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Title:

The MoXFo initiative – study design: Considerations related to study design and methodology in exercise research for people with multiple sclerosis

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Abstract

Background: Exercise as a subset of physical activity is a cornerstone in the management of multiple sclerosis (MS) based on its pleotropic effects, but continued progression of the field require better future designs and methodologies.

Objectives: The present paper outlines the work of the "Study design and methodology" group of the MoXFo (moving exercise research forward) initiative, and addresses critical aspects and future directions when defining the research question of interest, and subsequently, designing the study and exercise intervention in MS patients.

Methods: The work is based on the formation of an international expert panel formed within the MoXFo initiative. We provide a structured and concise synthesis of exercise-specific MS research challenges and considerations when designing randomized controlled trials (RCT).

Results: Challenges and considerations are presented using the PICOTS (Patient population, Intervention, Comparator, Outcomes, Timing, Setting) framework, thereby forming a new and specific MS exercise PICOTS framework.

Conclusions: We propose that researchers should carefully consider and align all elements of this MS exercise PICOTS framework when developing future research questions and study designs, ultimately improving the quality of new exercise studies in people with MS.

Introduction

Exercise, defined as a subset of physical activity that is planned, structured and repeated with the objective to maintain or improve physical function (see the "definitions and terminology" paper of the Moxfo (Moving exercise research in multiple sclerosis forward" initiative), may play an important role in management of MS.(1) The quantity of exercise studies in MS has increased dramatically over recent decades, yet with apparent limitaitions in relation to the design and methodology og studies.(2)

The present paper outlines the work of the "Study design and methodology" group of the MoXFo initiative, and addresses critical aspects and future directions when initially defining the research question of interest and subsequently designing the study and intervention. While previous work has discussed generic challenges when designing rehabilitation trials,(3) we provide a structured and concise synthesis of exercise-specific research opportunities, challenges and considerations when designing randomized controlled trials (RCT) in MS. To fully understand whether and how exercise interventions work, we acknowledge the importance of using a variety of research designs. In this paper, however, we will focus mainly on RCTs, given the superior research design when studying the efficacy or (cost-)effectiveness of interventions.(4) Challenges and considerations will be presented using the PICOTS (Population, Intervention, Comparator, Outcomes, Timing, Setting) framework. This has been broadened to incorporoate relevant elements from the 2017 extension of the CONsolidated Standards Of Reporting Trials (CONSORT) for non-pharmacological trials,(5) the Consensus on Exercise Reporting Template (CERT),(6) the Template for intervention description and replication (TIDieR),(7) as well as general exercise trial guidelines.(8) We deliberately do not wish to present a standardized checklist for MS exercise trials, but we do intend to inspire and facilitate the

design and conduct of well-defined high-quality MS exercise research by outlining a specific MS exercise PICOTS framework.

Defining the research question

A clear and specific predefined research question is an important prerequisite for the design of the subsequent study. To develop a strong research question a compelling and widely recognized clinical problem, (supposed) related physiological and/or psychosocial mechanisms of action, and targets as well as active ingredients of the intervention must be identified and specified. The development of the research question might also explicitely consider the phase of the study (phases ranging from preclinical to phase IV trials), with most human exercise studies being phase I, II or III trials. A study is optimally based on a comprehensive literature review and a pilot study to clarify the study rationale, direct the study design, and build sound hypotheses.

MS exercise-specific PICOTS

In the following sections each element of the PICOTS framework will be discussed in relation to factors relevant for MS exercise trials. The MS exercise-specific PICOTS framework is illustrated in Fig. 1, also illustrating the interdependence of the different elements.

