PROTOCOL

An Online Educational Course for People with MS: A randomised controlled trial of course effectiveness

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Sponsor/s:
None

CONFIDENTIAL

Statement of Compliance

This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 updated 2018). Australian Code for the Responsible Conduct of Research, 2018 *(the Code)* and the principles of the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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1. STUDY SYNOPSIS

Provide brief information

Title:	An Online Educational Course for People with MS: A randomised controlled trial of course effectiveness
Short Title:	Online Educational Course RCT
Design:	Randomised controlled trial (RCT)
Study Centres:	The University of Melbourne
Hospital:	None
Study Question:	This study proposes to conduct a RCT to test the effectiveness of an intervention/product providing information on MS-related lifestyle behaviour in the form of an online course that was developed by researchers from the Neuroepidemiology Unit (NEU) at the University of Melbourne in modifying participant's behaviour and improving health outcomes in people with MS. The control arm consists of an online course providing general MS-related material that was also developed by the NEU. The research question of the study is: Will a Multiple Sclerosis (MS) Online lifestyle modification course that delivers evidence-based lifestyle modification recommendations to people with MS (the intervention) result in sustained lifestyle behaviour change and improved health outcomes post-intervention compared with people undertaking an MS Online standard-care course (the control)?
Study Objectives:	To quantitatively and qualitatively assess the outcomes of participants enrolled in the MS Online intervention course compared with the MS Online standard-care course in an RCT. In particular, we aim to: 1) To assess the uptake and maintenance of recommended lifestyle modifications in a cohort of people with MS after undertaking an MS Online intervention course compared with people undertaking an MS Online standard-care course. 2) To assess whether people with MS undertaking and adhering to the guidelines of the MS Online intervention course have improved health outcomes of depression, fatigue, disability, and quality of life over the short-term and medium-term compared with people undertaking and adhering to the MS Online standard-care course.

Primary Objectives:	To determine whether participants adhering to lifestyle modification recommendations outlined in the MS Online intervention course have clinically significant increased health-related quality of life (HRQOL) in both domains of physical and mental health compared with participants following recommendations of the MS Online standard-care course. These outcomes will be examined in the short-term (6 and 12 months) and in the medium-term (2.5 years). That is, we aim to determine whether participants in the Online intervention course following recommended lifestyle modifications have clinically significant and material increases in Physical Health Composite (PHC) and Mental Health Composite (MHC) scores, as derived from the validated tool designed to measure HRQOL in people with MS (MSQOL-54) compared with participants following recommendations of the Online standard-care course.
Secondary Objectives	To determine whether participants following the lifestyle modification recommendations in the Online MS intervention course have improved depression, anxiety, fatigue, disability and self-efficacy in the short-term and medium-term compared with people following recommendations of the Online MS standard-care course.
Inclusion Criteria:	Eligible participants must: 1. Be able to read, write, and speak English; 2. Be 18 years old or over; 3. Have a confirmed diagnosis of relapsing-remitting MS by a neurologist preceding recruitment; 4. Be able to access the internet and be able to view sessions.
Exclusion Criteria:	Exclusion criteria of participants include: 1. Experiencing any serious co-morbid chronic illness or neurological illness/injury other than MS that would threaten regular participation or significantly affect the outcome measures in its own right, such as motor neurone disease or stroke, as determined by the study investigators; ~~2.~~ Currently participating in another study ~~or self-management program involving modification of lifestyle.~~
Number of Planned Participants:	1054 participants, 527 in each arm at 1:1 allocation (intervention and standard-care arm)
Investigational product:	Not applicable
Safety considerations:	Participation in the study poses no physical risk to participants as the proposed RCT involves taking part in an Online MS

	educational course and completing self-reported questionnaires and possibly two semi-structured qualitative interviews. Any potentially psychological risks from participating in the study have been addressed by contingency plans to provide links to Online help resources and the contact details of study team members to provide further information for participants.
Statistical Methods:	Analysis of outcomes: Characteristics of quality of life (QoL) will be measured by the MSQOL-54, including physical and mental health composite scores and multiple subdomains. Linear regression will be used to determine cross-sectional and prospective relationships with QoL. Characteristics of disability will be assessed using linear regression. Characteristics of dichotomous clinically significant fatigue and depression will be assessed by log-binomial regression. Characteristics of self-efficacy composite scores will be assessed by linear and log-binomial regression for continuous and dichotomised self-efficacy, respectively. All models will be assessed for potential clinical and demographic confounders and appropriate adjustments will be made in analyses.
Subgroups:	Not applicable
Consumer Involvement	Consumers have been involved in the co-design of the MSOC RCT. A consumer advisory group comprising of 6-8 people with MS in a series of focus groups was involved in the co-design of the MS Online intervention and standard-care course. The devised course was then tested in a feasibility study (MSOC – Feasibility) involving a subgroup of people with MS (n = 31) and the quantitative and qualitative outcomes of the MSOC – Feasibility study were used to co-design the MS Online intervention and standard-care courses in the proposed RCT.

2. GLOSSARY OF ABBREVIATIONS & TERMS

Insert or delete information as required

Abbreviation	Description (using lay language)
MS	Multiple Sclerosis
RCT	Randomised Controlled Trial
MSOC	Multiple Sclerosis Online Course
MSOC - Feasibility	Multiple Sclerosis Online Course - Feasibility study
MSOC - RCT	Multiple Sclerosis Online Course – Randomised Control Trial
QoL	Quality of life
HRQOL	Health Related Quality of life
UoM	The University of Melbourne
HREC	Human Research Ethics Committee
NHMRC	National Health and Medical Research Council
DHQ	Dietary Habits Questionnaire
HADS	Hospital Anxiety and Depression Scale
MSQOL-54	Multiple Sclerosis Quality of Life-54 instrument
IPAQ-SF	International Physical Activity Questionnaire - Short Form
FSS	Fatigue Severity Scale
MAQ	Mindfulness Adherence Questionnaire
PDDS	Patient-Determined Disease Steps
PHC	Physical Health Composite
MHC	Mental Health Composite
MSPSS	Multidimensional Scale of Perceived Social Support
UWSE	University of Washington Self-Efficacy

3. STUDY SITES

3.1 STUDY LOCATION/S

[List all locations, their address & contact details this study or parts of the study will be conducted]

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4. INTRODUCTION/BACKGROUND INFORMATION

4.1 LAY SUMMARY

The Multiple Sclerosis Online Course (MSOC), both the intervention and standard-care arms, was delivered as part of a feasibility study (MSOC - Feasibility study) in April to June 2021. In the MSOC – Feasibility study 31 participants from Australia, New Zealand, and the United States completed the MS Online course (n=15 intervention course and n=16 standard-care course). Examination of the acceptability and usability in the MSOC – Feasibility study was conducted via quantitative and qualitative analyses, with the results of these analyses currently in preparation for publication in a peer-reviewed journal.

In the proposed study, we plan to perform a randomised controlled trial (RCT) utilising the results from the MSOC – Feasibility study. That is, the MS Online course has been modified and redeveloped to test the effectiveness of the MS Online intervention and standard-care courses in a large international RCT (MSOC – RCT).

This RCT will analyse participant uptake and retention, adoption and adherence to lifestyle recommendations and health outcomes at baseline, and 6 months, 12 months, and 2.5 years after completing either the MS intervention or standard-care course. The significance of this study is that the RCT will test:

1) whether an MS Online educational intervention course, compared with a standard-care course, can change behaviour in people with MS and
2) whether an MS online educational intervention course, compared with standard-care course, leads to superior improved health outcomes in people with MS.

4.2 INTRODUCTION

Although genetic factors are responsible for roughly 25% of the risk of multiple sclerosis (MS) onset, they play less of a part in disease progression. By contrast, disease progression and disability are associated or influenced by environmental factors including modifiable lifestyle behaviours. These risk factors include smoking, a diet high in saturated fat and low in omega-3 polyunsaturated fatty acids, lack of physical activity, inadequate vitamin D level, and stress. The amelioration of these risks is associated with a reduction in the chronic inflammatory state associated with MS(Fragoso, 2014), and subsequent improved health outcomes including improved mental and physical health quality of life(Hadgkiss, Jelinek, Weiland, et al., 2015; Jelinek et al., 2013; Marck et al., 2014), reduced relapse rate(D'Hooghe M, Nagels, Bissay, & De Keyser, 2010), depression risk(K. L. Taylor et al., 2014), clinically significant fatigue(T.J. Weiland et al., 2015; T. J. Weiland et al., 2015), and less disability and symptom burden(Fitzgerald et al., 2018; Jelinek et al., 2016). Lifestyle modification of these risk factors represents an effective, low cost and low risk intervention in MS.

