opportunities for interaction, social learning, peer support and development of self-management skills (e.g., problem-solving, self-monitoring, active decision making).

<Insert Table 1 here>

Approximately one week before beginning the program, each participant was sent a cordless telephone, headset, and a program manual. The phone was pre-programmed with the toll-free conference call number. Dial-in instructions were also provided in the manual. The participant manual was divided into six sections, one for each session. Each section contained the session outline, worksheets and homework activities. All materials were designed to minimize the need to write in case participants had fine motor symptoms. The manual was available in alternative formats for individuals who required accommodation. One participant used the large print version.

On the designated day and time, participants and the facilitator dialed into the conference call line. If a participant missed a session, the facilitator contacted the individual by telephone prior to the next session in order to provide an abbreviated session (i.e., key points from the missed session, a summary of the group discussion, and an explanation of the homework assignment for the next session).

Outcome Measures

The primary outcomes were fatigue severity, fatigue impact, and HRQOL. All tools were administered by telephone by a trained research assistant who was not involved in the delivery of the intervention. There were no changes in the primary trial outcomes after the study commenced. Data collection time periods are indicated on Figure 1.

Fatigue impact was measured using the Fatigue Impact Scale (15). This 40-item scale evaluates the perceived impact of fatigue on everyday life and is valid and reliable among people with MS. Respondents rate each statement using a 5-point Likert-type scale ranging from 0 (no problem) to 4 (extreme problem). A total score and three subscale scores (physical, social, cognitive) can be produced from participants' responses. Higher scores reflect greater fatigue impact.

Fatigue severity was measured using the Fatigue Severity Scale (21). Participants rate each of nine items on the 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). Responses are summed and averaged to produce a single score with higher scores indicating more severe fatigue. The scale has documented reliability and validity in MS samples.

HRQOL was measured with the SF-36 (16). This generic measure consist of 36 items that produce 8 subscales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health) and 2 composite measures of quality of life (physical health, mental health). Raw scores are calculated and then transformed into a 0-100 scale using the instructions from the instrument manual. For all scales, a higher transformed score indicates better health. The SF-36 has documented validity and reliability for MS samples.

The secondary outcome, self-efficacy, was measured using the Self-Efficacy for Energy Conservation Questionnaire (17). This questionnaire was specifically designed to address the 14 fatigue management strategies addressed in the *Managing Fatigue* program. For each item,

participants are asked to rate their level of confidence (1 to 10) in their ability to utilize the specific strategies. Responses are summed and averaged, so that higher scores indicate greater confidence in performing strategies. The scale has documented reliability in a MS sample.

Demographic information was also collected from participants for the purposes of description and statistical control. Items included age, sex, educational level, Patient Determined Disease Steps Scale (self-reported severity of MS-related disability) (23), current medications, and involvement in any other rehabilitation programs.

Sample size

Sample size was determined using FIS physical subscale effect size from the pilot study (d=0.51) (19), a 0.05 α-level, a power of 80%, and assumed an attrition rate of 12% over the duration of the study. Results indicated that 140 individuals would be required to detect a significant difference in the primary outcomes attributable to the intervention.

Randomization and Allocation Procedures

Randomization and allocation were completed by the statistician (CC) using a random permutated block design with each block consisting of four people. Within each block, two participants were allocated to the immediate start group and two to the wait-list control group. One hundred and forty opaque envelopes were prepared in advance of recruitment and 50 additional ones were prepared approximately 1 year into recruitment. The envelopes were numbered sequentially and a statement indicating the allocation (immediate or wait-list) was placed in each envelope. As consent forms were returned to the study office, they were numbered sequentially and matched to one of the opaque envelopes. When the research assistant contacted the participant, the appropriate envelope was opened and the participant was offered intervention days and times that corresponded with his/her group allocation. Participants were

blinded to the group to which they were assigned (i.e, immediate start versus wait list control). There was no movement (switching) of participants between the groups after assignment.

Statistical methods

For hypotheses 1 and 2, the primary endpoint was reduction in fatigue impact immediately post-intervention for both efficacy (per protocol) and effectiveness (intent-to-treat) analysis. The group for the efficacy analysis was defined *a priori* as those individuals who participated in 5 of 6 group sessions (n = 138). The group for the effectiveness analysis was defined as all participants who were allocated to an intervention group and had data for at least the first data point, regardless of how many subsequent measurements were completed (n=181). The effectiveness analysis was approached using two different ITT methods: available case with maximum likelihood estimation and last-observation carried forward imputation. Since both methods produced the same pattern of findings, only the available case results are presented in this paper.