Population

In general

A mandatory element of a clear and focused research question is the target population. It is important to clearly define the study population, and both sociodemographic and clinical characteristics (including co-morbidities) might be considered. The target population depends on whether an efficacy (i.e. typically a homogeneous sample meeting specific enrolment criteria) or an effectiveness study (i.e. more heterogeneous sample, to enable generalizability) is undertaken.(3) In RCTs the required sample size is preferably defined a priori to minimize the risk of a type II error (i.e. false negative conclusions) and, if possible, based on available data related to the specific primary outcome of the study and the specific intervention applied.(9)

MS exercise-specific opportunities and challenges

A well-known and often mentioned aspect related to populations in exercise studies is the generalizability of the sample, given that participants who sign up for exercise studies are typically motivated to participate in the intervention, placing the study at high risk of selection bias. Study findings from a specific MS study population should therefore be interpreted in relation to the general and targeted MS population. One approach to achieve this, is to include registry-based population-based control data, allowing evaluation of the representativeness of the study sample. Such an asset has recently been adapted in a MS exercise trial.(10) Further compromising the generalizability of many MS exercise studies, potential participants are often excluded if they have had a recent relapse, or present with co-morbidities, cognitive disorders, or severely impaired walking ability.(11) To investigate these populations, researchers might consider to evaluate safety issues first. Furthermore, it might be needed to broaden both the types of exercise modalities used and methods of exercise delivery, to overcome challenges with the application of conventional exercise interventions.(12) Another common selection bias is age. Almost one third of all persons

with MS are 60 years or older(13), yet most MS exercise studies exclude people above 60 years of age; the effects of exercise in older adults with MS are therefore essentially uninvestigated.(14) Considering that the efficacy of medical disease-modifying treatment decreases with increasing age,(15) non-pharmacological supplemental treatment strategies, such as exercise, are highly warranted. Future MS exercise studies that include this population, may consider the age-related challenges in the control and interpretation of the parallel and/or synergistic detrimental effects of MS and aging.(16) Another avenue for future MS exercise research is in the early stages of the disease course, with only one study investigating early stage exercise in MS.(10, 17) A research question targeting the newly diagnosed may, however, encounter a challenge in the selection of outcome measures because of possible ceiling and/or floor effects in persons with mild MS, and may also need a longer trial duration to detect potential effects. Finally, study participants should have a clinical deficit at inclusion when the study purpose is to improve a specific symptom or impairment (i.e. have a clinical fatigue level at study entry if the study purpose is to reduce fatigue).

Intervention

In general

The intervention is the active ingredient in any interventional study and hence should be well-defined and well-described.(6, 7) Contextual factors such as prior, concurrent, and/or post treatments should ideally be considered as they may influence the response to the intervention.

/MS exercise-specific opportunities and challenges

The principles of exercise training are described in many overlapping versions, yet most often include "*specificity"*, "*progression",* and *"overload"*.(18) These principles are the core of exercise science and a prerequisite for optimal treatment response. Unfortunately, a recent systematic review evaluating the quality of interventions in MS exercise research determined that these principles have not been consistently utilized,(2) compromising the quality of interventions, and potentially leading to findings not accurately reflecting the efficacy of exercise training. Future MS exercise studies are therefore encouraged to carefully design exercise interventions so that the exercise modality applied has relevant *specificity* towards the physiological, symptomatic and/or neurological target of the study. Furthermore, the exercise programme optimally ensures a safe and *progressive overload* (i.e. gradual increase of the total workload) of the targeted physiological and/or pathological systems. Both "*specificity*" and "*progressive overload*" can be applied in standardized protocols at the group-level but also when investigating patient-tailored interventions. Patient-tailoring of interventions, however, can come with the cost of reduced generalizability and increased complexity of replication. In both cases, a detailed description of the intervention delivered is crucial. This is currently not the case in almost 50% of the existing exercise trials (2) and all MS exercise trials are therefore strongly encouraged to provide comprehensive and detailed descriptions of all exercise components applied, in accordance with the CERT and/or TIDieR.(6, 7)