Studies of a lifestyle modification programs for MS including evidence-based recommendations regarding diet, exercise, stress management, sun exposure, and vitamin D delivered via intensive face-to-face residential workshops. These workshops have demonstrated 11.3% and 19.5% improvement in overall quality of life at one and 5-year time-points post workshop, respectively, compared to baseline measures (Hadgkiss et al., 2013), and that behaviour change was feasible and sustainable (Marck et al., 2018). However face-to-face interventions are resource intensive and present potential barriers to participation for people with MS, including geographical, financial and disease specific factors such as fatigue and mobility. The COVID-19 pandemic has highlighted the highly unpredictable ability to travel and presented further MS specific challenges relating to potential immunosuppression and subsequent vulnerability of participants in face-to-face education.

Web-based interventions have shown great efficacy at promoting positive lifestyle changes in a range of populations for a variety of medical conditions (Bardus, Smith, Samaha, & Abraham, 2016; Bossen, Veenhof, Dekker, & de Bakker, 2014; Knittle et al., 2018; Kohl, Crutzen, & de Vries, 2013; Neve, Morgan, Jones, & Collins, 2010; Olson, 2016), including MS (Fischer et al., 2015; Hind et al., 2014; Kirsten van, Trecia, & Rona, 2015; Moss-Morris et al., 2012). However, there is a paucity of studies that incorporate multiple lifestyle recommendations into one program. To date, no evidence-based lifestyle modification program for people with MS has been translated into a web-based Online intervention that has been tested in a randomised controlled trial (RCT) with long-term follow-up.

People with MS are a highly motivated population that show modest levels of engagement and retention in lifestyle management programs, and previous Online self-assessments have found favourable levels of engagement and retention in the short- and long-term (Jongen et al., 2017). An Online educational intervention for people with MS would potentially alleviate resource issues, ameliorate barriers of geography and mobility and meet all the requirements post pandemic of reaching an already potentially vulnerable population.

Our research team, together with a community advisory group of people with MS, has developed the Multiple Sclerosis Online Course (MSOC) in two arms: the MS online intervention course and the MS online standard-care course. Each course delivers educational modules regarding the biological basis of MS and preventing MS in family members through lifestyle modification in diet, exercise, stress reducing activities, sunlight and vitamin D, omega 3 and smoking and alcohol intake. The intervention course provides evidence-based recommendations for lifestyle modification across these modules, delivered via a mixture of videos, presentations, and reading components. The

standard-care course is similar in structure and functionality but contains standard MS health recommendations from a range of international MS websites. Results from the MSOC – Feasibility study (The University of Melbourne HREC 1851781.1) comprising the MS Online intervention course versus the MS Online standard-care course demonstrated that people with MS completed both the intervention and standard-care course at satisfactory rates, believed the course was readily accessible and enjoyable, and participated in follow-up evaluation (quantitative and qualitative manuscripts currently in preparation).

Our research question is: Will a Multiple Sclerosis Online Course that delivers evidence-based lifestyle modification recommendations to people with MS (the intervention) result in greater post-intervention sustained lifestyle behaviour change and improved health outcomes compared with a standard-care course (the control)?

Results of the RCT will be disseminated through international conference presentations and in peer-review international journals with open access to ensure research findings are readily available for people with MS, clinicians and the general public.

Following completion of the RCT, the MS Online Course will be made available free of charge to people with MS worldwide via the Overcoming MS Charity to empower people with MS to adopt a program of positive lifestyle change to improve their health and well-being.

Potential benefits of participants enrolling in the RCT:

Increasing evidence in the scientific literature suggests that lifestyle modification could be a point of intervention for improving quality of life and clinical outcomes in people with MS. In the NEU at the University of Melbourne we have developed an online course that will deliver the relevant information to people with MS that has the potential to improve their health outcomes. While we have developed an intervention course and a standard-care course, both online courses have the potential to improve health outcomes in people with MS. Topics included in the online courses that have been associated with improved health outcomes which may prove to be beneficial to RCT participants are outlined below. However, findings in the literature are conflicted and emphases there is need for a RCT to directly identify any causal associations between lifestyle factors and health outcomes (our proposed MSOC – RCT study):

Diet

Topics covered in the MS-online related course include a module on diet quality. Several studies have found better quality-of-the-diet is associated with reduced relapses,(Simpson-Yap et al., 2020) and disability.(Fitzgerald et al., 2018; Jelinek et al., 2016; Simpson-Yap, Nag, Probst, Jelinek, & Neate, 2021) Other studies have found diet is associated with improved QoL.(Evers, Heerings, de Roos, Jongen, & Visser, 2021; Hadgkiss, Jelinek, Weiland, et al., 2015; Marck, Probst, Chen, Taylor, & van der Mei, 2021) In particular, a study from our group of a large international cohort found a 10% improvement in diet quality as assessed by the Diet Habits Questionnaire was associated with 6% and 5% higher physical and mental-QoL at baseline, respectively, and this was most evident for fruit/vegetable and fat.(Hadgkiss, Jelinek, Weiland, et al., 2015)

Vitamin D

In a cross-sectional study, Vitamin D supplementation was found to be associated with improved health outcomes in people with MS.(Jelinek et al., 2015) A further study by Simpson-Yap et al. found vitamin D supplementation was associated with higher physical and mental QoL in a cross-sectional analysis but only associated with higher physical QoL in a prospective analysis.(Simpson-Yap, Jelinek, et al., 2021) Other observational studies have found lower vitamin D levels are associated with increased risk of MS and progression.(Duan et al., 2014; Martinez-Lapiscina, Mahatanan, Lee, Charoenpong, & Hong, 2020)

Omega-3

Studies have found increased Omega-3 intake or oily fish consumption is associated with improved health outcomes in people with MS. In particular, Jelinek et al. found Omega-3 intake improved QoL and reduced relapses,(Jelinek et al., 2013) and Coe et al. found consuming fish decreased fatigue.(Coe et al., 2021)

Stress relief

Observational studies have found stress reduction can reduce exacerbations in people with MS and improve QoL and emotional wellbeing in people with MS.(Mohr et al., 2012; Senders et al., 2019; P. Taylor, Dorstyn, & Prior, 2020) In particular, the randomised controlled trial by Mohr et al. demonstrated stress management training reduced disease activity by reducing the presence of new lesions in the brain of people with relapsing-remitting MS.(Mohr et al., 2012) However, other studies found stress reduction did not improve QoL.(Agland et al., 2018)

Physical activity

Observational studies have found physical activity is associated with increased energy and social functioning and improved physical and mental health outcomes.(Marck et al., 2014; Marck, Learmonth, Chen, & van der Mei, 2020; Motl & Gosney, 2008)

Key questions:

Does participation of people with MS in the MS Online intervention course change lifestyle behaviours compared with participants in an MS Online standard care course in the:

1) Short-term
2) Medium-term

What is the effect on participant health outcomes from different levels of adoption and adherence to lifestyle recommendations in the MS Online intervention course compared with MS Online standard-care course with respect to:

1) Quality of life

2) Fatigue
3) Depression
4) Anxiety
5) Disability
6) Self-efficacy

4.3 BACKGROUND INFORMATION

Lifestyle factors are known to affect the progression of multiple sclerosis (MS). Studies of participants with MS attending an evidence-based lifestyle modification program, delivered via face-to-face workshops in Australia, have demonstrated improved mental and physical health, reduced relapse rate and improved quality of life over three years follow-up, and that behaviour change has been found to be feasible and sustainable. However, the face-to-face modality of this educational intervention is resource-intensive and accessibility may be impeded by geography, cost, and MS-specific factors such as illness, fatigue, and disability. Furthermore, the COVID-19 pandemic has highlighted the unpredictable ability to travel and the importance of flexibility of health-related education.

