Changing Behaviour towards Aerobic and Strength Exercise (BASE): Design of a randomised, phase I study determining the safety, feasibility and consumer-evaluation of a remotely-delivered exercise programme in persons with multiple sclerosis

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Changing Behaviour towards Aerobic and Strength Exercise (BASE): Design of a randomised, phase I study determining the safety, feasibility and consumer-evaluation of a remotely-delivered exercise programme in persons with multiple sclerosis.

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Abstract

Background

Multiple sclerosis is a chronic progressive neurological disease. Evidence attests to the benefits of exercise, guidelines for exercise in multiple sclerosis are available. Remote-delivery of exercise adherence programmes based on the exercise guidelines require urgent testing.

Aims

The design, and outcomes of Behaviour towards Aerobic and Strength Exercise in MS (BASE-MS), a remotely-delivered exercise training study based principles of behaviour change, will further evaluate the remote-delivery of the current exercise guidelines.

Methods

BASE is a 4-month clinically relevant randomised controlled trial to explore the delivery of a remotely supervised, guidelines-based exercise programme for persons with multiple sclerosis, underpinned by principles of health behaviour change. Initially, 72 persons with mild to moderate multiple sclerosis will be randomised in a 1:1:1 allocation to receive the BASE programme, or act as controls continuing usual care. On programme completion, exercise participants will be further randomised to an optimised adherence treatment or usual adherence. Our online survey assesses the primary outcome of exercise participation, and secondary outcomes of symptoms, and correlates of behaviour change at baseline, month four, month five and month eleven. Online surveys will capture coach and participant feedback to identify the contexts, mechanisms and outcomes of BASE implementation.

Conclusions.

The research and clinical landscape for MS management must remain in-step with public health and health communication. BASE tests the remote-delivery of the current exercise guidelines for exercise in persons with MS. Safety, feasibility and evaluative outcomes will provide rich data for future remote-delivery of exercise in neurological conditions.

Keywords

Exercise training

Remote-delivery

Tele-rehabilitation

Multiple sclerosis

Exercise guidelines

Highlights

Clinical trials of exercise in multiple sclerosis have been slow to adopt interventions which explore the safety, feasibility and evaluation of the guidelines for exercise in multiple sclerosis

Few trials of exercise in multiple sclerosis have methodology designed to test for participation and adherence to exercise.

Protocols for the remote-delivery of exercise training in persons with multiple sclerosis are urgently needed to inform researchers and clinicians of the safety, feasibility, consumer evaluation and efficacy of telerehabilitation.

Protocols to gather the health-economic cost, and consumer feedback are critical to understand the context, mechanisms and outcomes inherent in remote-healthcare.

Authors Contributions

YL is responsible for the design of the protocol, the creation of the manuscript, overseeing delivery of the intervention and supervising and advise junior researchers. Corresponding author

IK is responsible for the design of the protocol and will oversee intervention delivery

SB is responsible for the design of the protocol and will oversee intervention delivery

TF is responsible for the design of the protocol, supervision and advising junior researchers

LP is responsible for the design of the prescribed exercises and advising junior researchers

FvR is responsible for the design of the protocol, supervision and advising junior researchers

Declaration of Competing Interest

The authors certify there is no conflict of interest with any financial organisation regarding the material discussed in the manuscript.

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Introduction

Multiple sclerosis (MS) is a chronic, autoimmune-mediated, disease of the central nervous system, with no known cure (1). MS affects over 2.8 million people globally(2), and commonly results in cumulative physical and cognitive disability. The burden of MS has both personal and societal impacts, and this extends into participation in optimal health behaviours, such as exercise. Upwards of 80% of persons with MS are not engaging with sufficient amounts of exercise necessary for health-related quality of life benefits(3).

Three decades of scientific enquiry have established the many health benefits of exercise training in persons with MS (4). Original guidelines, for aerobic and resistance exercise, for persons with mild to moderate MS, were developed in 2013 (5,6), with recent updates for advanced exercise(7) (abbreviated in Table 1). However, qualitative inquiry of healthcare providers indicates that many clinicians may not be promoting the guidelines(8,9). Further barriers to persons with MS participation in exercise may also stem from reduced access to relevant healthcare services(10,11) identifying a need for remote-delivery of exercise training programmes. The most pressing and urgent need to develop, and report on remotely-delivered exercise programmes based on the MS exercise guidelines, occurred in early 2020 when global rehabilitation services were restricted or stopped during the ongoing COVID-19 pandemic. There is further concern, as it is becoming clear that despite exercise interventions clearly resulting in benefits over the course of the intervention, improvements are not sustained after the intervention concludes(12). Exercise interventions in MS research must design studies to better understand long term adherence to exercise after an exercise intervention(13).

	General aerobic exercise	Advanced aerobic exercise	Resistance exercise
How often	Minimum 2 days/wk	Minimum 5 days/wk	Minimum 2 days/wk
How much	30 minutes per session	40 minutes per session	Up to 3 sets of 8-15 repetitions of whole body exercises
How intense	11-13 RPE	Approaching 15 RPE	Where 8-15 repetitions are comfortable

Note: RPE – Rating of Perceived Exertion, based on the 20 point scale.

Table 1 Abbreviated exercise guidelines(5–7)

Herein we describe the protocol our study to change Behaviour towards Aerobic and Strength Exercise (Project BASE), a remotely-delivered exercise training programme based on the current exercise guidelines, for persons with mild-to-moderate MS. The BASE study is a Phase I clinical trial, which utilises a two-stage, blinded, block-randomisation design and incorporates long-term follow-up. The primary scientific aim is to assess the nationwide remote delivery of the BASE intervention in Australian-dwelling persons with mild-to-moderate MS, for improving immediate exercise participation as measured via the Godin Leisure Time Exercise Questionnaire (GLTEQ)(14); and to provide data for a future Phase II multisite study. The secondary aims are to evaluate the long-term effect of participation in the BASE intervention on exercise participation, and to determine the effect of strategies to boost exercise adherence (i.e., communication with another participant). Further via a realist approach to programme implementation we will determing ; How do the guidelines work", "Why do the guidelines work", "For whom do the guidelines work" and "In what circumstances do the guidelines work"(15). Such knowledge is needed to ensure we can move forward in a meaningful way, to encourage research and clinical uptake of health guidelines in MS.

Methods

This protocol describes a remotely supervised, telehealth delivered, guidelines based exercise programme for persons with mild to moderate MS which is underpinned by Social Cognitive Theory (SCT) (16) of health behaviour change.

Trial Design

The BASE study was developed with stakeholder engagement and represents a remotely-supervised remotely-delivered exercise-training trial that follows a two-stage randomised controlled design. In Figure 1 a CONSORT-relevant (17) overview of the enrolment and randomisation steps displays the randomisation process for our participants, recruited over two waves. They will be randomised into general exercise training, advanced exercise training, or a usual care control condition. The general and advance exercise programmes align to the recommended general and advanced exercise prescription for persons with mild to moderate MS(7). A second randomisation will occur when the exercise training participants are randomised into an optimised adherence condition or usual adherence condition.