Exercise recommendations for people with MS across the disability spectrum have recently been proposed.(19) To ensure these are comprehensively evidence-based more knowledge is needed on the optimal dose-response in relation to specific exercise modalities and their target to develop the optimal personalized dosage of a given exercise prescription. Robust evidence about frequency, intensity, time, and type of exercises is therefore required, preferably by head-to-head designs

comparing different dosages. One approach to address the question of the optimal dosage is an adaptive design approach termed “dose-finding”, adapting a predefined algorithm for dose escalation/de-escalation. This approach, inspired from medical treatment algorithms applied in pharmaceutical studies, has been successfully applied in stroke rehabilitation research.(20)

Comparison

In general

It is important to define the type of comparator and to consider the potential risks and benefits of the comparator.(21) Active comparators are preferably relevant to current practice, and if the comparator is “usual care” then its components needs a clear description.

MS exercise-specific opportunities and challenges

One of the major challenges when designing MS exercise trials is to choose the right type of comparator. Moreover, the comparator choice may cause ethical dilemmas as withholding active treatment may not be an option because exercise is considered an effective symptomatic treatment in MS. (1) Therefore, MS exercise trials must often design the controlled part of their RCT design without withholding treatment from the participants. One possibility is to compare with “usual care”. However, clearly defining what comprises “usual care” is challenging, given that it may be highly variable – due to the variability of symptoms in patients, but also within and especially across different countries.(22) Furthermore, larger sample sizes than when applying “no treatment”, are likely needed to obtain adequate statistical power, when “usual care” is the comparator.

Another possibility is to apply a waitlist-control design which may facilitate adherence to the control condition and allows replication and verification of the findings within the same study. This design

has been adapted in several MS exercise trials.(23, 24) The waitlist-control design does, however, pose the risk of control group participants changing behavior simply due to anticipation-induced motivation caused by the forthcoming intervention. In addition, sufficient wash-out periods are important in waitlist designs if the study findings after the cross-over are to be interpreted as a representative replication of the findings prior to the cross-over.

If active treatments are used as the comparator superiority, non-inferiority and equivalence designs can be of relevance. The trial should be designed as a classical superiority trial in exercise studies comparing exercise interventions having marked differences in proposed active ingredients and subsequent treatment responses. This approach has been successfully applied in previous MS exercise trials.(25, 26)

Another possibility when applying an active comparator design, is to design a non-inferiority or equivalence study, where it is hypothesized that the new intervention is not worse or provides a similar effect, when compared to the existing active treatment.(27) However, to the authors knowledge, such approaches have not yet been applied in MS exercise studies, but may be relevant in future trials. Non-inferiority and equivalence trials, however, are complex to design, conduct and interpret and careful consideration of the drawbacks of such designs, and the use of available frameworks,(28) is needed before initiating such studies.

No matter the comparator type, one important methodological tool to consider is the monitoring of physical activity level and exercise behaviour. This is particularly important given the susceptibility of patients in control groups to change behavior when enrolled in an exercise trial, which may contaminate potential exercise-induced effects from the applied intervention.

Outcomes

In general

Choosing and pre-registering (e.g. at www.clinicaltrials.gov) the right primary outcome is crucial to the success of a trial, and therefore, needs thorough consideration. The primary outcome must be clearly defined and aligned with the purpose of the trial and be relevant, feasible, valid, reliable and responsive to change. To assist the interpretation, outcomes having established minimal clinically important differences are recommended, but this is not always available. While guidance on statistical principles for clinical trials exists (e.g. CONSORT statement),(29) many researchers base their interpretation on p-values, rather than on recommendations from contemporary statistical guidelines(30), which suggest a down toning of p-values and a more comprehensive presentation and interpretation of confidence intervals and clinical relevant changes.(31) Moreover, researchers should report (using confidence intervals when appropriate) and consider all results including those that are non-significant (to avoid "cherry picking" of data) and also transparently acknowledge known uncertainties related to the applied outcomes. Furthermore, it is recommended to use the primary outcome for a sample size calculation to estimate the required number of participants. Finally, the interpreteation of a study can often be advanced by including a variety of outcomes, including both objective and patient-reported outcomes, or outcomes at different International Classification of Functioning (ICF) domains (i.e. body structure, function and participation). This variety in outcomes can provide key information about how the exercise intervention is impacting the participant as a whole.