The Neuroepidemiology Unit, Melbourne School of Population and Global Health, has developed the Multiple Sclerosis Online Course (MSOC) to deliver a widely accessible and user-friendly educational tool for people with MS. The course aims to deliver the best available evidence regarding lifestyle-related risk factors in the development and progression of MS and behaviour modification to improve health outcomes.

Two forms of the course were developed:

1. an MS Online intervention course based delivering evidence-based information regarding modifiable lifestyle related risk factors implicated in disease progression; and

2. an MS Online standard-care course, similar in format and presentation, but containing general information sourced from standard MS websites. Both courses have seven modules delivered over six weeks.

A feasibility study involving the delivery of the intervention and standard-care course was conducted from April to June 2021 (MSOC – Feasibility). This study assessed the primary outcomes of attrition in both the intervention and standard-care arm. Secondary outcomes assessed the completion of the baselines survey, and quantitatively assessed learnability, accessibility, and desirability via a Likert scale follow-up survey. A qualitative analysis examining motivation, expectations and outcomes was also conducted. Based on the MSOC – Feasibility study, we have modified recruitment, functionality, and the community forum aspects of the course. We now aim to test the effectiveness of the intervention arm of the course compared with the standard-care arm in a larger randomised controlled trial (MSOC - RCT).

Choice of comparators in RCT:

The proposed study aims to prospectively determine whether an Online MS Lifestyle Modification Course (the intervention arm) can deliver an evidence-based educational intervention that results in behaviour change which is sustained and is translated into improved health outcomes for people

with MS, and whether these effects are superior to the Online standard-care course (the control arm).

In this RCT, we will be comparing two interventions/products that were developed by researchers at the Neuroepidemiology Unit (NEU) at the University of Melbourne:

1. the MS Online intervention course that delivers information on diet, exercise, Vitamin D and omega-3 supplementation and stress relief/meditation
2. the MS Online standard-care course that delivers standard MS-related information that can be obtained through publicly-available Websites.

In people with MS, we aim to compare health outcomes of people enrolled in the intervention (the MS Online intervention course) with the control arm (the MS Online standard-care course) by assessing:

- assess the uptake and maintenance of recommended lifestyle modifications in a cohort of people with MS after undertaking an MS online educational lifestyle course compared with people undertaking an online standard-care course.

- assess whether people with MS undertaking an MS online educational lifestyle intervention course results in improved clinical outcomes and health outcomes of depression, fatigue, disability, and quality of life over the short-term and medium-term compared with people undertaking an online standard-care course.

5. STUDY OBJECTIVES

5.1 HYPOTHESIS

People with MS who undertake the MS Online intervention course (the intervention arm) delivering evidence-based lifestyle modification education will have sustained behaviour change and improved health outcomes that are superior to the health outcomes in people with MS undertaking the MS Online standard-care course (the control arm).

5.2 STUDY AIMS

To quantitatively and qualitatively assess the arms of the Multiple Sclerosis Online Course in an RCT (the MS Online intervention course and MS Online standard-care course). We aim to measure:

1) The degree of engagement with and participation in the course
2) Adoption of lifestyle behaviours change following course completion
3) Adherence to lifestyle behaviour change over time
4) Short-term and medium-term health outcomes and
5) To compare all these outcomes between both arms.

Overall, the proposed RCT will enable a causal relationship between lifestyle factors and clinical and health outcomes to be examined.

5.3 OUTCOME MEASURES

QUANTATIVE OUTCOMES

Lifestyle behaviour of participants will be assessed at baseline and 6 months, 12 months and 2.5 years after completion of the Online MS course (intervention or standard-care). Lifestyle/behaviour outcomes to be measured include:

a. Exercise

To assess physical activity we will use The International Physical Activity Questionnaire - Short Form (IPAQ-SF), a 7-item 7-day recall of frequency and duration of vigorous and moderate physical activity, walking, and sitting assessed in nine items(Craig et al., 2003). The IPAQ and its short form have been validated in several studies and populations globally, and the long form has been used previously for people with MS(Stroud, Minahan, & Sabapathy, 2009; Weikert et al., 2012).

b. Diet

Since we aim to assess diet broadly with a particular consideration for fats, we will modify the Diet Habits Questionnaire (DHQ)(McKellar et al., 2008). The original 24-item DHQ has eight dietary sub-scores, and assesses saturated and unsaturated fat intake, fruit and vegetable, fibre, takeaway, snack habits, and omega-3 consumption, among other estimates. In our modified version, we removed three items regarding sodium intake, and one item on alcohol was replaced with an alternate alcohol assessment measure. We added a researcher-devised item regarding oily fish consumption that was separate from the DHQ: “How often do you eat oily fish such as sardines, mackerel, herring, salmon, tune or trout? (Never; Less than once a week; About 1 - 2 times a week; About 3 - 4 times a week; At least 5 times a week) and options regarding “I don’t eat meat” and “I don’t eat dairy”.

c. Alcohol consumption

Volume and frequency of alcohol consumed will queried. In Australia a standard drink is considered to be 10 grams of ethanol. Frequency of binge drinking, defined by the Australian Bureau of Statistics as more than 7 drinks a week for men, and more than 5 for women, will be queried.

d. Smoking

Smoking status (never/ex-smoker/current smoker) will be queried. For current smokers, typical number of cigarettes per week will be queried along with the total years they have been smoking. For ex-smokers, their typical number of cigarettes per week when they smoked will be queried, as well as the total years they smoked and the duration since they quit smoking.

e. Omega-3 uptake

We will assess both the type and daily dosage of omega-3 supplementation used on average in the last 12 months. Types of omega-3 will include fish oil, high potency fish oil, and flaxseed oil.

f. Vitamin D uptake

We will assess vitamin D supplementation by measuring dosage and frequency of vitamin D intake.

g. Sun exposure

To assess sun exposure we will modify the Ausimmune Longitudinal Study in people with MS (Lucas et al, Neurology, 2011). For each of summer and winter, participants will be asked to report number of days per week they were out in the sun; average duration spent in the sun on days they were out in the sun (none, 1-15 minutes to >60 minutes). We will also query whether participants deliberately increased their sun exposure to increase their vitamin D levels.

h. Stress management

We will use 2 questions of the Mindfulness Adherence Questionnaire (MAQ)(Hassed et al., 2021), a 6-item subset of main questionnaire, to measure the type and frequency of the participant's experience of meditation.

Other measures:

a. Sociodemographics

Data will be collected for date of birth, sex, current location of residence, country of birth, cultural background (Australian Standard Classification of Cultural and Ethnic Groups(Statistics, 2012)) and highest education level completed at baseline only, whereas marital status and employment status will be queried at all timepoints.

b. Medication use

Participants will also be asked to indicate whether they take prescription antidepressant, anxiolytic/sedative, or antifatigue medications.

c. Comorbidities

The Self-administered Comorbidity Questionnaire (SCQ) will be used to assess the presence of comorbidities in the absence of medical record review(Sangha, Stucki, Liang, Fossel, & Katz, 2003). It has demonstrated criterion validity when assessed against medical records(Stolwijk et al., 2014), and has been used in studies of participants with MS (Giovannetti et al., 2016; Holper et al., 2010). The clinically meaningful difference in the number of comorbidities for MS assessed using the self-administered comorbidity questionnaire has not been determined.

d. BMI

Body Mass Index $(weight/height)^2$ will be calculated from data collected on self-reported participant weight and height and classified using the WHO classification system(Organization, 2017). A meaningful change in BMI is difficult to will be defined by comparing to BMI at baseline.

e. Perceived Social Support

The 12-item multidimensional Scale of Perceived Social Support (MSPSS) will be used to measures participants' social interaction and satisfaction with social support(Zimet, Dahlem, Zimet, & Farley, 1988). Higher score of MSPSS indicates higher quality of social support.