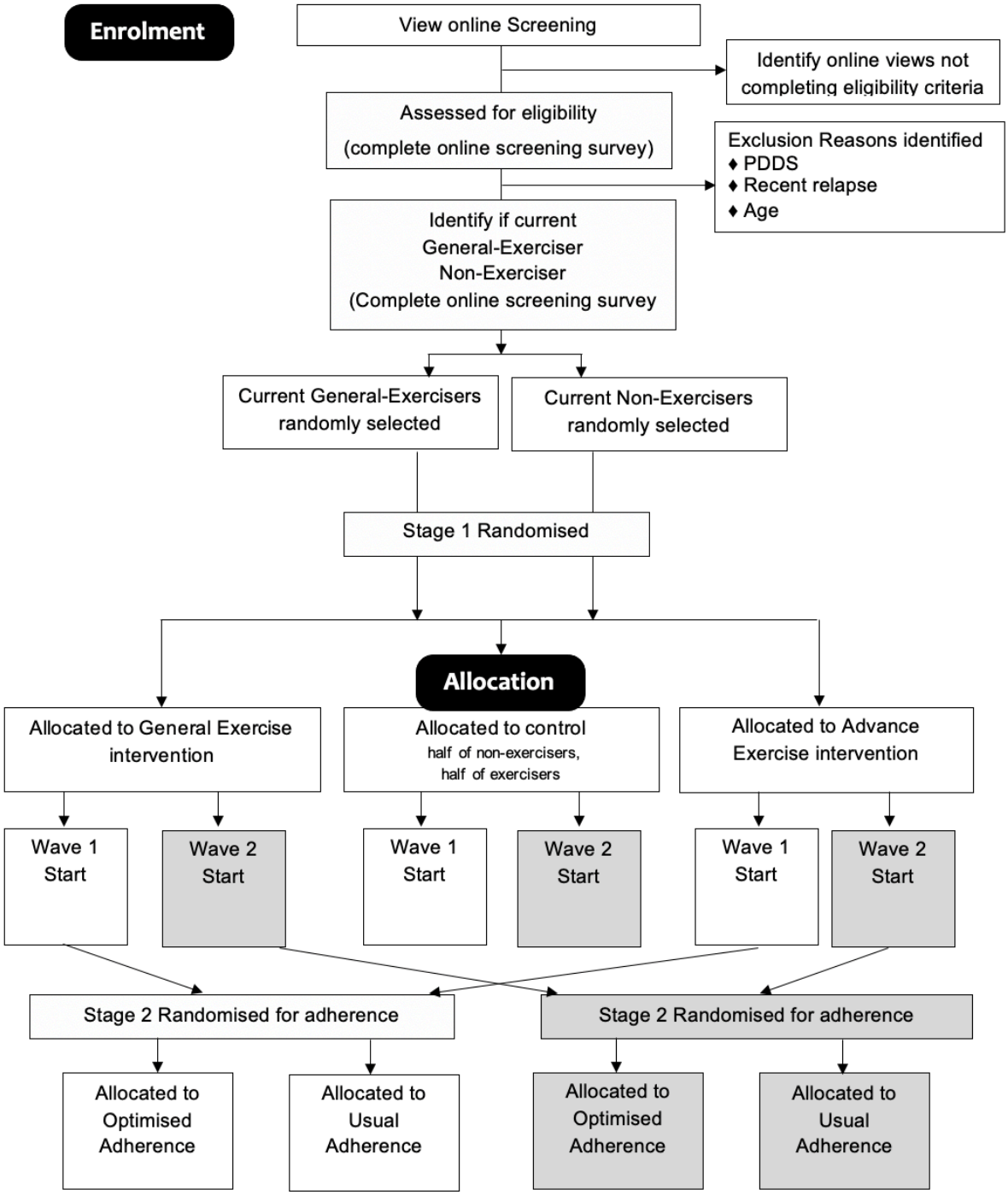


Figure 1 Participant recruitment and randomisation

The trial will identify the safety, feasibility and consumer evaluation of a 20-week evidence-based exercise programme delivered over tele-health compared with usual care in persons who have mild-to-moderate disability as a result of MS. Elements of the programme follow previous feasibility studies delivering the guidelines for exercise in MS(18,19). The participants in the exercise condition will all receive the BASE package of manual, individualised exercises accessed via an online library of exercises, reminder text messages, behavioural coaching video calls, behavioural newsletters to encourage exercise adherence, mini-pedometers, and resistance bands. The behavioural principles will be based on SCT (16), and delivered in an order similar to previous study protocol(18,19).

Exercise participants allocated to the optimised adherence condition will be introduced to another BASE participant after month four of the intervention, and encouraged to maintain contact.

The primary outcome is exercise participation as reported via the GLTEQ(14). The secondary outcomes are focused on adherence and are also all self-report, they are; the Exercise Goal Setting and Planning Scale (EGSPS); the Exercise Self Efficacy Scale (ESES), and physical activity habits at each time point. We note that this serves the unique opportunity to gather exercise habits of persons with MS during public health restrictions. Further measures are focused on symptoms, health status, and quality of life. The outcomes were selected based on previous use in the literature, consumer discussion and research aims. The outcomes will be collected via online surveys at baseline, after month 4, after month 5 and after month 11. All data will be downloaded from the server and stored on password protected computers of the research team. The study has obtained ethical approval from the associated Institutional Review Board (Murdoch University 2019/021). All participants will provide written informed consent (online via our survey platform, as described below), consistent with the National Health and Medical Research Council's National Statement of Ethical Conduct in Human Research.

Consumer engagement

In line with recommendations of consumer involvement in research(21) we based study methods on outcomes reported in previously associated research(22,23). Further, feedback from participants in previous research (22) was considered, in particular the use of walking for the aerobic component, and the progressive nature of the programme to achieve the guidelines. We will provide variety in the resistance exercises, and add balance and flexibility exercises. We will aim to maintain consistency in participants coaches to encourage connectedness. In line with feedback from the research community after presentation of GEMS results(22), we will test the role of social connectedness (via our optimised adherence arm of the study) by randomly allocating participants to another BASE participant, and we will gather opinions from both intervention and control participants to guide future programme delivery.

We further engaged with consumers prior to beginning the study, and important concerns were raised around the impact of public health events affecting Australians at the beginning of the project (namely the aftermath of the Australian Bushfires and the beginning of the COVID19 pandemic). Additions made at this time following consultation with consumers, were 1. an increase in participant recruitment, as a response to the closure of many exercise-based health services; 2. adjustment to the exercises delivered in the first two weeks of the programme to reduce the definite reliance on equipment, as a response to delays in purchasing home-exercise equipment and delays in postal services delivering equipment to participants; 3. the addition of survey questions to establish the immediate impacts on the pandemic health service and exercise service closures on the activities of participants. Further, consumer engagement and release of new data(24) identifying difference in motivation between active and less active persons with MS, supported the post hoc addition of outcomes of Self-Determination Theory and Theory of Planned Behaviour.