To test the first hypothesis, analysis was restricted to the first two measurement times for both groups. Time 1 scores were subtracted from Time 2 scores for each participant. T-tests assessed whether the mean individual participant difference for the immediate group was different (greater) than that of the wait list control group.

Before testing the second hypothesis, paired t-tests were used to compare the first and second scores for participants in the wait list control group to determine if their scores remained stable in the control period. No significant differences were found and therefore the second pre-intervention score was used for subsequent analyses. Mixed effects ANOVA models with random intercept were used to examine the pre-post intervention change across all participants combined (hypothesis 2).

The secondary endpoint for the study was maintenance of the fatigue impact reduction at 6 months post-intervention (hypothesis 3). To evaluate this hypothesis, a mixed effect ANOVA model was used with an unstructured variance-covariance structure, a random intercept and terms for both a linear time and a quadratic time trend. A quadratic time trend is characterized by a significant sharp improvement immediately after the intervention (post 1) and then a gradual stabilization of the improvement across subsequent measurement times. Both FIS and SF-36 outcomes were modeled simultaneously and individually. Since these outcomes had multiple subscales, type I error rates were adjusted (simultaneous models - .05/2; individual models - FIS - .05/3; SF-36 - .05/8).

RESULTS

Participants

A total of 301 individual contacted the study office expressing interest in the study. Figure 2 shows the participant flow through the trial. In total, 190 individuals returned their consent forms and were randomly assigned to the two intervention groups. Nine of these individuals could not be contacted for initial data collection and did not participate in the intervention. Therefore, data were available for 89 participants in the immediate group and 92 in the wait-list control group.

<Insert Figure 2 here>

Baseline characteristics of the 181 participants who started the study are provided on Table 2. Allocation group comparisons confirmed the success of the random allocation. Per protocol participants (i.e., efficacy analysis) had been diagnosed 4.4 years less, on average (13.5 versus 17.9 years, p=.0345), compared to ITT participants (i.e., effectiveness analysis). No other

differences between per protocol and ITT participants were identified. No adverse events were identified during the trial.

<Insert Table 2 here>

Findings for hypothesis 1 are provided on Table 3. In the effectiveness analysis, participants in the immediate intervention group showed significant reduction in all three FIS subscales and in the SF-36 Role-Physical subscale compared to participants in the wait list control group. Similar positive findings were not observed for FSS, the remaining SF-36 subscales (including Vitality), or the self-efficacy measure. Relative to the wait-list control group, participants in the immediate group exhibited significant reductions for the FIS cognitive and social subscales and significant improvement in the SF-36 Role-Physical subscale in the efficacy analysis. No other significant differences were observed between the immediate group and wait-list control group in the efficacy analysis.

<Insert Table 3 here>

Pre-post intervention differences for all outcome measures and the 95% confidence intervals for these differences are summarized in Table 4. As the data show, participants exhibited significant reductions in all three FIS subscales and the FSS, as well as significant improvement in the SF-36 Vitality subscale during both effectiveness and efficacy analysis. Across the other SF-36 subscales, only the physical functioning and bodily pain subscales failed to show significant improvement. Self-Efficacy for Managing Fatigue Scale also showed significant improvement. Overall, the pattern of findings was consistent across effectiveness and efficacy analyses for all outcomes. A post-hoc stratified analysis revealed that the participants in the immediate group experienced significantly greater improvements in two HRQOL subscales

compared to the wait-list control group (role-physical and social). No other differences were found through these additional analyses.

<Insert Table 4 here>

Figures 3, 4 and 5 graphically depict the significant findings for hypothesis 3. As the graphs show, participants' scores on all three FIS subscales (Figure 3), the FSS and self-efficacy scale (Figure 4), and 5 of the 8 SF-36 subscales (Vitality, Role-Physical, Social Functioning, Role-Emotional, Mental Health) changed sharply in the expected direction after the intervention and then were maintained over time. The results from mixed effect ANOVA indicated that these trends were curve-linear and significant. The findings were consistent across both the efficacy and effectiveness analyses for the FIS, SF-36 and self-efficacy measures. For the FSS, effects over time were maintained for the effectiveness analysis, but not for the efficacy analysis.