MS exercise-specific opportunities and challenges

After determining the primary outcome, selecting further outcomes from a "MS exercise battery" of outcomes for use across MS exercise studies, but still based on the study design and research question, would seem to be a way forward. This would support future literature reviews and meta-analyses within the MS exercise field. Previously, a core-set was proposed by Paul et al.(32). However, as part of the MoXFo initiative the "reporting and outcome group" provides a systematic overview of all outcomes applied that is structured based on ICF classification(33). Important to consider when evaluating the effectiveness of an exercise intervention, is whether the outcomes are suitable and relevant for the targeted MS population. As an example, severely disabled persons with MS may require less demanding or adapted outcome measures to avoid flooring effects, whereas newly diagnosed persons may require more demanding tests to avoid ceiling effects. Differing levels of disability may also impact interpretation, for example the test-retest variation for several functional outcomes has been reported to increase substantially in populations with higher disability levels.(34) Another aspect related to outcomes that is often inadequately reported is participant safety, and it is strongly recommended that future studies pre-plan how to record and report safety plans and adverse events. Finally, future MS exercise studies should strive to build strong pre-trial rationales on potential underlying mechanisms of action, and subsequently include (secondary) supportive mechanism-oriented outcomes. This should not only consider (patho-) physiological mechanisms but should also consider psycho-social and psychological mechanisms.

Timing

In general

Many trials apply testing at multiple time points and often include follow up periods, making it important to clearly define (and power the trial in accordance with) the primary time point of interest. Most studies assess the intervention effects immediately after the intervention, which is typically where the largest effects are observed, and where the frequently observed "wear off" effect during follow up is avoided.(3)

MS exercise-specific opportunities and challenges

A major challenge related to timing, which is particularly pertinent to long-term MS exercise studies, relates to adherence, as high adherence is a prerequisite for robust long-term data. A recent systematic review showed that longer study duration seemed to lower adherence, further highlighting the importance of optimizing long-term adherence in future MS exercise studies.(35) For detailed discussion about adherence please see the MoXFo "adherence and compliance to exercise" paper. Another MS exercise timing challenge is how a relapse is handled both around study entry, during the study, and in the post-treatment assessment period. Many MS exercise studies include relapsing-remitting participants that are relapse free for a period of time before baseline testing to ensure a stable participant at study entry, thereby limiting the influence of natural remission. Furthermore, it is not always clear how a relapse during an exercise intervention is handled, and studies investigating exercise as a supplemental acute/subacute treatment of MS relapses are therefore warranted.(36) Particularly in studies with progressive MS patients, the baseline assessment could be duplicated, creating two or more baseline timepoints in order to understand the trajectory of disease progression. Such an approach could also reduce the marked day-to-day variation observed in some MS patients.

Setting

In general

The setting of a trial has several inherent components that interact with other elements of the PICOTS framework. These include whether the *population* is newly diagnosed patients or severely disabled patients, whether the *intervention* is supervised, non-supervised or remotely supervised, and if the trial is a single or multi-site national or multi-national trial (impacting delivery of the *intervention,* the collection of *outcomes* and content of a "usual care" *comparison* group). Choosing the setting (e.g. in-patient or out-patient setting) will also impact whether the study is an efficacy or a effectiveness trial.