Participant Recruitment

Participants will be enrolled from existing university databases of participants who have previously taken part in research, and through the social media accounts of MS Research Australia, MS Australia and associated State and Territory advocacy organisations. Participants will be provided with a weblink for further study details, and the research team e-mail address and contact phone number should they require information. They will provide informed consent via an online form. Screening for the study will occur in two-steps. First via the weblink asking participants to confirm they meet the eligibility criteria; 1. 18 years or older, 2. Self reported diagnosis of MS, 3. Relapse-free in past 30 days, 4. Patient Determined Disease Step(25) score of ≤4. Second via a telephone call

from the research team. The eligibility criteria were selected based on the appropriateness of the sample for completion of the physical activity guidelines. In line with the protocol for the intervention, which requires participants walk 1000 steps in 10 minutes the PDDS score of ≤4 was selected.

Eligible participants will be informed that if randomly selected for the programme they will be contacted by the research team. Participants who are not eligible to participate will be thanked for their interest and asked if they would like to be notified of future research opportunities at the University. Non-eligible participants will also be provided with a link to MS Australia's *Wellbeing & MS* resources. To identify if the potential participants are to be categorised as non-exercisers (i.e., not currently meeting the original guidelines), or exercisers (i.e., currently meeting the original guidelines) a second screening will ask participants if they participate in two sessions of moderate aerobic exercise per week, and two sessions a week of whole body resistance exercise. This will help identify whether participants are meeting the original physical activity guidelines(5,6). Further clarification of exercise behaviour will be confirmed by researchers over telephone to ensure correct group allocation. These participants will be phoned by the research team to explain the details of the study, directly answer questions, and to confirm their responses to screening questions (i.e., current exercise behaviour). A researcher not associated with programme delivery or outcome assessment will use a computer generated randomisation order to select participants for participation. In this Phase I study, participants will be allocated to the study over one of two waves, there will be no difference in recruitment-method, participants or intervention delivery between waves. Two waves of participants are required due to staff availability. The planned participant flow through to wave allocation is indicated in the Consort diagram, Figure 1.

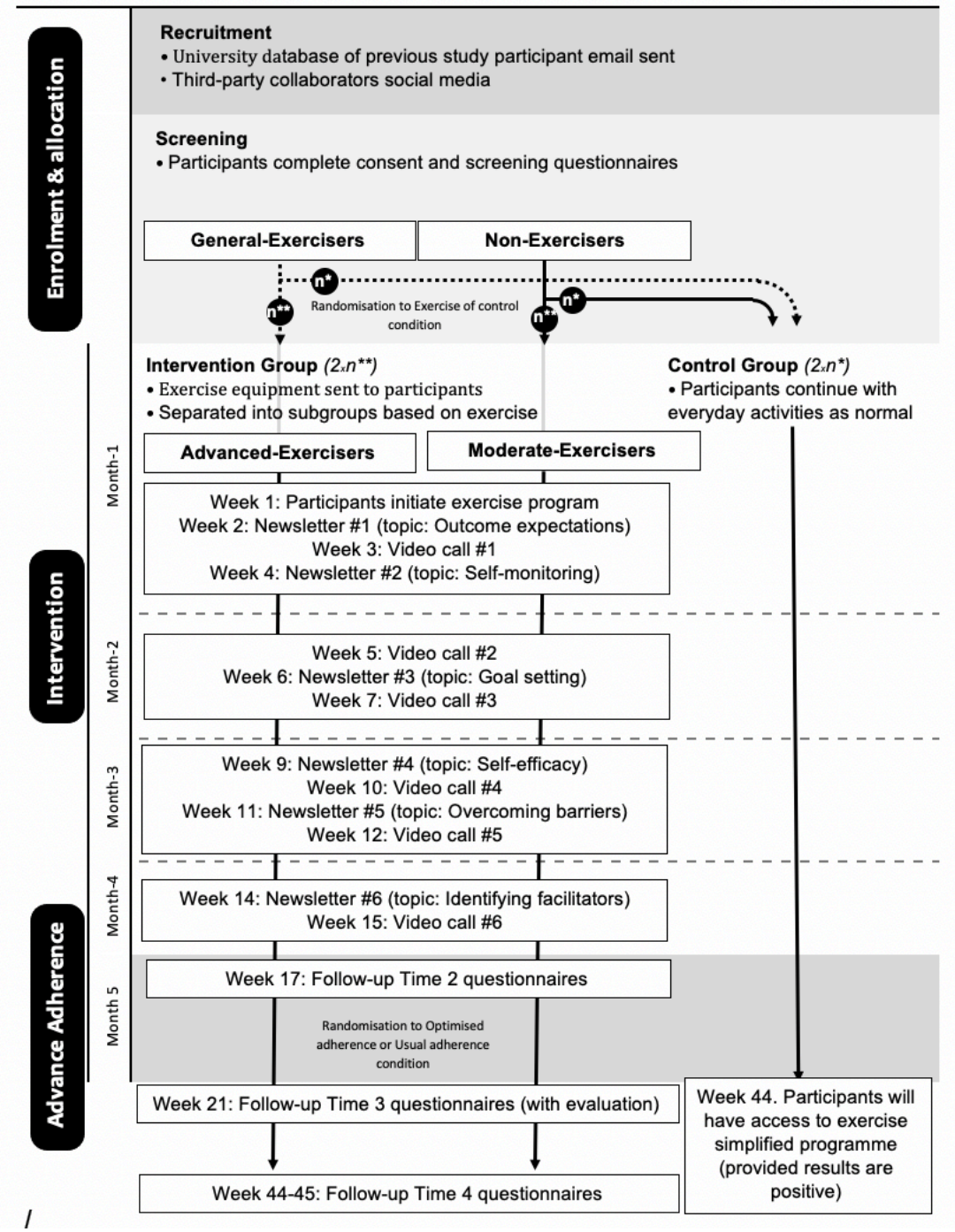
Sample Size Calculation

The primary aim of our phase I study is to assess safety, feasibility, and to gather consumer evaluation of a nationwide remote delivery of the BASE intervention in persons with mild-to-moderate MS. In this exploratory study we will determine safety and feasibility of the current exercise guidelines in a small group, the sample number will be maximised however will be limited by available time for study duration and financial resources. Our *a-priori* power analysis, determined with our primary outcome (GLTEQ), over the initial 2 timepoints X 3 groups will provide a large effect size (*f=0.40) as follows;* assuming a standard *a* of .05 when testing the significance of between groups effects, our sample *n* = 52 had an estimated Power of 0.83, assuming moderate relatedness (*r* = 0.50) between the two waves of measurement. If we modified the relatedness between repeated measures to be weaker (*r* = 0.30, Power = 0.88) and stronger (*r* = 0.70, Power = 0.78), this will have a minor influence on statistical power. For a future Phase II trial we will determine sample size based on the results of this phase I study with the aim of assessing efficacy of the BASE study for improving immediate exercise participation as measured via the GLTEQ (14).