Health outcomes of participants will be assessed at baseline and 6, 12 and 30 months after completion of the respective Online MS course. Health outcomes measured include:

f. Mental and physical quality of life (qol)

The MSQOL-54 will be used to assess a spectrum of HRQOL outcomes. In particular, the two primary outcome measures for this study will be change in Physical Health Composite (PHC) and Mental Health Composite (MHC) derived from the MSQOL-54. PHC and MCH are derived by combining scores of relevant subscales (Vickrey, Hays, Harooni, Myers, & Ellison, 1995). Although minimal clinically important differences have not been established for the MSQOL-54 composite scores, differences of at least five points have previously been determined as the minimum clinically meaningful change in an HRQOL measure (Osoba et al., 1998; Taphoorn, et al., 2005). This is based on recommendations that a difference

equivalent to half the standard deviation be universally considered an important magnitude for all HRQOL tools (Norman, Sloan, & Wyrwich, 2003). The MSQOL-54 has been psychometrically validated since 1995, used online and also translated into many different languages.

g. Fatigue

Clinically significant fatigue will be measured by the 9-item Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). The FSS has good internal consistency, stability, and sensitivity to change over time(Amato et al., 2001; Smedal et al., 2011). A mean score ≥4 has been suggested as a cut-off to indicate clinically significant fatigue and is widely used for people with MS (Lerdal, Celius, & Moum, 2003; Marrie et al., 2005; Smedal et al., 2011). A meaningful change on the FSS has been reported demonstrated to be a change of ≥1.9 points in people with MS (Learmonth et al., 2013) and so here a change in mean score of 1.9 points or more will be considered clinically meaningful.

h. Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) for the presence of and severity of anxiety and depressive symptoms. The HADS is commonly used for screening for anxiety and depression, as well as selecting and monitoring treatment and has been used to measure depression in MS (Zigmond & Snaith, 1983).

i. Patient-reported disability

The Patient-Determined Disease Steps (PDDS) is a self-reported measure of ambulatory disability. The PDDS is scored ordinally from 0 (normal) to 8 (bed bound) with detailed descriptors and definitions. It correlates well with the EDSS and moderately with the widely used Multiple Sclerosis Functional Composite and has excellent test-retest reliability. PDDS is considered a practical tool to use to assess changes in disability over time (Hohol, Orav, & Weiner, 1999). One step will be considered a clinically meaningful change in the PDDS.

j. Self-efficacy

Self-efficacy (the belief in one's ability to produce the effects or outcomes one wants) will be measured using the University of Washington Self-Efficacy (UWSE) survey, a psychometrically sound instrument that includes 6 items for measuring self-efficacy, validated in MS (Amtmann et al., 2012).

Primary intervention quantitative outcomes/endpoints:

The two primary outcome measures for this study are changes (improvements) from baseline in 1. Physical Health Composite (PHC) and 2. Mental Health Composite (MHC) derived from the MSQOL-54 in the short-term and medium-term. Differences of at least five points have previously been determined as the minimum clinically meaningful change in an HRQOL measure (Osoba, Rodrigues, Myles, Zee, & Pater, 1998; Taphoorn & Bottomley, 2005). Previous data suggests a difference of five points is achievable in a sample of people with MS (Hadgkiss, Jelinek, Taylor, et al., 2015).

Secondary intervention quantitative outcomes/endpoints:

Secondary outcomes include clinically relevant changes (improvements) in depression, anxiety fatigue, disability and self-efficacy in the short-term and medium-term.

QUALITATIVE OUTCOMES

A qualitative study using semi-structured interviews will be conducted within one month and 12 months after completing the MS Online course (the same group of people with MS will be interviewed at both time points).

A randomly selected sample of approximately 15 participants from each the standard-care course arm and intervention course arm will receive an email or phone call requesting their participation in 30 to 60 minutes qualitative interview. Interviews will be conducted by telephone or via the internet by 3 trained interviewers. All interviewers will be involved in the first three interviews to ensure consistency in the format and content of qualitative interviews.

Semi-structured interviews have been developed based on an iterative process by researchers. *Schedules of qualitative interviews are described in the attached file, MSOC RCT qualitative interviews schedule.docx*

The 1-month interview guide will cover the following domains:

1) Participants' views regarding motivation to undertake the course
2) Views of the content of the course
3) Participants' experiences
4) Use of community
5) Initial changes to lifestyle
6) Initial changes to attitudes to MS, health and the future

The 12-month interview will cover the following domains:

1) Adoption of lifestyle recommendations
2) Perceived health
3) Sense of community and support
4) Attitude to MS, health and the future

Interviews will be digitally recorded and transcribed by voice recognition software. All recordings and transcribed files will be securely stored in a re-identifiable format.

6. STUDY DESIGN

6.1 STUDY TYPE & DESIGN & SCHEDULE

1. Study Type: Clinical trial

Randomised controlled trial, involving:

a. Epidemiological analysis of quantitative data
b. Qualitative analysis of semi-structured interviews

2. Study Design (refer to Table 1)

I. This is a single-site study that will be conducted at the Neuroepidemiology Unit in the Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health at The University of Melbourne, involving online recruitment of participants with MS from Australia, New Zealand, USA, UK and Canada. The decision was made to make this a single-site study to guarantee that all data collected from participants (both personal participant data and responses to self-reported questionnaires) will be safely and securely stored in one location (on the University of Melbourne server).

II. For participant recruitment, details of the RCT will be published on MS society websites and social media sites throughout Australia, New Zealand, USA, UK and Canada seeking interested people with MS to participate in the MSOC - RCT.

III. Interested participants (people with relapsing-remitting MS) will be asked to click on a link on the notice advertising the MSOC - RCT which will direct them to 7 eligibility questions related to: (1) their age; (2) the type of MS they were diagnosed with; (3) the year they were diagnosed with MS (4,5) whether they follow a MS-specific diet and if so, the diet they follow (6,7) whether they follow a MS-specific program and if so, the program they follow.

IV. Participants with MS over the age of 18 fulfilling inclusion and exclusion criteria from Australia, New Zealand, USA, UK, Canada and other countries who read, write and speak English will be invited to participate in the study. Note, the recruitment period will be up to two months from the date of the first participant recruitment or earlier, if the required number of eligible participants have been recruited.

V. Interested participants meeting the study eligibility criteria (Refer to Section 6.2 and 6.3 for eligibility criteria) after completing the eligibility questions will be emailed a participant information form and consent form. Once participants have provided their consent by ticking a box online, participants will be emailed a link to the baseline questionnaire to obtain demographic data and obtain data on lifestyle and outcome measures (Section 4.3, Table 1). Interested participants not meeting the study eligibility criteria will be excluded and notified by email that they were not eligible to participate in the study and thanking them for their interest.

VI. Participants will be randomised to either the MS Online intervention course or the MS Online standard-care course at a ratio of 1:1 using simple randomisation. Randomisation will occur over a 2-week period after recruitment of eligible participants.

VII. Participants will undertake the MS Online course (intervention arm or standard-care arm) over a 6-week period. Note, each arm is of comparable length and content-type (video, interviews, images, interactivity), to minimise variability in 'dose' received between intervention and standard-care groups. Both courses will follow a similar structure throughout, limiting differences in how the content of the course is presented.

VIII. Patient-reported outcomes measures (Section 4.3, Table 1) will be determined after a period of 6 months, 12 months and 2.5 years after the completion of the MS Online course. This will involve participants from the MS Online intervention arm and the MS Online standard-care arm completing validated questionnaires online (following instructions and reminders, if necessary, from study team members). These measures will determine participants adherence to lifestyle recommendations of the Online intervention and standard course with respect to diet, exercise, omega 3 intake, vitamin D intake, meditation and sun exposure (Table 1). Health outcomes related to participant's quality of life, depression, anxiety, fatigue, disability and self-efficacy.

IX. The primary objective of the study will be assessed at the 12-month and 2.5 year follow-up. That is, Health-related quality of life (HRQOL) calculations for Physical Health Composite

(PHC) and Mental Health Composite (MHC) scores derived from the MSQOL-54 for participants in the intervention and standard-care arm will be calculated in the intervention and standard-care arms.

We will consider amending the RCT protocol to allow participants in the standard-care arm access to the MS Online intervention course before the end of the study (ie before the 2.5-year follow-up) in the event:
a) clinically significant increases in either the PHC and MHC scores of MSQOL-54 (≥5)(Osoba et al., 1998; Taphoorn & Bottomley, 2005) from baseline are found in participants in the intervention arm at the 12-month follow-up who are *adhering to lifestyle recommendations* of the Online Lifestyle modifications course, but
b) clinically significant improvements in either PHC or MHC are not found in participants in the standard-care arm at the 12-month follow-up.