Table 5 presents the Cohen's D effect size and associated 95% confidence interval (24) for the ITT analysis comparing post-intervention measurements to the pre-intervention measure; similar effects sized were obtained in the efficacy analyses.

<Insert Tables 5 here>

DISCUSSION

The findings of the study partially support all three stated hypotheses. Specifically, the results for hypothesis 1 indicated that the teleconference-delivered group fatigue management intervention was more effective than control for reducing fatigue impact (total and all three subscales) and improving one aspect of HRQOL (role physical subscale). The per protocol analysis supports that the intervention was more efficacious than control for reducing two subscales of fatigue impact (cognitive and social) and the same aspect of HRQOL (role physical subscale). Findings from hypothesis 1 did not provide support for the effectiveness or efficacy

of the intervention in terms of reducing fatigue severity. This result may be an artifact of the study inclusion criteria (FSS≥4) and limited scale range (0-7) as well as the focus of the intervention, which is to enable participants to find ways to manage the impact of fatigue on their daily life. Although the FSS includes some items that are more impact-oriented (e.g., "Fatigue interferes with carrying out certain duties and responsibilities"), it also include items that are more consistent with underlying pathology (i.e., "My fatigue prevents sustained physical functioning"). Hence, the lack of significant findings for hypothesis 1 specific to the FSS may be a function of inadequate conceptual match between the intervention and this measure.

The findings of hypothesis 1 also uncovered improvement in only one aspect of HRQOL and this may be the result of two possible factors. First, the time frame used for hypothesis 1 (immediately post-intervention) may have been insufficient to capture changes in other dimensions of HRQOL as a consequence of the intervention. This possibility is supported by a recent study of 300 people with MS indicated that health related HRQOL as measured by the SF-36 is relatively stable over a 2-year period (25). Furthermore, behavior change takes time to incorporate into daily life (26), and until these changes occur consistently, participants may not experience major changes in HRQOL. Alternatively, it may be that the generic nature of the SF-36 is not capturing important aspects of HRQOL that matter to people with MS (27). Although the SF-36 has been critiqued in the MS literature (28), it was intentionally used in this study to maximize comparability to previous studies (5;19). This decision may have restricted opportunities to capture HRQOL changes as a consequence of the intervention.

The findings for hypothesis 2 supported the effectiveness and efficacy of the intervention for reducing fatigue impact, reducing fatigue severity, and improving 6 out of 8 dimensions of HRQOL. The stronger findings from these analyses suggest that hypothesis 1 may have been

underpowered since the larger, pooled sample uncovered pre-post differences that hypothesis 1 did not. The two dimensions of HRQOL that did not change (bodily pain, physical functioning) are consistent with the fact that intervention does not provide direct strategies that would be expected influence these outcomes. It is interesting to note that participants in the wait list control group experienced fewer HRQOL benefits than those in the immediate group, in post-hoc analysis. This finding is consistent with behavior change theories such as the Transtheoretical Model of Behavior Change (26) which asserts that an individual's readiness for change is an important factor in actually making behavioral changes. It may be that participants lost some of their initial motivation to manage their fatigue while waiting for the intervention, contributing to reduced overall HRQOL benefits. This possibility will be important to examine in future research and to consider in terms of rehabilitation caseload management (e.g., avoiding long waitlists for services).

The effects found immediately after the intervention were maintained at the three month and six month follow-up, indicating that the effects of the intervention were lasting. This maintenance suggests that participants were integrating fatigue management strategies into everyday life, even after the intervention ended. This finding is consistent with previous research that has asked people with MS about the ways in which they continue to use fatigue management strategies (18;29).

Overall, the pattern of results for this study was consistent with the results of the evaluation of the face-to-face group delivery of method of this program (5;30). Although we found smaller effect sizes across all outcomes as compared to the face-to-face version, we were able to attract a more diverse sample in terms of age, race/ethnicity, education and geographical location. Our participants were older (55 years versus 48 years) and had MS longer (15 years

versus 9 years). In addition, our sample included 4% more non-white participants (12% versus 8%) and were distributed across an entire state rather than clustered in two major urban centers. This level of diversity suggests that the teleconference delivery may be more accessible and more attractive to a wider range of individuals.