Randomisation

After participants qualify for the study, a number will be randomly selected to enter the study, randomisation will occur in two stages (Figure 1). Stage 1 randomisation will occur after baseline measurements are collected, allocation to exercise (general or advanced) or control group will be stratified by non-exerciser and general-exerciser in a 1:1:1 configuration (Figure 2 for diagrammatic explanation). Participants will be allocated to the exercise groups according to current physical activity levels (i.e., general exercisers meeting original physical activity guidelines or non-exercisers not meeting guidelines) using two separate computer-generated randomisation sequences. Only participants not currently meeting the guidelines will be allocated to the General exercise group, and only those participants meeting the guidelines will be allocated to the Advanced exercise group. The

control group will be matched to contain both participants not currently meeting guidelines, and participants who are meeting guidelines. For randomisation participant deidentified identification (ID) codes will then be forwarded to a researcher not involved in the delivery of the programme. That researcher will then randomly allocate participants to either General Exercise Intervention or Advanced Exercise Intervention, or Control group (the control group will contain equal quantities of those meeting guidelines and those not meeting the guidelines). After the first four months of the study period, the second stage of randomisation will occur. Both the moderate and advanced exercisers will be randomised to either the optimised adherence group or the usual adherence group during the Stage 2 randomisation. Stage 2 randomisation will follow a similar strategy to stage one. Our research study allows for participants who are exercising at the start of the study to continue in these pursuits. We collect data on physical activity habits at each time point to report on, and potentially account for, these behaviours.



Note: further questionnaires are conducted at week 21 (month 6) and 44 (month 12) as part of the larger BASE trial, however they are omitted from this Figure. n* one sixth of the total number of study participants, n** two sixths (one third) of the total number of study participants

Figure 2. Full overview of study timings, intervention delivery and online surveys

Outcomes and metrics

Feasibility Metrics

Per the recommendation in Learmonth and Motl(27), we will gather data on process, resource, management and scientific feasibility.

Process Feasibility will be measured via; 1. Recruitment rate (number of interested and eligible participants/number of persons viewing recruitment site) and 2. Reaction to both randomisation stages (based on reasons for drop-out after the announcement of group allocation).

Resource feasibility will be measured via 3. Retention rate (reported via a CONSORT diagram(28), 4. Reported barriers to participation, 5. Adherence with the protocol (total sessions completed/prescribed sessions (i.e., 2 aerobic, 2 resistance sessions per week), 6. Compliance with the protocol (e.g., total completed exercises (set x reps x exercise)/prescribed exercises (set x reps x exercise), 7. Participants reaction to the survey for outcome measures (response to question on length of study), 8. Access to and cost of equipment, and staff time requirements (total hours/participant), 9. Hours of staff training, and 10. Participant and coaches evaluation of the programme.

Management will be measured via: 11. Access to/delivery of equipment, 12. The number of data collection prompts required (number of e-mails/telephone calls required as survey reminders to participants).

Scientific feasibility will be measured via the scientific outcomes next discussed.

Scientific outcomes

Data for primary and secondary outcomes will be collected via Qualtrics (Qualtrics©, Provo, UT(29)), a survey software tool. Participants will be provided a unique survey ID to enter at each time point, and questions on date of birth and year of diagnosis will be collected at all time points. These measures are to confirm participant data between surveys at the different time points. All data are self-report.

Primary outcome*The Godin Leisure-Time Exercise Questionnaire (GLTEQ)*(14,30), is the primary outcome and provides a self-report measure of physical activity. The GLTEQ is a valid self-report measure of physical activity, it is a simple and effective tool for monitoring physical activity, and is noted as a highly appropriate primary outcome for measuring the change in physical activity in response to an intervention(31). The tool includes three questions, to determine 7-day participation in strenuous exercise, moderate exercise, and mild exercise. Scores are calculated from these three questions using the established protocol(14). Participants will be asked to report on all forms of exercise they participate in when responding to the GLTEQ.

While self-report measures are vulnerable to recall bias and overestimation of physical activity behaviour, they are unobtrusive and cost effective. Further, for home-based country-wide studies, online self-report measures are not reliant on the postal service to send and return physical activity data collection devices promptly.

Secondary outcome measures

The Leeds MS Quality of Life Scale (LMSQOL)(32) determines disease related quality of life. The LMSQOL is an 8-item scale which is well-documented psychometric properties in MS(33).
Health related quality adjusted life years (QALYs) will be measured via the European Quality of life 5 Dimensions 5 Levels (EQ-5D-5L) scale. The scale determines health-related quality of life by deriving a health state utility from the EQ-5D-5L multi-attribute utility instrument(34). Versions of this scale have been used in few exercise intervention studies for MS(35), and such data is important in clinical

and healthservice decision making to identify cost-effectiveness and quality in intervention delivery(36). We will compare results from the EQ-5D-5L with the Australian set of QALYs to provide a cost-utility analysis of the BASE programme(37).

Modifiable psychosocial constructs of exercise behaviour will be measured for constructs of SCT (16) with Exercise Goal Setting and Planning Scale (EGSPS)(38) and the Exercise Self-Efficacy Scale (ESES) (39). The 20-item EGSPS (40) and the 6-item ESES are consistently shown to correlate with predictors of physical activity in MS(41,42). We will capture data on Exercise Habits outwith of the BASE prescribed exercises by asking participants to report on the previous 7-day participation in aerobic exercise, team sports, other physical activity, resistance exercise, balance exercise, and stretching exercise. We will ask for information on the use of equipment, sessions of activity per week, average session duration, intensity, the venue of each type of exercise (i.e., performed inside or outside), and alone or with other people.

Symptoms of fatigue will be assessed with the Fatigue Severity Scale (FSS), the 9-item FSS has established psychometric properties in persons with MS(43). Symptoms of anxiety and depression will be assessed with the Hospital Anxiety and Depression Scale (HADS). The 14-item HADS is an appropriate tool for identifying mood-constructs in MS (44). Self-perception of balance and walking will be assessed with the Activities Balance Confidence scale (ABC) and MS Walking Scale (MSWS), respectively. The ABC scale is a 16-item questionnaire and the MSWS is a 12-item questionnaire, both have previously been shown appropriately for use in MS(45,46).

Evaluation plan

To take a Realist evaluative approach to determine how the intervention works, we will gather feedback from both participants and coaches. A survey will be sent at the end of the 5-month intervention period, with questions based on 1. realist principles of evaluation (15) (i.e., to understand context, mechanisms, and outcomes) and 2. understanding adherence using behaviour change models (47), (i.e. Capability, Opportunity and Motivation); and exercise programme preferences (23). Feedback questions are summarised in Table 2. A brief survey will be sent to coaches following completion of the intervention to understand the realist principles of context and mechanisms associated with the intervention delivery.