If clinically significant improvements in either the PHC and MHC scores of MSQOL-54 are not found between baseline and 12 months in participants in the intervention arm *adhering to lifestyle recommendations* of the MS Online intervention course, the RCT will continue to as described to the 2.5 year follow-up.

If there are no amendments to the study, all participants will be notified of the study arm they were allocated to at the completion of the study. All participants in the standard-care arm will be provided with a link to access the MS Online intervention course.

X. Qualitative interviewing consisting of semi-structured interviews by trained qualitative interviewers will be conducted on a randomly selected subset of participants (approximately 15 participants from intervention and standard-care arms, respectively) will be performed within 1 month of and 12 months after completing the MS Online course.

XI. During enrolment in the trial, participants in both arms of the RCT will be advised to continue with normal medical treatment with their existing neurologists and healthcare providers and to continue with their usual medications, as recommended by their physicians.

Intervention group (*MS Online intervention course*):

Structure of delivery

In a seven-module, seven-session, self-administered program, participants in the intervention arm would be presented with an integrated lifestyle modification program including information and

support regarding each of the key lifestyle modifications. Modules will be released on a timed-schedule, twice per week, with future modules gated until completion of preceding modules, but previous modules available for review throughout the entire intervention period. The total length of course is six weeks (7 sessions, 2 sessions per week with 2 weeks added on to the end for catch-up), specified by participants in the MSOC – feasibility study to be of suitable length. The course remains open for a total of six weeks to enable participants to complete the course.

Mode of delivery

Delivery of the lifestyle intervention will be via invitation-only, online course. Participants will be required to complete each module within specified six weeks of the course. There is no time limit set for the completion of each module; however, the next module cannot be accessed until the previous module is complete, and all must be completed by the end of the intervention period for participant to be considered a 'completer'. Modules are composed of video content, written content, interactive (non-assessed) content, and non-hurdle assessments. Participants are required to self-navigate modules with technical support provided only to address functionality issues within the software.

Content

The integrated lifestyle modification program translates the research evidence regarding modification of lifestyle related risk factors and health outcomes based on a detailed review of the literature around modifiable lifestyle risk factors that may influence MS disease progression, as outlined in the book Overcoming Multiple Sclerosis: the 7-step recovery program (Jelinek, 2016).
The MS Online Course also contains a community forum. Links to articles and other prompts will encourage participants to contribute their thoughts. A researcher will be delegated to oversee the forum to moderate the forum to facilitate participant engagement and ensure appropriateness of content.

Session 1: Introduction to the Program and participants

Welcome to the course and overview of MS (medical definition). How to study the course; introduction to the web-based intervention: how to proceed, how to navigate, what to expect and to outline the endpoints for participants. Validating Overcoming MS program → providing previous research/evidence on efficacy.

Session 2: Diet

Evidence behind a dietary influence on MS disease activity and QOL: evidence on saturated fat, and evidence regarding diet and its relationships with MS onset and progression. Introduction to dietary plan and benefits of different food groups.

Session 3: Sunlight and vitamin D

Detailed background information about how vitamin D is made from the action of sunlight is presented, along with evidence supporting a role of vitamin D in MS disease activity. Recommendations for optimal levels of supplementation and blood levels are presented.

Session 4: Physical activity/Exercise

The benefits of exercise are explained for people with MS (neurological, cognitive, physical), how and why. In addition, evidence regarding the benefits of exercise will be presented. How to implement an exercise plan with video examples provided.

Session 5: Stress and stress reduction

Introduction to mental health and relevance in MS. Participants are introduced to the science behind stress and its link to inflammation/MS. Mind-body connection, meditation and other stress reduction techniques to supplement the practical sessions on meditation they receive throughout the program. How to develop a mental health and wellbeing improvement strategy.

Session 6: Family primary prevention

Participants are introduced to the issue of primary prevention of MS in close family members who are at increased risk of developing the disease, and strategies for reducing this risk. This session will cover risks associated with smoking and excessive alcohol intake and MS progression.

Session 7: Review and consolidation

Program overview and recap, and an outline of next steps to take. Advise on follow-up questionnaires for longitudinal follow-up, and link to forums for further engagement (aimed at enhancing retention).

Standard-Care Group (*MS Online standard-care course*):

Structure and mode of delivery:

The standard-care course will be structured and delivered in the same way as the intervention course. That is, the total length of course is six weeks (7 sessions, 2 sessions per week with 2 weeks of catch-up).

Content:

The content of the standard-care course will be delivered in the same seven modules as the intervention course (as above). The standard-care course will be populated with information collected from a multitude of MS society websites from around the world, such as MS Australia, MS Research Australia and The National MS Society (United States); text, video and image/animation content has been compiled into modules to mirror the intervention course's modules. The standard-care course aims to reproduce the advice that people with MS typically receive during medical consultations and online advice from MS Societies.

A separate community forum is available as part of the standard-care course specifically for standard-care participants.

MS Online Intervention course group and MS Online Standard-care course group:

Data collection, management and analysis:

Quantitative data

Quantitative data will be collected via validated self-reported questionnaires completed by participants at specified time points (Table 1).

Para data (administrative data such as number of participant logins, etc) will be collected via Google Analytics and functionality integrated into the WordPress platform. Google Analytics provides data tracking on how participants interact with the online course, such as average time per page, what interactive elements participants are engaging with, what pages people commonly exit the course on, and many others. The analytics integrated into the platform itself will allow us to analyse the number of participants that drop-out over the length of the course, and when they do so.

Data will be stored in a re-identifiable format as described in Section 10.

Quantitative data collection feasibility

As assessed by the qualitative component of the MSOC – Feasibility study, participants indicated that the MS Online course over six weeks with two sessions every week was feasible to complete. Importantly, participants have the option to complete the MS Online course at a time and location that is convenient to them.

The complete patient-reported questionnaire with approximately 150 questions has been found to take approximately 60 minutes to complete. Participants will be able to login and complete this questionnaire over time. The participants will be requested to complete this questionnaire on four separate occasions (baseline, 6 months, 12 months and 2.5 years) and due to previous studies that we have performed within the Neuroepidemiology Unit utilising questionnaires of a similar length over 7.5 years ((Marck et al., 2018; Weiland et al., 2018), we do not believe the questionnaire will create an unacceptable burden on participants.

Quantitative data analysis:

We will measure adherence to lifestyle modification recommendations in people with MS enrolled in the MS Online intervention and the MS Online standard-care arm (control) using validated patient-reported questionnaires.

We will examine and compare clinical and health outcomes of depression, anxiety, fatigue, disability, self-efficacy and quality of life in people with MS in the short-term (6 months and 12 months) and medium-term (2.5 years) in people enrolled in the MS Online Intervention course arm and people enrolled in the MS Online standard-care course arm.

Statistical analyses will enable us to examine whether a causal relationship exists between lifestyle factors and clinical and health outcomes in people with MS. These analyses are anticipated to be completed within 6-12 months of collecting data for short-term and long-term analyses, respectively.

Qualitative data:

Qualitative data will comprise edited transcripts of recordings from semi-structured interviews from 15 randomly selected participants from the intervention arm and the standard-care arm carried out within one month of completing the MS Online course and 12 months after completing the MS Online course (the same people will be interviewed at both time points).

Interviews will be digitally recorded and transcribed by voice recognition software. Data will be stored in a re-identifiable format and encrypted files will be securely stored as described in Section 10.

Qualitative data collection feasibility:

The qualitative component of the MSOC – RCT is similar to the qualitative component of the MSOC – Feasibility study we performed. This interviewing technique was found to be both effective and participants reported positive feedback following interviews.

Qualitative data analysis:

Data interpretations from interviews one month after completing the MS Online course and 12 months after completing the MS Online course will be performed individually at each time-point. Comparisons between data interpretations at the different time intervals will also be performed.

Student participation:

This protocol may be used towards a student PhD project in the future but at present, no student has been assigned to work on this research project.