Study Limitations

The major limitation of this study was its use of self-report rather than objective measures of MS disability. An objective measure of MS disability would have provided a more definitive assessment of disability status, and would have been more consistent with data gathered in other fatigue management intervention studies. However, the use of an objective measure would have required an in-person screening process which, in turn, would have made the study inaccessible for some participants. One way to address this limitation in future studies would be to obtain clinical disability data from a participant's neurologist (e.g., EDSS score). A second limitation of the study is that only the participants were blinded to their allocation status, not the research assistants who were conducting the outcome measures. Nevertheless, these individuals were not involved in the delivery of the intervention, which provided some degree protection against bias. Finally, although co-intervention was tracked and was not significantly different between the groups, there is no way to know whether or not other interventions contributed to or contaminated the results.

CONCLUSION

The results of this RCT support that the teleconference delivered fatigue management education facilitated by occupational therapists is superior to a wait list control condition for reducing fatigue impact, improving the role-physical subscale of the SF-36, but not for reducing fatigue severity. When the participants were pooled, and before and after scores compared, the

intervention demonstrated efficacy and effectiveness for reducing fatigue impact and fatigue severity, and for improving 6 of 8 dimensions of HRQOL. These changes were maintained for 6 months after the completion of the intervention. Together, these findings offer strong support for the viability of teleconference delivered fatigue management education for enabling people with MS to manage this disabling symptom.

Acknowledgments

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Table 1: Overview of the Intervention Sessions.

Session	Major Topics for Session
1	• Introductions, overview and orientation to course • Discussion of fatigue – Discussion of fatigue, the impact of fatigue on life and the fatigue cycle. • Overview of major fatigue management principles. • Instructions for homework (planning and using rests).
2	• Homework review • Teaching session & discussion: Communication - when, where and how to communicate with others about fatigue. • Instructions for homework (communicating with others).
3	• Homework review • Teaching session & discussion: Body mechanics, using tools and technology. • Instructions for homework (changing body positions and using tools)
4	• Homework review • Teaching session & discussion: Activity analysis, evaluating priorities, and making active decisions. • Instructions for homework (analyzing and modifying a fatiguing activity).
5	• Homework review • Teaching session & discussion: Living a balanced life, taking control of your day, analyzing and modifying a day. • Instructions for homework (planning a day to manage fatigue)
6	• Homework review • Teaching session: Course review • Goal Setting and discussion: long term vs. short term goals. • Wrap-up.

TABLE 2: Characteristics of the Study Sample.

Characteristics	ITT (n = 181)		Per Protocol (n =138)	
	Mean	*SD*	*Mean*	*SD*
Age (in years)	56	9	55	8
Fatigue Severity Scale Score	5	1	5	1
Years Since Symptoms Started	20	11	19	10
Years Since Diagnosis	15	9	14	8
PDDS	4	2	4	2
	n	*%*	*n*	*%*
Gender				
Women	143	79	110	80
Male	38	21	28	20
Ethnicity				
White	159	88	123	89
African-American	18	10	13	9
Hispanic	0	0	0	0
Other	1	1	1	1
I'd Rather Not Say	2	1	0	0
No Response	1	1	1	1
Type of MS				
Relapsing - Remitting	95	52	73	53
Secondary Progressive	39	22	33	24
Primary Progressive	16	9	11	8
Progressive Relapsing	11	6	7	5
Unknown	17	9	11	8
Missing	3	2	3	2
Education				
> 15 Years	89	49	72	52
12 - 15 Years	88	49	63	46
≤ 12	4	2	3	2
Employment Status				
Full Time (≥ 40 Hrs/Wk)	38	21	31	22
Part Time (20 - 39 Hrs/Wk)	12	7	8	6
Part Time (1 - 19 Hrs/Wk)	16	9	12	9
Unemployed - Unable to Find Employment	7	4	7	5
Unemployed - Chose Not to be Employed	9	5	6	4
Unemployed - On Disability Insurance	68	38	54	39
Retired	30	17	19	14
Missing	1	1	1	1

TABLE 3: Results from t-test of within-person differences (i.e., Week 7 – Week 1) comparing Immediate group to Wait-list control group.