Respondent	Questioning	Response style	Associated principle and theory
Coaches	What positive outcomes did your clients experience from engaging with GEMS?	Free text	Realist - outcomes
	Why do you think they have these positive outcomes from GEMS?	Free text	Realist - mechanisms
	What circumstances might have made them unable to experience these positive outcomes	Free text	Realist - contexts
	How suitable was the BASE program to the symptoms associated with MS?	0-5 Likert scale	Realist - mechanisms
	How suitable was the BASE program to the fitness level of your clients?	0-5 Likert scale	Realist - mechanisms
	How much would you recommend the BASE program to other clinicians?	0-5 Likert scale	Realist - outcome
	In what circumstances (to who, for when, for what) would you recommend the BASE to other clinicians for delivery to persons with MS?	Free text	Realist - contexts
	In what circumstances (to who, for when, for what) would you not recommend the BASE to other clinician for delivery to persons with MS?	Free text	Realist - contexts
	How satisfied do you think your clients were with: The overall BASE program? Why do you think that? The program manual? Why do you think that? The exercise videos? Why do you think that? Logging exercises on the website? Why do you think that? The exercises you had to do? Why do you think that? The e-mailed newsletters? Why do you think that? The video coaching calls? Why do you think that?	0-5 Likert scale Free text	Realist - outcome Realist - mechanisms
	How appropriate was: The BASE programme during the COVID19 pandemic? Why do you think that? The BASE as a programme delivered as part of the healthcare system? Why do you think that?	0-5 Likert scale Free text	Realist - outcome Realist - mechanisms
Intervention participants	What positive outcomes have you experienced from engaging with GEMS?	Free text	Realist - outcomes

	Why do you think you have experienced these positive outcomes from GEMS?	Free text	Realist - mechanisms
	In what circumstances might have made you unable to experience these positive outcomes	Free text	Realist - contexts
	How suitable was the BASE program to your MS symptoms?	0-5 Likert scale	Realist - mechanisms
	How suitable was the BASE program to your personal fitness level?	0-5 Likert scale	Realist - mechanisms
	How much would you recommend the BASE program to others like you?	0-5 Likert scale	Realist - outcome
	In what circumstances (to who, for when, for what) would you recommend the BASE to others like you	Free text	Realist - contexts
	In what circumstances (to who, for when, for what) would you not recommend the BASE to others like you	Free text	Realist - contexts
	How satisfied were you with: The overall BASE program? Why do you think that? The program manual? Why do you think that? The exercise videos? Why do you think that? Logging exercises on the website? Why do you think that? The exercises you had to do? Why do you think that? The e-mailed newsletters? Why do you think that? The video coaching calls? Why do you think that?	0-5 Likert scale Free text	Realist - outcome Realist - mechanisms
	How appropriate was: The BASE programme during the COVID19 pandemic? Why do you think that? The BASE as a programme delivered as part of the healthcare system? Why do you think that?	0-5 Likert scale Free text	Realist - outcome Realist - mechanisms
Optimised Adherence participants	How satisfied were you with: The buddy program? Why do you think that?	0-5 Likert scale	Realist - mechanisms
	To what extent do you agree that being partnered with a buddy helped you complete adhering to the programme Why do you think that? To what extent do you agree that you will stay in touch with your buddy over the next 6-months Why do you think that?		Realist - outcome

All participants	Please reflect on your experiences over the past 5-months, think about your ideal exercise programme		
	How many days per week would you like to do exercise?	1 2 3 4 5 6 7	Realist - mechanisms Behavioural – capability and opportunity
	How hard would you like to work? Light, moderate, moderate-to-vigorous, vigorous*		Realist – mechanisms Behavioural – capability and motivation
	How long would you like the programme to last? Up to a month, 1-4 months, 4-6 months, 6+ months		Realist – mechanisms Behavioural – capability, opportunity and motivation
	What type of exercise would you like to do** Category 1 Yoga Archery Fishing Bowling/bowls Golf Stretching exercises Balance exercises Category 3 Running Jogging Hockey Football Soccer Squash Basketball Boxing Judo Roller skating Vigorous swimming Vigorous bicycling Category 2 Brisk-walking Cricket Tennis Easy bicycling Volleyball Badminton Surfing Stand-up paddle boarding Easy swimming Dancing Pilates Exergaming (e.g. Wii fit) Strength and resistance exercises	Choose a maximum of 3 per category	Realist – mechanisms Behavioural – motivation
	Where and with who would you like to do your exercise programme? On your own inside (in your home, in another venue, where?) Please describe On your own outside With other people inside (in your own, in another venue, where?) Please describe With other people outside	Choose 1	Realist – mechanisms Behavioural – opportunity and motivation
	Would you like a behavioural and exercise coach (i.e., someone to help support you throughout your program with knowledgeable feedback and encouragement)? If yes, if you could choose your ideal behavioural and exercise coach what	Yes No Yes No don't mind	Realist – mechanisms Behavioural – opportunity

	would you choose? Same Gender Similar Age Someone with MS Someone with similar fitness as you Someone you aspire to be like in terms of fitness Other – please explain		
	If yes through which form of communication would you like to use to reach this person? E-mail Phone calls Zoom/Facetime In person Other (please state)	Choose 1	Realist – mechanisms Behavioural – capability
	How often would you like to be in contact with this person Once per week Once per month More frequently in the beginning and then taper off as it progresses Once per week Once per month More frequently in the beginning and then taper off as it progresses		Realist – mechanisms Behavioural – capability and motivation
	Would you like to track your progress in your exercise program? How would you like to track you exercise program A paper logbook Through a website App on your phone Other (please state)	Yes No	Realist - mechanisms
	What type of information would you like to receive as part of your program? Safety and exercise for MS Relapsing and exercise Fatigue and exercise Remembering to exercise The link between exercise and MS The purpose of exercise Monitoring your exercises Setting exercise goals Understanding the consequences of not exercising Setting up my exercise environment/space Using equipment to exercise Fitting exercise into my daily routine Working out what might prevent you	Choose a maximum of 5	Realist – mechanisms Behavioural – Capability Behavioural - Capability and motivation Behavioral – Opportunity

	exercising Working out what might help you keep exercising		Behavioural – Opportunity and motivation

Note: *Light - feels like you can maintain for hours. Easy to breathe and carry out a conversation, Moderate - breathing heavily, can hold short conversation. Still somewhat comfortable, but becoming noticeably more challenging, Moderate-to-vigorous - becoming more uncomfortable and challenging. Can hardly hold a conversation, Vigorous - Borderline uncomfortable, short of breath, can speak a sentence. **Based on examples from GTLTEQ and modified for Australian culture.

Table 2 Mapping of Evaluation plan to the Realist principles and behaviour change model theory

Demographic and clinical descriptors

We will gather demographic information on age, sex and employment. We will gather clinical data on disability level using the Patient Determined Disease Steps(25) which has been shown to correlate highly with clinically determined disability(48), years since diagnosis, MS-type at diagnosis, use of disease modifying therapies, and use of symptom modifying therapies.

Intervention

Exercise prescription is based on the original (5,6) and updated (7) exercise guidelines for persons with mild-to-moderate MS. The progression rates (Table 3) and order of information on behaviour change (Figure 2) are based on previous delivery of the exercise guidelines (18,19). Neurological physiotherapists (YL and LP) and an exercise physiologist (TF) developed the content of the exercise programme. A neurological physiotherapist (YL) and exercise psychologist (FvR) developed the behaviour change materials in association with a graphic designer (OC Clothing, Perth, WA).