Table 1: Summary of RCT time frame

		Timeframe						
Assessment/Measure	No. Questions	Screening	Baseline	Complete Online course	One month after Online course	6 months after Online course	12 months after Online course	2.5 years after Online course
Informed consent	1		X					
Age	1	X	X					
MS type diagnosed	2	X	X			X	X	X
MS duration	2	X	X			X	X	X
Do you follow a MS-specific lifestyle program?	2	X	X			X	X	X
Do you follow a MS-specific diet	2	X	X			X	X	X
Sex and gender	2		X					
Residential address and country	1		X					X
Country of birth	1		X					
Height/weight	2		X			X	X	X
Comorbidities	2		X			X	X	X
Marital status	1		X			X	X	X
Education	1		X					
Employment status	1		X			X	X	X
Alcohol and smoking	4		X			X	X	X
Medications	4		X			X	X	X
Perceived Social Support	12		X			X	X	X
Lifestyle factors								
Physical activity: IPAQ-SF	7		X			X	X	X
Meditation: MAQ	3		X			X	X	X
Sun exposure	4		X			X	X	X
Diet quality: DHQ	21		X			X	X	X
Omega-3 intake: dose, frequency	3		X			X	X	X

Vitamin D intake: dose, frequency	3		X		X	X	X
Health outcomes							
HRQOL: MSQOL-54	54		X		X	X	X
Disability: PDDS	1		X		X	X	X
Anxiety and depression: HADS	14		X		X	X	X
Fatigue: FSS	9		X		X	X	X
Self-efficacy: UWSE-6	6		X		X	X	X
Qualitative interviewing	(7)			X		X	
If clinically significant improvement in HRQOL subset scores in Intervention group from baseline, we will consider an amendment to the RCT to provide participants in the standard-care access to the intervention course						X	
If no clinically significant improvement in HRQOL subset scores in Intervention group from baseline, the RCT will not be amended						X	
Total no. quantitative data questions (not including qualitative)		5	166		159	166	160

6.2 Standard Care and Additional to Standard Care Procedures

Not applicable.

6.3 Randomisation

Allocation

Sequence Generation

Participants will be randomly assigned to either control or intervention group with a 1:1 allocation as per a computer-generated simple randomisation program such as https://www.randomizer.org/.

Implementation

All patients who: 1. fulfil the study inclusion and exclusion criteria 2. give consent for participation in the study, and 3. complete the baseline assessment questionnaire will be randomised to either the intervention or standard-care arm of the study before being provided with a link to access to the MS Online course.

An assigned study investigator will be responsible for allocating participants to either the intervention or standard-care arm.

Participants will be blinded to the nature of the other study arm. That is, there will be no identifying information in the MS Online course and participants will be notified that they are enrolled in a “MS Online Education Course”. Participants will be allocated to the intervention or standard-care arm at a 1:1 ratio using simple randomization.

Research staff (including those researchers performing statistical analyses) will be blinded to the group allocation. Only the researcher responsible for allocating participants to either the intervention or standard-care arm and the data manager will have access to participant allocation information. The same researcher will be responsible for inviting participants to be involved in the qualitative study. In the event this researcher leaves the study, an external researcher will take over this position.

Group allocation information will be concealed from study participants.

6.4 Study Methodology

No clinical or laboratory assessment/s will be carried out as part of this study.

7. Study Population

7.1 Recruitment Procedure

Our study group comprises people over the age of 18 years with a neurologist-confirmed diagnosis of relapsing remitting MS.

Details of the RCT will be published on MS society websites, Facebook and Instagram sites throughout Australia, New Zealand, USA, UK, Canada, providing information about the MSOC - RCT and asking them to contact members of the study group by email if they are interested in participating. These sites include:

UK MS Register website
Multiple Sclerosis Research Australia (MSRA) website
Multiple Sclerosis Association of America (MSAA) website
Multiple Sclerosis Society of New Zealand website
MS Society of Canada website
Multiple Sclerosis Trust (UK-based)
National Multiple Sclerosis Society

The same information will also be posted on related Facebook sites including:

National Multiple Sclerosis Society
Multiple Sclerosis Australia
Multiple Sclerosis Foundation
Multiple Sclerosis Society of Canada
Multiple Sclerosis Trust (UK-based) https://www.facebook.com/groups/multiplesclerosistrust/
https://www.facebook.com/groups/multiplesclerosiswarriors/
https://www.facebook.com/groups/LDNRT/
https://www.facebook.com/groups/32407464137/
https://www.facebook.com/groups/48020086285/
https://www.facebook.com/groups/49480728240/
https://www.facebook.com/groups/msclerosis/
https://www.facebook.com/groups/MSnDIET/
https://www.facebook.com/groups/msfriends/
https://www.facebook.com/groups/149551588442843/
https://www.facebook.com/groups/tifms/
https://www.facebook.com/groups/multiplesclerosisawareness/
https://www.facebook.com/groups/raiseawareness/
https://www.facebook.com/groups/mshopeandhealing/
https://www.facebook.com/groups/340467112677741/
https://www.facebook.com/groups/1000713966608065/
https://www.facebook.com/groups/1718909785011262/

The information about the study will be posted on a Facebook webpage and Instagram that will be available to individuals with MS and MS social groups worldwide.

Interested participants (people with relapsing-remitting MS) will be asked to click on a link on the notice advertising the MSOC - RCT which will direct them to seven eligibility questions related to: (1) their age; (2) the type of MS they were diagnosed with; (3) the year they were diagnosed with MS (4,5) whether they follow a MS-specific diet and if so, the diet they follow (6,7) whether they follow a

MS-specific program and if so, the program they follow. Eligibility will be assessed by the research team and those participants fulfilling study eligibility will be will invited to participate in the study and will be a sent a Participant Information Sheet and Consent Form to confirm their consent to participate in the study. Once consent has been confirmed, participants will be sent a link to complete the baseline questionnaire online. Following the collection of baseline data from all recruited participants, randomisation of participants to their respective study arm will be performed. Each participant will then be emailed a link to the MS Online course they have been allocated to (either the MS Online intervention or the MS Online standard-care course) along with general information about the respective MS Online course.

Interested participants assessed as being ineligible for the study will receive an email thanking them for their interest and notifying them of their study ineligibility and explaining why they were ineligible for the study.

Strategies for retention

Retaining participants in the study will maximise the study sample number, the power of statistical analyses, and the likelihood of representativeness. We will undertake multiple strategies to encourage participants to retain in all aspects of the study through consistent follow-up correspondence and social media engagement. All participants will be annually thanked for participating in the RCT.

7.2 INCLUSION CRITERIA

Eligible participants must:

1. Be able to read, write, and speak English;
2. Be 18 years old or over;
3. Have a confirmed diagnosis of relapsing-remitting MS (by a neurologist);
4. Be able to access the internet and be able to view sessions.

7.3 EXCLUSION CRITERIA

Exclusion criteria of participants include:

1. Experiencing any serious co-morbid chronic illness or neurological illness/injury other than MS that would threaten regular participation or significantly affect the outcome measures in

its own right, such as motor neurone disease or stroke, as determined by the study investigators;

2. Currently participating in another study ~~or self-management program involving modification of lifestyle~~.

7.4 CONSENT

Potential participants will be informed of the requirements of participating in the study, which will include:

- Willingness to participate in an MS Online course related to lifestyle modification over a six-week study period;
- Follow-up protocol at baseline, 6 months, 12 months and 2.5 years;
- Potential invitation to be involved in a voluntary qualitative study
- Ability to opt-out at any time.

Consent forms will be provided for review by the Human Research Ethics Committee at the University of Melbourne.

8. PARTICIPANT SAFETY AND WITHDRAWAL

8.1 RISK MANAGEMENT AND SAFETY

There will be no physical distress to participants in the proposed study as the study involves watching an educational course and completing questionnaires online. The exercise component of the MS Online Course in both arms of the study recommends a gentle exercise regimen, if participants decide to implement recommendations, that would not be expected to cause harm.

The research team in conjunction with participants involved in the qualitative interviewing component of the MSOC – Feasibility study found that the MS Online course, questionnaires and qualitative interviewing posed very low psychological distress to participants.