Outcome	Effectiveness Analysis Intent-To Treat (n = 181)				Efficacy Analysis Per Protocol (n = 138)			
	Mean	STD	t	p	Mean	STD	t	p
Fatigue Impact Scale								
Cognitive	-3.12	6.10	-3.27	0.0013*	-3.72	5.75	-3.76	0.0003*
Physical	-2.53	6.47	-2.48	0.0144*	-2.58	6.42	-2.31	0.0223
Social	-6.01	12.06	-3.13	0.0021*	-5.98	11.26	-3.02	0.0030*
Fatigue Severity Scale	-0.18	0.96	-1.21	0.2403	-0.13	0.94	-0.81	0.4212
SF-36								
Vitality	6.68	15.70	1.50	0.1367	5.41	16.00	1.96	0.0516
Role-Emotion	8.69	40.26	1.38	0.1699	9.85	38.28	1.49	0.1375
Mental Health	5.32	13.38	2.53	0.0123	5.18	13.70	2.19	0.0304
Social Function	7.54	25.35	1.90	0.0594	7.47	25.87	1.68	0.0960
General Health	3.37	14.96	1.44	0.1522	4.31	14.66	1.71	0.0905
Role-Physical	18.06	30.49	3.78	0.0002*	18.90	29.54	3.71	0.0003*
Physical Function	1.20	12.40	0.62	0.5384	-0.14	12.86	-0.06	0.9515
Bodily Pain	5.02	19.64	1.63	0.1044	3.94	18.97	1.21	0.2300
Self-Efficacy	0.14	1.56	0.57	0.5679	0.27	1.57	0.99	0.3235

*Indicates significant difference after adjusting for multiple tests (P<.05/3 for FIS subscale and P<.05/8 for SF-36 subscales)

TABLE 4: Results from mixed effects ANOVA models with unstructured covariance examining pre-post intervention differences in outcome of interest.

Outcome	Effectiveness Analysis ITT (n = 181) Pre-Post Difference (95% CI)		Efficacy Analysis Per Protocol (n = 138) Pre-Post Difference (95% CI)	
Fatigue Impact Scale				
Cognitive	-3.11	(-4.15, -2.06)*	-3.49	(-4.58, -2.39)*
Physical	-3.29	(-4.36, -2.22)*	-3.55	(-4.66, -2.44)*
Social	-7.12	(-9.06, -5.18)*	-7.50	(-9.55, -5.45)*
Fatigue Severity Scale	-0.30	(-0.46, -0.14)*	-0.31	(-0.48, -0.14)*
SF-36				
Vitality	6.99	(4.29, 9.69)*	7.61	(4.64, 10.58)*
Role-Emotion	10.08	(4.13, 16.04)*	10.11	(3.71, 16.51)*
Mental Health	5.78	(3.89, 7.67)*	5.69	(3.67, 7.71)*
Social Function	7.95	(4.09, 11.82)*	7.46	(3.20, 11.71)*
General Health	3.61	(1.37, 5.85)*	3.54	(1.10, 5.98)*
Role-Physical	11.12	(6.22, 16.02)*	11.58	(6.30, 16.86)*
Physical Function	2.62	(0.52, 4.71)	2.18	(-0.07, 4.33)
Body Pain	4.01	(0.90, 7.11)	4.28	(0.97, 7.60)
Self-Efficacy	0.51	(0.26, 0.76)*	0.52	(0.25, 0.79)*

*Indicates significant difference after adjusting for multiple tests ($P<.05/3$ for FIS subscale and $P<.05/8$ for SF-36 subscales

TABLE 5: Cohen's d Effect-size across time.