The BASE intervention is a remotely-delivered exercise training intervention comprising aerobic and resistance exercise. The intervention includes delivery of educational materials grounded in Social Cognitive Theory (SCT) of behaviour change (16), and coaching calls to monitor exercise prescription and educate participants on principles of behaviour change. The resistance training will consist of two days per week of resistance training. Each resistance training session will consist of 1–2 sets, 10–15 repetitions of 10 exercises targeting the lower body, upper body, and core muscle groups. Participants will receive elastic resistance bands (Progymnasium, Resibands™, NSW, Australia), and access to a dedicated website of individualised exercises (www.giraffehealth.com), models in the videos represent diversity in age, gender, race and body shape. Each participants individualised exercise programme is progressed fortnightly, per Table 3 with exercises chosen from the range of wholebody exercises indicated in Table 4. Coaches will demonstrate and supervise these exercises during coaching calls

Table 3. Ongoing aerobic and resistance exercise prescription for the Advanced and General and exercise group, with three rates of progression

	Advanced-Exercisers Group						General-Exercisers Group					
Week	Red		Black		White		Red		Black		White	
	Walking	RE	Walking	RE	Walking	RE	Walking	RE	Walking	RE	Walking	RE
1	10 min	1-10-5	10 min	1-10-5	10 min	1-10-5	10 min	1-10-5	10 min	1-10-5	10 min	1-10-5
2	10 min	1-10-5	10 min	1-10-5	10 min	1-10-5	10 min	1-10-5	10 min	1-10-5	10 min	1-10-5
3	15 min	1-15-5	15 min	1-12-5	10 min	1-12-5	15 min	1-15-5	15 min	1-12-5	10 min	1-12-5
4	20 min	2-10-5	15 min	1-15-5	15 min	1-12-5	20 min	2-10-5	15 min	1-15-5	15 min	1-12-5
5	25 min	2-10-7	20 min	1-15-7	15 min	1-15-7	25 min	2-10-5	20 min	1-15-7	15 min	1-15-7
6	30 min	2-12-7	20 min	2-10-7	20 min	2-10-7	**30 min**	**2-12-5**	20 min	2-10-7	20 min	2-10-7
7	30 min	2-15-7	25 min	2-12-7	20 min	2-10-7	**30 min**	**2-15-7**	25 min	2-12-7	20 min	2-10-7
8	35 min	2-15-7	30 min	2-15-7	25 min	2-12-7	**30 min**	**2-15-7**	**30 min**	**2-15-7**	25 min	2-12-7
9*	35 min	2-15-9	30 min	2-15-9	25 min	2-12-9	**30 min**	**2-15-9**	**30 min**	**2-15-9**	25 min	2-12-9
10	**40 min**	**2-15-9**	35 min	2-15-9	30 min	2-15-9	**30 min**	**2-15-9**	**30 min**	**2-15-9**	**30 min**	**2-15-9**
11	**40 min**	**2-15-9**	35 min	2-15-9	35 min	2-15-9	**30 min**	**2-15-9**	**30 min**	**2-15-9**	**30 min**	**2-15-9**
12	**40 min**	**2-15-9**	**40 min**	**2-15-9**	35 min	2-15-9	**30 min**	**2-15-9**	**30 min**	**2-15-9**	**30 min**	**2-15-9**
13	**40 min**	**2-15-10**	**40 min**	**2-15-10**	35 min	2-15-10	**30 min**	**2-15-10**	**30 min**	**2-15-10**	**30 min**	**2-15-10**
14+	**40 min**	**2-15-10**	**40 min**	**2-15-10**	**40 min**	**2-15-10**	**30 min**	**2-15-10**	**30 min**	**2-15-10**	**30 min**	**2-15-10**

Note RE – Resistance exercises (sets-repetitions-number of exercises). **Bolded text denotes meeting guidelines.** *Addition of stretching and balance exercises and modify/select exercise for each individual participant. Participants will be expected to log into the online exercise diary to see their prescribed exercises and prescription on a weekly basis. If this is not possible participants will be e-mailed a PDF copy of their exercises, or these can be sent via Australia post. Our coaches can also explain the exercises over standard phonecalls if required.

	Exercise Name
Resistance exercises	Bicep curl/overhead press combination
	Bodyweight hold in chair
	Front Raise
	Resistance-band row*
	Resistance-band lawnmower movement
	Press-up*
	Wrist flexion and extension
	Calf raises*
	Lunges
	Marching on the spot
	Resistance-band alphabet-symbol with ankle
	Sit to stand
	Squats*
	Standing hamstring curl*
	Steps up
	Tricep Dip in chair
Aerobic exercise	Walking at a minimal rate of 1000 steps per 10 minutes*$^{\$}$
From month three participants complete balance and stretching exercises	
Balance exercises	Heel toe walking (easy to hard continuum)**
	Single leg standing (easy to hard continuum)
Stretches/mobility exercises	Ankle ROM circumduction**
	Seated SCM stretch (head turn)
	Seated shoulder stretch
	Seated triceps stretch
	Sit-and-reach calf stretch
	Spinal extension (with arms behind body/posterior to glutes)
	Standing calf stretch
	Standing quadriceps stretch

Note. *Week 1 exercises; **Week 9 exercises. Exercises are added/changed incrementally. ROM Range of motion, SCM Sternocleidomastoid. $^{\$}$Participants may progress to jogging if they choose

Table 4 Exercises prescribed during the programme

All participants will complete walking and five core resistance exercises (i.e., seated row, press-up, calf raises, squats and standing hamstring curl). This will be progressed to 10 resistance exercises by week 13 of the programme and each exercise is offered at a minimum of three levels of difficulty. The exercise videos provide progressions and regressions of exercise, and coaches prescribe these based on clinical discussion with the participant (i.e. shared decision making), and subsequent discussion with senior researchers (YL and TF). For example, the press-up exercise varies from a seated press up on a table, a wall press-up, a kneeling press-up, to a toe press-up. The programme follows the same structure for all participants (in either the General or Advanced exercise group) in the first two weeks, and then progression varies as described in Table 3. The exercise programme offers three levels of progression towards achieving the guidelines, the pace towards achieving the guidelines is quickest in the red programme followed by the black and then the white programme.

As recommended in the updated (7) exercise guidelines, balance and stretching/mobility exercise will be incorporated into the programme (as described in Table 3) at week 9. Participants will be

asked to complete dynamic balance exercises on two days per week, and stretching/mobility exercise following the resistance exercises.

The aerobic exercise intensity will be achieved as first used in the original GEMS program programme (18,19). That is, a pedometer-based aerobic exercise prescription will encourage participants to walk at a minimum rate of 1000 steps per 10 minutes (the intervention is not restricted to walking, and participants may progress to jogging if they choose); this rate is considered moderate-intensity exercise(49). Participants will be permitted to use the step counter on their personal device if preferred (e.g., their personal wrist-worn step counter or mobile phone), but will be asked to calibrate this with a 500 step calibration test on first use(18). To further prescribe moderate aerobic intensity, we will ask participants to aim for a Rating of Perceived Exertion (RPE) of 11-14(7) on a standard scale of 6-20(50). We will progress the exercise training as described in Table 3, indicating that all participants following the moderate exercise programme should be at the exercise guidelines by week 10 of the programme. All participants following the active exercise programme should be at the exercise guidelines by week 14 of the programme.