MS exercise-specific opportunities and challenges

In exercise research it has long been known that supervised interventions have superior effects as compared to non-supervised interventions.(37) In MS exercise studies similar observations exist,(38) which suggest larger sample sizes are likely to be required when interventions are non-supervised and/or home-based. However, supervised exercise may not offer interventions that are suitable for effectiveness studies. More recently, interventions applying remote supervision have been tested in MS exercise studies,(39) and an ongoing large-scale phase III trial is currently comparing individualized exercise programmes delivered in a supervised, facility-based setting versus a remotely coached/guided, home-based setting using telerehabilitation.(40) When considering challenges fostered by the COVID-19 pandemic, by MS populations living in rural

areas,(41) or people's experiences of difficulties accessing support for exercise,(42) such approaches may pave a way forward for new remote-based settings. Regardless of the intervention type or setting, studies need to be adequately powered to enable firm conclusions to be drawn. This typically requires large scale studies, using multiple centres, and across multple countries. The sucessful delivery of such large-scale, costly projects requires strong leadership, a team ethos grounded in collaboration, a decision making approach based on consensus, and a longterm commitment by individuals to the group effort to achieve goals that cannot be reached by a single center effort.(43) Despite the increased focus on exercise as a supplemental treatment strategy in MS, funding of the costly supervised exercise interventions in well-powered large-scale multicenter studies remain a challenge. Funding agencies are therefore encouraged to support such highly needed studies.

Discussion

Designing a high quality MS exercise study is challenging and requires thorough consideration. Planning an exercise study starts with the identification of a relevant clinical question that may be addressed by a specific exercise intervention. A resulting clear and detailed research question and subsequent hypothesis then forms the starting point. We propose that the MS exercise specific PICOTS framework described here, in combination with the CONSORT statement for non-pharmacological trials, will be helpful tools for identifying and guiding crucial design elements of a RCT study. The decision-making process preferrably considers the interrelationship between the various components of the MS exercise PICOTS framework and therefore the subsequent impact each decision may have. Of note, patient involvement has demonstrated to enhance health-care

research and is increasingly an expectation that should be considered, particularly in relation to many funding bodies.(44) An additional recommended emerging approach to ensure transparency is the requirement by many journals to have a trial pre-registered (e.g. at www.clinicaltrials.gov), and also it has become common to publish a study protocol paper outlining the study methodology of the trial in accordance with the SPIRIT guidelines,(45) in combination with publication of a detailed statistical analysis plan.(46)

Historically exercise research has not always payed enough attention to important elements such as trial pre-registration, pre-defined primary outcomes, study power, assessor blinding and interpretation based on clinical relevance; and the quality of MS exercise studies are therefore generally sub-optimal.(35) However, alongside application of the MS exercise PICOTS framework presented here, inspiration obtained from methodologically rigorous research, and the introduction of pre-registration requirements and relevant checklists (e.g. SPIRIT, CERT, TIDieR, and CONSORT checklists, Fig. 1), can provide a template to improve the methodological quality and design of MS exercise studies (5-7, 45).

In conclusion, the design of robust studies are needed to improve the quality of MS exercise research. The MS exercise specific PICOTS framework presented here provides a systematic and comprehensive approach to aid this decision-making process.

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Disclosure/Conflict of interest