While we do not anticipate potential psychological distress, the following continency plans will be implemented to address any psychological distress that may arise:

Quantitative research risk management

To address any psychological distress associated with completing online questionnaires at baseline and after 6 and 12 months and 2.5 years after completing the MS Online Course, links will be

provided at the end of questionnaires to country-specific help resources that the participant could access in the event that completing the questionnaires has raised issues for the participant. Participants will also be provided with the contact details of study team members and reminded that they can make contact with a team member if completing the questionnaires has raised any issues for them.

With regards to the HADS survey, while it is a validated tool for assessment of depression, it is not a diagnostic tool. However, we will also provide relevant country-specific resources and/or provide information/links to country-specific help/information at the end of the HADS. Notably, the HADS is the final questionnaire in the survey so this information will be provided directly after answering questions with the greatest potential to cause distress.

Qualitative research risk management

Dr Sandra Neate is a specialist emergency physician with 30 years' experience dealing with critically ill and distressed patients. She has skills in managing people in crisis. She has extensive experience dealing with acute and chronic mental health conditions. She is also a member of the Victorian Mental Health Tribunal where she speaks directly with patients with acute mental health disturbance including depression and those at risk of suicide. Although Dr Neate will not provide formal counselling to any participants she has skills to manage difficult emotions and advise appropriate follow up.

Dr Pia Jelinek is a general practitioner with 5 years of clinical experience. She deals with patients experiencing emotional distress and providing counselling on a daily basis. Although Dr Jelinek does not intend to provide formal counselling to any participants she has skills to manage difficult emotions and advise appropriate follow up.

Dr Reece conducted qualitative interviews in the MSOC feasibility study but has no formal training in managing people with emotional distress.

At the completion of all qualitative interviews, interviewers will ask participants if the questions or discussions during the interview have raised any distress or psychological difficulties to the participant. In the event any issues have been raised, the interviewer will refer the participant to the relevant country-specific resources and/or provide information/links to country-specific help/information. The interviewer will also notify the participant that they are free to contact them at any later stage if they experience distress after the interview and the same country-specific resources will be supplied to the participant.

Withdrawing participants:

Withdrawing participants will be contacted and provided links to help resources.

8.2 HANDLING OF WITHDRAWALS

Participants will be notified that they can withdraw from the study at any time for any reason. If a participant wishes to withdraw from the study, we would advise them to contact us so as to avoid receiving unwanted study emails and phone calls related to follow-up in the future.

We do not anticipate any adverse events for the participant if they wish to withdraw from the study, however, we will provide withdrawing participants links to help resources. The participant will also be notified that all of their data we be retained and stored in a confidential and secure manner (Section 10).

8.3 REPLACEMENTS

Participants that withdraw from the study will not be replaced. (That is, participants that do not complete the MS Online course and all related follow-up in the form of completing MS Online questionnaires). The calculation of the sample size (Section 8.1) allows for a proportion of participants not complete to all components of the MS – RCT study (42% loss to follow-up) and still retain sufficient statistical power.

9. STATISTICAL METHODS

9.1 SAMPLE SIZE ESTIMATION & JUSTIFICATION

The two primary outcome measures for this study are changes in Physical Health Composite (PHC) and Mental Health Composite (MHC) derived from the MSQOL-54. PHC and MCH are derived by combining scores of relevant subscales (Vickrey et al., 1995). For the proposed MSOC – RCT, sample sizes were calculated in order to detect a 5-point difference in the PHC and MHC scores (a minimum clinically meaningful change in these HRQOL measures, between the intervention and standard-care arms).

To further account for loss-to-follow-up from the study period, based upon MSOC - Feasibility results, we anticipated a 42% loss-to-follow-up between randomisation and follow-up at 12 months. It is likely

this level of loss-to-follow-up is an overestimate of what will be observed in the proposed MSOC – RCT due to redevelopment of the intervention based upon feasibility data, but this overestimate will account for participants in the standard-care course that request access to the MS Online Intervention course after unblinding at 12 months after participants undertake the MS Online Standard-care course.

Taking these factors into account, we estimate 1054 participants, 527 in each arm (1:1 allocation) with data at baseline and follow-up would give 80% power to detect a 5-point change in HRQOL across both PHC and MHC outcomes. This estimation of power is based on the mean PHC and MHC scores and their SD, which is the SD between groups at baseline.

9.2 POWER CALCULATIONS

Power calculations were estimated using the Bonferroni correction. The Bonferroni correction adjusts probability (*p*) values because of the increased risk of a type I error when making multiple statistical tests (in this instance, the increased risk of type I error for the multiple outcomes of PHC and MHC scores of HRQOL, as assess by the MSQOL-54 questionnaire) (Osoba et al., 1998; Taphoorn, et al., 2005).

9.3 STATISTICAL METHODS TO BE UNDERTAKEN

Quantitative data analysis:

Clinically significant fatigue will be defined as a mean FSS>5 (Krupp et al., 1989). Anxiety and depression will be defined as higher HADS (Zigmond & Snaith, 1983). The UWSE will be assessed as a continuous term and dichotomised at the median as there is no established cut off point indicating sufficient self-efficacy.

Characteristics of quality of life (QoL) will be measured by the MSQOL-54, including physical and mental health composite scores and multiple subdomains. Linear regression will be used to determine cross-sectional and prospective relationships with QoL.Characteristics of disability will be assessed using linear regression. Characteristics of dichotomous clinically significant fatigue, depression and anxiety will be assessed by log-binomial regression. Characteristics of Self-efficacy composite scores will be assessed by linear and log-binomial regression for continuous and dichotomised self-efficacy, respectively. Characteristics of perceived social support scores will be

assessed by linear regression. All models will be assessed for potential confounders and appropriate adjustments will be made in analyses.

Qualitative data analysis:

Audio recordings will be transcribed for analysis and stored within Nvivo Software (www.qsrinternational.com) to enable data management. Data analysis will be conducted within a qualitative paradigm using reflexive thematic analysis (Braun 2014). Reflexive thematic analysis is considered the most appropriate analytic process due its lack of grounding in a particular philosophy (Braun 2006), and as a method suitable to exploring people's experiences, views and perceptions (Braun 2014) and its allowing expression of results in a way accessible to those in the wider community. Reflexive thematic analysis also emphasises the importance of the researcher being deeply involved in the research. Data will be analysed by the process of data familiarisation, coding, and theme development and refining. Data extracts (quotes) will illustrate themes.

10. STORAGE OF BLOOD AND TISSUE SAMPLES

10.1 DETAILS OF WHERE SAMPLES WILL BE STORED, AND THE TYPE OF CONSENT FOR FUTURE USE OF SAMPLES

Not applicable. No blood or tissue samples will be taken from participants.

11. DATA SECURITY & HANDLING

11.1 DETAILS OF WHERE RECORDS WILL BE KEPT & HOW LONG WILL THEY BE STORED

Data storage:

All data from baseline and follow-up surveys will be entered by the participant themselves and stored electronically. This data will be managed and stored in accordance with the Information Privacy Principles of the Privacy Act,1988 (Cth) (see Appendix 2), the Standards Australia Personal Privacy Protection in Health Care Information Systems (AS4400-1995) and the National Statement 3.1.45 and 3.1.56.

All computer files will be password protected and participant data will be coded to a re-identifiable format.

11.2 CONFIDENTIALITY AND SECURITY

The data will be stored on the University of Melbourne's secure server. The server room at the University of Melbourne is a locked room with limited access and has uninterruptible power supply. Access to server room is permitted to authorised University of Melbourne IT staff. Data backup and restoration checks are routinely undertaken in accordance with documented procedures. Manual and automated log files document the status of each backup. The outcome of each backup process is checked daily. Backup media is securely stored off-site at an organisation that specialises in the storage of such equipment. The backup site is monitored by closed circuit television with keypad entry to all entrances. McAfee Active Defense is employed to protect servers and desktops from the threat of viruses. Virus definition files are automatically and routinely updated to ensure that The University of Melbourne systems are protected from the constant threat that new viruses present.

Only the five principal investigators from the Centre of Epidemiology and Biostatistics at The University of Melbourne will be have access to the secure drive where the data will be stored (Sandra Neate, Will Bevens, Jeanette Reece, Maggie Yu, Steve Simpson-Yap). All access to data files will be available by password and only the five PIs listed will have permission to access this data. Access by the five PIs will be exclusively to check the data and perform statistical analyses relevant to the proposed study and the data will not be used for any other purpose.