Participants in the exercise intervention receive an e-mail containing a PDF manual. The manual will be tailored dependant on whether the participant is in the Moderate exercise group or the Advanced exercise group; however, the only difference will be the quantity of aerobic exercise, per Table 3. The manual will contain information on; safety with home exercise, the exercise equipment, the exercise website, explanations on the use of the ratings of perceived exertion scale and explanation on the delivery of newsletters and coaching calls. As new exercise are added at week 9, participants will be sent updated manuals. In addition, for participants in the optimised adherence arm of the study, they will receive appropriate instructions in month five via an updated manual.

We will e-mail six newsletters over the course of the programme, in weeks 2, 4 ,6, 9, 11 and 14 (Figure 2). Each newsletter draws attention to SCT-topics in the following order; outcome expectations, self-monitoring, goal-setting, self-efficacy, identifying and overcoming barriers and identifying and using facilitators. In line with research on appropriately tailoring the GEMS programme (23) we will ensure the content is appropriate for an Australian audience in terms of exercise opportunity and gender representation in the enviroments and models of our photographs and protagonists of our inspiration stories. The layout of each newsletter includes explanation of the topic in relation to MS maintaining ongoing exercise behaviours, topic-relevant "experience-stories" from other people with MS who have benefited from exercise, topic-relevant written tasks for participants (for discussion with coaches) and website links to topic-relevant national and international online content. An example of the week six newsletter is provided as supplementary material. In the week following receipt of the e-mailed newsletters, participants will receive their one-to-one coaching call.

The coaching calls follow a semi-structured scripted content for consistency between coaches. There will be an introductory coaching call before week one which will cover topics of safety, equipment, exercise intensity, and an overview of the first two weeks of exercises. Then six video coaching calls will be delivered in weeks 3, 5, 7, 10, 12, and 15 (Figure 2). An example coaching call is available as supplementary material. Following the first coaching call, and on hearing participants goals and progress the coaches and senior research team will discuss which programme to follow. During the video-coaching calls coaches will also watch, and advise participants on their exercises, making appropriate correction on form and technique. This also assists coaches to know which exercises from the online video library to be prescribed for the next week of the intervention. On the weeks when coaching calls do not occur, weeks 1, 2, 4, 6, 8, 9, 11, 13, and 14 participants will receive reminder text messages to encourage adherence and compliance with the programme.

Participants will be asked to record all sessions attended (we will report this as adherence) and the number of sets and repetitions of each resistance exercise, and minutes of each aerobic exercise session (we will report this as compliance) in their diary on the exercise website. Text messages will be sent as reminders. In our analyses we will include the prescribed aerobic (i.e., duration of walk, number of steps, and Rating of Perceived Exertion (RPE) score) and prescribed resistance exercises in our primary reporting of compliance to meet the exercise guidelines. Participants may continue participation in any exercise prior to beginning the BASE programme, and if participants report on more exercise than is prescribed we will report adherence and compliance based on the most complete data sets.

Optimised adherence programme.

A second randomisation round will occur following Month four data collection. Participants following both the moderate and advanced exercise protocol will be randomised into the optimised adherence intervention, or asked to continue exercising following the programme as before. The optimised adherence will involve participants being introduced to another BASE participants, from either the moderate or advanced exercise grouping. In week 17 coaches will set up a mutual phone call between themselves and the two BASE participants. It will be explained that participants are encouraged to stay in touch with each other, and to encourage exercise participation amongst each other. Optimised adherence participants will be asked to record, and provide a report of their interactions with their BASE partner until the end of month 5 via a online log book.

Control participants

Participants allocated to the control group at the first randomisation period will be asked to maintain their lifestyle. If the intervention is deemed to show positive results, at the end of the study control participants will be offered the BASE manual and newsletters. They will not receive the exercise equipment (mini-pedometer and resistance bands), the behaviour coaching calls or have access to the website. Recent evidence indicates that the provision of written or PDF material of the exercise guidelines (or in our case the BASE manual and newsletters) has beneficial outcomes for positive exercise behaviour in persons with MS(51).

Safety and adverse events protocol

Exercising safely at home is the first topic in the BASE manual, and safety discussions underpin the first, and all future, coaching calls. Coaches discuss possible risks and harms of exercise with participants. We will gather data on relapse and adverse events in one of two ways. First, we will report on any relapses, adverse events or serious adverse event communicated to research staff during the intervention period of the study. We will include in all follow-up data collection time points questions on the following. 1. Consultations with a healthcare professional (in person or via telehealth), 2. Visits to a hospital, 3. Change(s) in MS symptoms, 4. Change(s) in muscular or joint health, and 5. Falls frequency.

We will classify relapse as an acute onset of new or worsening neurological symptoms, lasting over 24 hours (52). We will classify an adverse event as an unfavourable health outcome that occurs during or after the intervention (53), we will report on adverse events which have a causal relationship, or not, to the intervention. We will classify a serious adverse event as an unfavourable health outcome that results in death or is life-threatening, requires hospital admission, or results in significant or permanent disability that occurs during or after the intervention(54), we will report on serious adverse events with a causal relationship, or not, to the intervention.

During the study, serious adverse events will be reported appropriately to the university ethics committee, and researchers will act appropriately following ethical protocol. For example, should a

serious adverse event be reported from a participant, we will follow ethical procedures and if required remove the participant from the study. Per our planned intention to treat protocol, we will include data from any participants removed or who choose to leave the study in our analysis.

Coaches training

Coaches will be physiotherapists, exercise physiologists or student exercise physiologists. BASE participants will be partnered with the same coach for the duration of the first 4 months of the intervention. These behavioural coaches will receive manualised training on the BASE programme, and the six steps of SCT included in the programme, described below. Coaching video calls to participants will follow a semi-structured script including; participant updates on status since last call, discussion on newsletter content and supervision of exercises. The manualised training, and semi-scripted coaching calls. Resources to create a comprehensive BASE clinical trial training course will be developed from the coaches training, and video calls during this trial. We will use these *real trial experiences* to train researchers and clinicians involved in future delivery of BASE (i.e., our Phase II multisite clinical trial).

Coaches will meet online with all BASE collaborating researchers on a fortnightly basis to discuss study progress. These meetings allow for discussion of issues, and reflection of coaches experiences with senior rehabilitation experts (YL and TF).

Procedures

Confirmation of recruitment, screening and consent will be via an online surveys. Participants randomly selected for participation will be contacted by the research co-ordinator, and a full description of the study provided. Interested participants will then be sent a link to complete the online survey. Following baseline survey completion participants will be randomly allocated to the exercise intervention group or the control group. All patient reported outcomes will be reported at baseline, after four months of the intervention, after five months of the intervention, and six months following completion of the intervention (i.e., month 11). Coaches and participant evaluation feedback will be captured after the end of the intervention delivery (i.e., month five). Participants will be sent an e-mail with a link to complete their survey at each time point, they will further be contacted via phone up to three times to remind them to complete the survey. Coaches will further remind exercise intervention participants to complete upcoming surveys. If a survey is missed participants will remain in the study, and will receive e-mails, phone calls and text message reminders for the future survey.