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References

1. Dalgas U, Langeskov-Christensen M, Stenager E, Riemenschneider M, Hvid LG. Exercise as Medicine in Multiple Sclerosis-Time for a Paradigm Shift: Preventive, Symptomatic, and Disease-Modifying Aspects and Perspectives. Curr Neurol Neurosci Rep. 2019;19(11):88.
2. Schlagheck ML, Joisten N, Walzik D, Wolf F, Neil-Sztramko SE, Bansi J, et al. Systematic Review of Exercise Studies in Persons with Multiple Sclerosis: Exploring the Quality of Interventions According to the Principles of Exercise Training. Neurol Ther. 2021;10(2):585-607.
3. das Nair R, de Groot V, Freeman J. Beyond current research practice: Methodological considerations in MS rehabilitation research (is designing the perfect rehabilitation trial the Holy Grail or a Gordian knot?). Mult Scler. 2019;25(10):1337-47.
4. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. The New England journal of medicine. 2016;374(22):2175-81.
5. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Ann Intern Med. 2017;167(1):40-7.
6. Slade SC, Dionne CE, Underwood M, Buchbinder R, Beck B, Bennell K, et al. Consensus on Exercise Reporting Template (CERT): Modified Delphi Study. Phys Ther. 2016;96(10):1514-24.
7. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.
8. Hecksteden A, Faude O, Meyer T, Donath L. How to Construct, Conduct and Analyze an Exercise Training Study? Front Physiol. 2018;9:1007.
9. Nayak BK. Understanding the relevance of sample size calculation. Indian J Ophthalmol. 2010;58(6):469-70.
10. Riemenschneider M, Hvid LG, Ringgaard S, Nygaard MKE, Eskildsen SF, Petersen T, et al. Study protocol: randomised controlled trial evaluating exercise therapy as a supplemental treatment strategy in early multiple sclerosis: the Early Multiple Sclerosis Exercise Study (EMSES). BMJ open. 2021;11(1):e043699.
11. Lai B, Cederberg K, Vanderbom KA, Bickel CS, Rimmer JH, Motl RW. Characteristics of Adults With Neurologic Disability Recruited for Exercise Trials: A Secondary Analysis. Adapted physical activity quarterly : APAQ. 2018;35(4):476-97.
12. Edwards T, Pilutti LA. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: A systematic review and future research directions. Mult Scler Relat Disord. 2017;16:31-9.
13. Magyari M, Sorensen PS. The changing course of multiple sclerosis: rising incidence, change in geographic distribution, disease course, and prognosis. Curr Opin Neurol. 2019;32(3):320-6.
14. Horton S, MacDonald DJ, Erickson K. MS, exercise, and the potential for older adults. European Review of Aging and Physical Activity. 2010;7(1):49-57.
15. Jakimovski D, Eckert SP, Zivadinov R, Weinstock-Guttman B. Considering patient age when treating multiple sclerosis across the adult lifespan. Expert Rev Neurother. 2021;21(3):353-64.
16. Hvid LG, Feys P, Baert I, Kalron A, Dalgas U. Accelerated Trajectories of Walking Capacity Across the Adult Life Span in Persons With Multiple Sclerosis: An Underrecognized Challenge. Neurorehabilitation and Neural Repair. 2020;34(4):360-9.
17. Riemenschneider M, Hvid LG, Stenager E, Dalgas U. Is there an overlooked "window of opportunity" in MS exercise therapy? Perspectives for early MS rehabilitation. Mult Scler. 2018;24(7):886-94.
18. J H. Physiological aspects of sport training and performance: Human Kinetics; 2014.