	Effectiveness Analysis (ITT)							
	Post 1		Post 2		3 MTH		6 MTH	
Outcome	Effect Size	95% CI	Effect Size	95% CI	Effect Size	95% CI	Effect Size	95% CI
Fatigue Impact Scale								
Cognitive	0.48	(0.43, 0.53)	0.59	(0.52, 0.66)	0.58	(0.48, 0.68)	0.55	(0.46, 0.64)
Physical	0.49	(0.41, 0.57)	0.52	(0.42, 0.62)	0.68	(0.55, 0.82)	0.61	(0.50, 0.72)
Social	0.59	(0.52, 0.66)	0.60	(0.51, 0.69)	0.65	(0.53, 0.77)	0.67	(0.58, 0.76)
Fatigue Severity Scale	-0.31	(-0.36, -0.26)	-0.23	(-0.25, -0.21)	-0.38	(-0.45, -0.31)	-0.33	(-0.36, -0.30)
SF-36								
Vitality	0.41	(0.12, 0.70)	0.39	(0.09, 0.69)	0.35	(0.07, 0.63)	0.33	(0.06, 0.60)
Role-Emotion	0.26	(0.02, 0.50)	0.32	(0.01, 0.63)	0.22	(-0.09, 0.53)	0.17	(-0.07, 0.41)
Mental Health	0.48	(0.29, 0.70)	0.34	(0.13, 0.55)	0.16	(-0.01, 0.32)	0.27	(0.04, 0.50)
Social Function	0.32	(0.05, 0.59)	0.39	(0.04, 0.74)	0.49	(0.16, 0.82)	0.29	(0.02, 0.56)
General Health	0.26	(0.12, 0.40)	0.16	(0.03, 0.29)	0.07	(-0.05, 0.19)	0.19	(0.03, 0.35)
Role-Physical	0.37	(0.10, 0.64)	0.31	(0.03, 0.59)	0.36	(0.03, 0.69)	0.39	(0.07, 0.71)
Physical Function	0.19	(0.10, 0.28)	0.29	(0.19, 0.39)	0.32	(0.24, 0.40)	0.27	(0.17, 0.37)
Body Pain	0.20	(0.07, 0.33)	0.12	(-0.02, 0.26)	0.12	(-0.03, 0.27)	0.05	(-0.07, 0.17)
Self-Efficacy	0.28	(-0.41, 0.97)	0.36	(-0.34, 1.06)	0.40	(-0.58, 1.38)	0.41	(-0.47, 1.29)

NOTE: Pre intervention Measurement is the reference point.

Figure 1: Graphic Depiction of Study Design

Week 0	Intervention Group	Assessment Time (Week)									
		1	2 to 6	7	8 to 12	13	19	25	37	49	61
Screening	Immediate Intervention	Pre – Test	Intervention	1st Post Test		2nd Post Test		3-Month Follow-up		6-Month Follow-up	
	Wait-List Control	1st Pre – Test		2nd Pre - Test	Intervention	1st Post Test	2nd Post Test		3-Month Follow-up		6-Month Follow-up