Data management and analysis

Feasibility metrics

Process, and management outcomes will be reported and analysed where relevant as total counts and means (SD). Resource outcomes will be analysed as percentage rates, counts and free text responses to relevant evaluation survey questions. The qualitative free text responses will be analysed for common themes and reported for trends to compliment quantitative evaluative responses. In our analyses we will include the prescribed aerobic (i.e., duration of walk, number of steps, and RPE) and prescribed resistance exercises in our primary reporting of compliance to meet the exercise guidelines. We will report on adherence to balance and flexibility exercises as prescribed.

Scientific outcome data

Participants outcomes and participant and coaches evaluation data will be entered directly by them into the Qualtrics online survey site. Research staff will then download the data directly from the website into Microsoft Excel SPSS (v 24). Data will be cleaned and tested for normality. Missing data will be replaced using multiple imputation techniques in SPSS unless attrition rates are very high (i.e., exceeding 33%).

The effect of the intervention on primary and secondary outcomes will be examined using a Condition (i.e., advanced exercise v moderate exercise v control) x Time (i.e., baseline v month 4 outcomes) mixed-model ANOVA. We will undertake exploratory analysis for Condition x Longitudical Time (i.e., all time points), adjustifying for adherence group using a mixed model ANOVA. We will undertake exploratory analysis of other study variables, for example the effect of; second level randomisation, wave, coach. Effect sizes associated with F-statistics will be expressed as eta-squared (η2). Effect sizes based on a difference in mean scores will be expressed as Cohen's d. The η2 values for the interaction-term from the ANOVAs will serve as the effect sizes for future power analyses.

We will use accepted principles(55–57) to determine clinically meaningful change in symptoms and disease specific QOL based on established benchmarks (33,43,45), for cost utility we will adopt the Canadian and UK value of 0.037 utility points(58) as this data is not currently available for Australia. We will compare our findings with previous application of the guidelines and other relevant literature. Further, longitudinal analysis of cost utility (e.g. utilities derived from EQ-5D-5L) will be be made with concomitant collection of cost data (e.g., employment status, use of disease modifying therapies, and use of symptom modifying therapies).

Publication plan

Following this protocol paper, we have a priori plans for three associated papers, with further exploratory publications as appropriate. The three proposed publications will focus on 1. Physical participation during health service restrictions, 2. Primary outcomes, and 3. Implications of the realist evaluation for clinical delivery.

Trial Status

We initiated consumer feedback in July 2019. We registered the trial on 1/11/2019 with the Australian New Zealand Clinical Trials Registry ACTRN12619000228189. We received institutional ethical approval on 21/11/2019. We initiated recruitment in March 2020, and the final outcome assessments for all participant are planned for August 2021.

Discussion

The exercise guidelines (5,6) for persons with mild to moderate MS have a high potential for directing clinical care in MS. Few research studies have validated these guidelines for safety and feasibility, and have undertaken consumer evaluation(19,51). Important updates (7) have now been added to these guidelines, and we must validate these for safety, feasibility, consumer evaluation, efficacy and effectiveness (62). Further, clinical guidelines must be tested for value in a range of real-world situations, to establish the context, mechanisms and outcomes which make them either successful, or not, to the person, community, or service (15). Our protocol is timely as it addresses the need to focus on the distribution of remotely-delivered programmes (e.g., via telehealth). Not only will our protocol provide data to help inform the development of a robust randomised controlled trial of a home based, remotely-delivered, coached, behavioural exercise intervention,

based on established methodology(18,19). Our protocol will provide instructions for potential clinical approaches to the delivery of remote exercise training protocols to persons with MS.

This project builds on previous knowledge by virtue of including the most recent exercise guidelines for MS (5–7) and tests the feasibility of an optimised adherence social component to community-based exercise(63). Clarification of these elements, is crucial to tailoring guideline based, remotely supervised exercise in MS. Our study is novel in that we specifically recruit participants who are already meeting the original (5,6) exercise guidelines, and as part of our secondary outcomes we will provide data on the type of exercise, venue and level of social interaction these persons follow (prior to the BASE intervention, immediately after the intervention and at the six-month follow-up). We note that this pre-intervention data will be collected during the COVID19 pandemic which will provide unique data on exercise habits of persons with MS during public health restrictions.

This Phase I study design of BASE will provide safety, feasibility and evaluative insights into the long-term effects of a remotely-delivered exercise programme. In particular we will identify health-economic cost of the BASE for participants and potential healthcare cost. For example because participants in BASE will receive approximately 8 video coaching calls (dependent on randomisation to optimised adherence or not), estimated time of each being 30-45 minutes we can determine time clinicians should allocate to programme delivery. We will account for coaches preparation and follow-up reporting of participant notes, and consider this in clinicians time. Further, our realist approach to participant and coach evaluation will allow for systematic consumer evaluation, which has merit in directing the delivery and content of exercise training intervention to persons with MS in the future.

The design of the study is further strengthened as the structured coaches training and the semi-structured coaching calls lay the foundations for clinical application. The unique evaluation, including feedback from both participants and coaches, based on the context, mechanisms, and outcomes (15) inherent in programme delivery has not previously been clarified for exercise interventions in MS. Further we will gather data on the health economic impact of the intervention, and such data is rare in MS exercise interventions. Health economic data allows for those in government, non-government organisations, healthcare departments, and clinicians, to make decisions on healthcare policies or interventions(36) . Finally, we will gather data based on combined theories of behaviour change (47) to compare the capabilities, opportunities and motivations our participants perceive to be important to home-based exercise programmes.

This protocol describes a remotely supervised, telehealth delivered, guidelines based exercise programme for persons with MS which is underpinned by theory of health behaviour change. The protocol provides the platform for a realist evaluation of the programme prior to clinical use. The BASE project may be subject to some limitations. We may experience technology limitations in participants use of e-mail or video calls or pedometers. We will offer solutions to these as mail-out versions on information, non-video phonecalls or the use of the pedometer function on a mobile phone or wrist worn device to count steps. Our monitoring of aerobic intensity is directed by step-rate (as a minimum) and guided by RPE. Such monitoring is low cost and accessible for all.

As the clinical landscape of MS management continues to progress, and it remains reactive to changes in public health (e.g., healthcare restrictions as a result of the COVID19 pandemic) and health communication (e.g. increased reliance on communication technology). The comprehensive BASE study provides critical insights on how to study country wide remotely-delivered exercise training programmes, and how to optimise clinical knowledge (i.e., exercise guidelines) and delivery (i.e., underpinned by principles of behaviour change theory) into a model appropriate for times of restricted healthcare service access.

Conclusions

BASE is an important phase I study designed to closely build on the known literature to optimise participation in the MS exercise guidelines among persons with mild to moderate MS. It is the first study to test the latest exercise guidelines in MS, and it is assesses scientific outcomes of exercise participation, MS symptoms and correlates of behaviour change. In addition this study provides key data on the feasibility outcomes of process, resource, management, and will specifically report on safety, adherence and compliance of the programme. Participant and coaches evaluations, and data on long-term exercise adherence will provide urgent information on consumers needs and wants for home-based, remotely supervised exercise programmes for persons with MS. BASE will provide valuable information for the development of future remotely-delivered exercise training programmes in neurological populations.

Conflicts of interest

The authors declare no conflicts of interest.

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