In the event that any principal investigator ceases to be engaged in the project, the four other investigators will still have access. New staff members, as necessary, may be given access to the data in the event two or more of the main investigators are no longer involved in the study at the discretion of Dr Sandra Neate or the highest senior researcher involved in the project in the event that Dr Neate is no longer working in the NEU. In the event that all of the original researchers are no longer involved in the study, the ethics application will be updated with new researcher details.

Results of research will be published in a form that does not permit the identification of individual participants and in a form which gives due regard to cultural or other sensitivities.

All participant data will be stored indefinitely following completion of the study.

11.3 ANCILLARY DATA

Data will be stored indefinitely on a secure server indefinitely at the Centre for Epidemiology and Biostatistics at the University of Melbourne and will not be disposed of. 4 principle investigators will

have access to the drive where the data will be stored (Sandra Neate, Will Bevans, Jeanette Reece, Steve Simpson-Yap) at the Centre for Epidemiology and Biostatistics, The University of Melbourne. In the event that the principle investigator (Sandra Neate) ceases to be engaged in the project, the 3 other investigators will still have access and an additional person (Head of the Informatics at the Centre for Epidemiology and Biostatistics, The University of Melbourne, currently Dr. Adrian Bickerstaffe, or his equivalent at the time if he is no longer employed at the Centre for Epidemiology and Biostatistics, The University of Melbourne) will be given access to this drive.

Explain how confidentiality of participants and their data will be protected in the dissemination of research results:

The confidentiality of participants and their data will be protected by researchers applying new codes to participants at the Centre for Epidemiology and Biostatistics, The University of Melbourne in peer reviewed publications, presentations at international and international conferences and progress reports disseminating research findings. Additionally, no specific details to enable participants to be identified will be reported eg. specific dates of birth, death, clinical and demographic information will not be reported.

12. CONSUMER INVOLVEMENT

Consumers have been extensively consulted on developing the MS Online Course (both the delivery and the content).

Prior to commencing the feasibility study (MSOC - Feasibility) assessing the delivery of the intervention and standard-care course conducted between April and June 2021, a focus consumer advisory group comprising up to 6 people with MS was established. Regular meetings were conducted for participants to provide input towards the structure and content of the Online course. Questions asked of the consumer advisory group included:

- How can web-based technology improve the management of MS?
- What online resources do you currently use or are you aware of to manage MS?
- How could a web-based technology improve your self-management of MS?
- How could a web-based technology improve the delivery of the OMS program?
- What are your experiences with online communities? For MS? How do they compare for you to face-to-face communities?

The consumer advisory group were asked to provide feedback towards the MS Online course prior to the MSOC – Feasibility study. Questions asked of these groups included:

- How accessible is the format/layout to you? What are your thoughts on accessibility?

- What things about the format / layout do you find most / least appealing / inviting / engaging, and why?
- Are the technologies presented in the plan helpful or a hindrance? Will you use them? Do they hinder the learning?
- What are some ways the layout could be improved? Any technologies you would like to see included?

The consumer advisory group were then asked to review the MS Online course prior to implementation in a program participant questionnaire to assess:

1. Accessibility:
    a. What features make this course most accessible to you, considering your needs?
    b. What aspects are difficult for you, in terms of accessibility?
    c. Which of the accessibility features detract from the overall course?
    d. How can any of these accessibility features be improved?
2. Learnability:
    a. In what ways did you find the course easy or hard to navigate?
    b. What elements of the course (non-content) were difficult to grasp?
    c. How well or how poorly did this course and its elements work, compared to other websites with which you are familiar with?
3. Desirability:
    a. On a scale of 1 (not at all) to 10 (very much), how satisfying was your experience of doing this course? Please explain the rating you give
    b. What would you say about this course to other people with MS who might be considering it?
    c. What made this different from any other alternative learning program you have encountered?
    d. What changes would you prioritise for the developers of the course to improve it?
4. Are there any other comments you'd like to make about the design of this course?

As part of the MSOC - Feasibility, qualitative interviewing of 14 participants who undertook the course (8 intervention and 6 standard-care) was undertaken. These interviews assessed the experiences and perceptions of the course. In particular, participants were asked open-ended questions as to how the MS Online course could be improved for future people with MS undertaking the course. Some of the questions asked included:

- What parts of the course worked well for you?
- Were there any parts of the course that didn't work well for you?

- What areas or subject matter did you want more information on or hadn't been covered in the course?
- Were there any areas in the course that needed improving?
- Was there an adequate mix of presentations, videos and reading?
- Was there anything that you wanted less of
- Did the technical aspects of the course work well?

Participants of the MSOC - Feasibility study were also asked to provide any other information they considered relevant for improving the course.

An additional focus group was also organised with 5 people that participated in the MSOC – feasibility study aimed to specifically determine what type of research people with MS considered was important and whether or not they thought answering questions related to their lifestyle and health outcomes was important or burdensome to them.

All participants in this forum expressed that their primary motivation to participate in research studies was to improve their own health and to help others with MS by contributing to research into MS. They wanted to be part of a "new era" of MS management that focused on the positive aspects of what people with MS could do to help themselves and to continue to live full and active lives.

All participants provided very positive feedback that evidence-based research to examine whether changes in lifestyle behaviour led to improved mental and physical health was extremely important to them and potentially others with MS, especially as disease-modifying therapy was costly and had adverse side effects. Participants emphasised that they didn't want to have to rely on medications to achieve better health and quality of life and if they could make changes to their lifestyle that would benefit them then this was the research that they wanted to see conducted in the future. They also mentioned that the results of evidence-based research, if positive associations were found, would be most beneficial as it would help validate their own lifestyle choices and would provide the inspiration for other people with MS to also adopt potentially beneficial lifestyle changes.

We also asked people in this group if they would consider it a burden to be asked to answer questions online that would take around 1 hour. They were specifically asked to consider whether the proposed questions were interesting and relevant and whether they felt the questions would cause them distress. Importantly, all participants expressed that the length of the questionnaire did not influence whether or not they would enroll and participate in the proposed study. That is,

participants did not consider completing questions that would take around 1 hour to complete would be onerous and did not consider it would be a barrier for other people with MS participating in the study, provided it could be done over time (as is the case with our online questionnaires). Many said they would complete hundreds of questions if it could help other people with MS. In fact, all participants were commited to do what they could to help people with MS.

We asked whether they thought completing these questionnaires would pose any psychological distress to themselves or other people with MS. None of the participants experienced any psychological distress from either set of questionnaires and also thought other people with MS would also consider that the questionnaires would pose low psychological distress.

Following this consultative process, analysis of the qualitative interviews and focus group discussions, the MS Online course and validated participant questionnaires were modified to address the needs and research priorities of people with MS.

Additionally, study participants will be emailed with a plain language summary of results at the end of the study period. Additionally, as all publications will be open-access, participants and the general public will have access to them.

DATA ANALYSIS

This will be led by Dr Steve Simpson-Yap. Oversight will be provided by other study investigators.

Responsibilities of the data management team will include: development of a statistical analysis plan, participant tracking, data cleaning, and data analysis at the conclusion of the trial. Researchers responsible for data cleaning and validation throughout the study will be blinded to allocation.

Appendix

List of Attachments included:

Document Name	Version Number	Date (eg. 18 January 2012)
DHQ.pdf (Dietary Habits Questionnaire)	1	30 August 2021
HADS.pdf (Hospital Anxiety and Depression)	1	13 December 2021
Self-efficacy: UWSE-6	1	13 December 2021
Perceived social support: MSPSS	1	13 December 2021
MSQOL54.pdf	1	30 August 2021
FSS.pdf (fatigue severity score questionnaire)	1	30 August 2021
MSOC Qualitative interviews.docx (telephone/internet script)	1	30 August 2021
Participant Information form.docx (includes consent form)	3	13 December 2021
Withdrawal form – MSOC – RCT.docx	1	30 August 2021
Effectiveness survey.pdf	3	13 December 2021
MSOC protocol.pdf	3	13 December 2021

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