Figure 2: Participant flow through the trial


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                    ┌─────────────┐
                    │    301      │────────→ ┌────────────────────────────┐
                    │  inquiries  │          │ 46 not screened            │
                    └─────────────┘          │ (8 out of state,16 chose not│
                           │                 │ be screened, 22 unable to  │
                           ↓                 │ contact)                   │
                    ┌─────────────┐          └────────────────────────────┘
                    │    255      │
                    │  screened   │────────→ ┌────────────────────────────┐
                    └─────────────┘          │ Excluded - 65              │
                           │                 │ (26 not eligible, 39 did not│
                           ↓                 │ return consent form)       │
                    ┌─────────────┐          └────────────────────────────┘
                    │    190      │
                    │  enrolled   │
                    └─────────────┘
```

94 immediate group

96 wait-list control

77 - Received intervention
6 - Did not receive intervention (5 no baseline data)
10 - Discontinued intervention
1 - Lost to follow-up

74 - Received intervention
8 - Did not receive intervention (4 no baseline data)
10 - Discontinued intervention
4 - Lost to follow-up

Effectiveness analysis = 89
Efficacy analysis = 68

Effectiveness analysis = 92
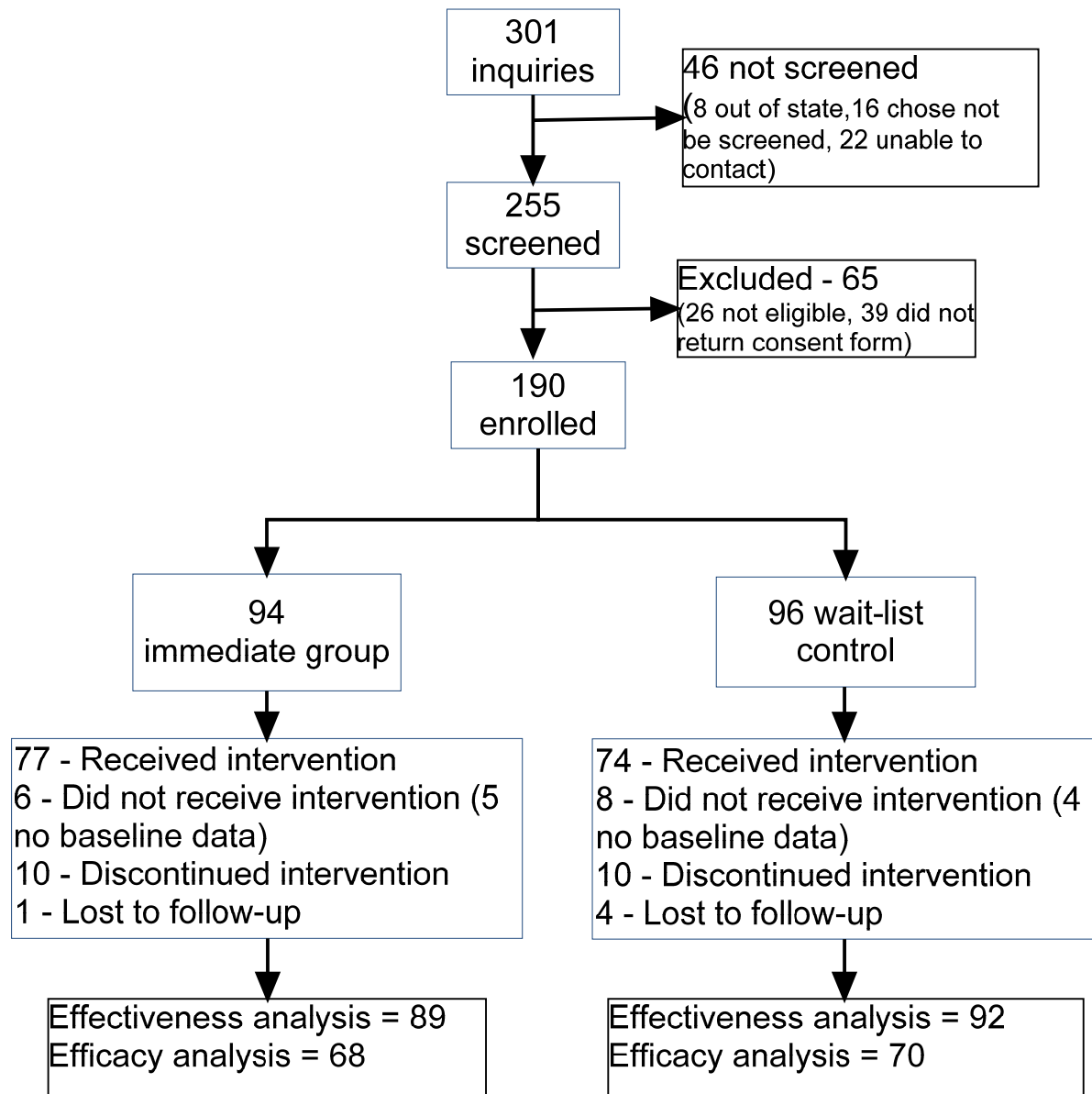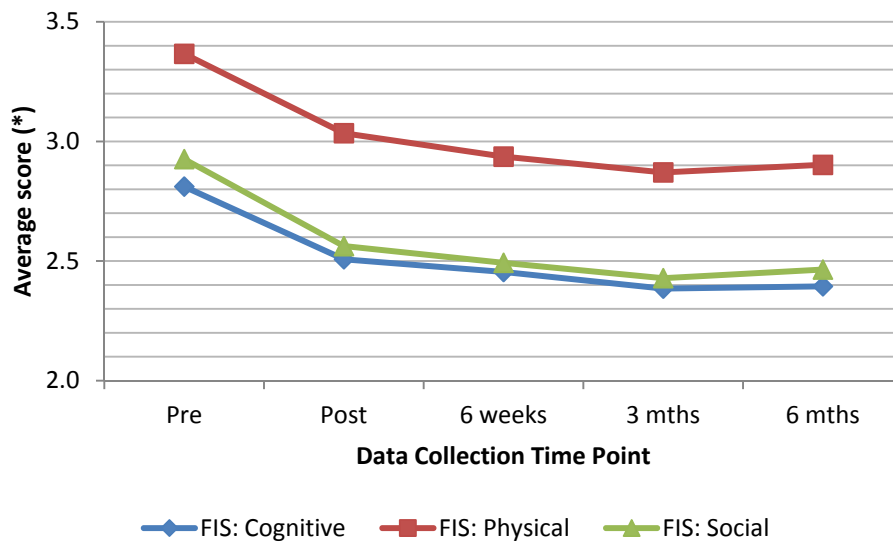Efficacy analysis = 70

Figure 3: Average observed FIS subscale scores across time, by FIS subscale. For all subscales, significant quadratic time effects were found based on mixed effect ANOVA models. Score reductions reflect less impact of fatigue on daily life.

Note: Average rather than total subscale scores are shown to limit the length of the vertical axis.

Figure 4: Average SF-36 subscale scores for which significant quadratic time effects were observed over time based on mixed effect ANOVA models. Subscales not displayed were not significant over time. Higher scores reflect greater health-related quality of life.
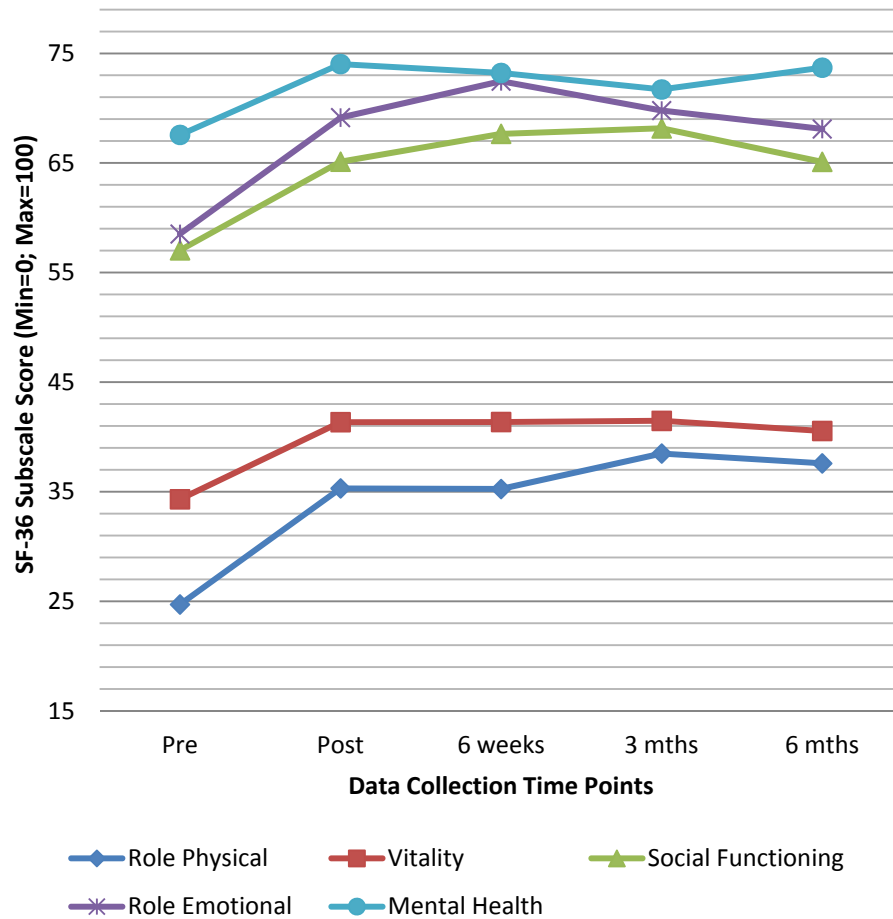
Figure 5: Average observed FSS and Self-efficacy scores, over time. For both scales, significant quadratic time effects were found based on mixed effect ANOVA models. FSS potential range equals 0-7 (lower scores indicate less severe fatigue). Self-efficacy range equals 0-10 (higher scores indicate higher self-efficacy).