19. Kalb R, Brown TR, Coote S, Costello K, Dalgas U, Garmon E, et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. Multiple sclerosis (Houndmills, Basingstoke, England). 2020;26(12):1459-69.
20. Colucci E, Clark A, Lang CE, Pomeroy VM. A rule-based, dose-finding design for use in stroke rehabilitation research: methodological development. Physiotherapy. 2017;103(4):414-22.
21. Levack WM, Martin RA, Graham FP, Hay-Smith EJ. Compared to what? An analysis of the management of control groups in Cochrane reviews in neurorehabilitation. Eur J Phys Rehabil Med. 2019;55(3):353-63.
22. Rasova K, Freeman J, Cattaneo D, Jonsdottir J, Baert I, Smedal T, et al. Content and Delivery of Physical Therapy in Multiple Sclerosis across Europe: A Survey. Int J Environ Res Public Health. 2020;17(3).
23. Langeskov-Christensen M, Grondahl Hvid L, Nygaard MKE, Ringgaard S, Jensen HB, Nielsen HH, et al. Efficacy of high-intensity aerobic exercise on brain MRI measures in multiple sclerosis. Neurology. 2020.
24. Heinrich I, Rosenthal F, Patra S, Schulz K-H, Welsch GH, Vettorazzi E, et al. Arm Ergometry to Improve Mobility in Progressive Multiple Sclerosis (AMBOS)—Results of a Pilot Randomized Controlled Trial. Frontiers in Neurology. 2021;12(1044).
25. Zimmer P, Bloch W, Schenk A, Oberste M, Riedel S, Kool J, et al. High-intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: A randomized controlled trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2018;24(12):1635-44.
26. Wens I, Dalgas U, Vandenabeele F, Verboven K, Hansen D, Deckx N, et al. High Intensity Aerobic and Resistance Exercise Can Improve Glucose Tolerance in Persons With Multiple Sclerosis: A Randomized Controlled Trial. Am J Phys Med Rehabil. 2017;96(3):161-6.
27. Hahn S. Understanding noninferiority trials. Korean J Pediatr. 2012;55(11):403-7.
28. Mauri L, D'Agostino RB. Challenges in the Design and Interpretation of Noninferiority Trials. New England Journal of Medicine. 2017;377(14):1357-67.
29. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
30. Harrington D, D'Agostino RB, Sr., Gatsonis C, Hogan JW, Hunter DJ, Normand ST, et al. New Guidelines for Statistical Reporting in the Journal. N Engl J Med. 2019;381(3):285-6.
31. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. 2019;567(7748):305-7.
32. Paul L, Coote S, Crosbie J, Dixon D, Hale L, Holloway E, et al. Core outcome measures for exercise studies in people with multiple sclerosis: recommendations from a multidisciplinary consensus meeting. Mult Scler. 2014;20(12):1641-50.
33. Ramari C, Awadia Z, Bansi J, Casey B, Feys P, Pilutti L, et al. The MoxFo initiative – outcomes: Outcome measures in studies of exercise training in multiple sclerosis; scoping review of reviews and classification according to the ICF Framework. Mult Scler J. 2023.
34. Feys P, Bibby B, Romberg A, Santoyo C, Gebara B, de Noordhout BM, et al. Within-day variability on short and long walking tests in persons with multiple sclerosis. J Neurol Sci. 2014;338(1-2):183-7.
35. Dennett R, Madsen LT, Connolly L, Hosking J, Dalgas U, Freeman J. Adherence and drop-out in randomized controlled trials of exercise interventions in people with multiple sclerosis: A systematic review and meta-analyses. Mult Scler Relat Disord. 2020;43:102169.
36. Rooney S, Albalawi H, Paul L. Exercise in the management of multiple sclerosis relapses: current evidence and future perspectives. Neurodegener Dis Manag. 2020;10(2):103-15.
37. Mazzetti SA, Kraemer WJ, Volek JS, Duncan ND, Ratamess NA, Gómez AL, et al. The influence of direct supervision of resistance training on strength performance. Med Sci Sports Exerc. 2000;32(6):1175-84.

38. Snook EM, Motl RW. Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. Neurorehabil Neural Repair. 2009;23(2):108-16.
39. Tallner A, Streber R, Hentschke C, Morgott M, Geidl W, Maurer M, et al. Internet-Supported Physical Exercise Training for Persons with Multiple Sclerosis-A Randomised, Controlled Study. Int J Mol Sci. 2016;17(10).
40. Motl RW, Backus D, Neal WN, Cutter G, Palmer L, McBurney R, et al. Rationale and design of the STEP for MS Trial: Comparative effectiveness of Supervised versus Telerehabilitation Exercise Programs for Multiple Sclerosis. Contemporary clinical trials. 2019;81:110-22.
41. Learmonth YC, Chan Z, Correia H, Hathorn D, Kermode A, Smith C, et al. Exercise participation and promotion in the multiple sclerosis community; perspectives across varying socio-ecological levels. Disabil Rehabil. 2020:1-16.
42. Latchem-Hastings J, Randell E, Button K, Jones F, Lowe R, Dawes H, et al. Lifestyle, exercise and activity package for people living with progressive multiple sclerosis (LEAP-MS): protocol for a single-arm feasibility study. Pilot Feasibility Stud. 2021;7(1):111.
43. Chung KC, Song JW. A guide to organizing a multicenter clinical trial. Plast Reconstr Surg. 2010;126(2):515-23.
44. Coupe N, Mathieson A. Patient and public involvement in doctoral research: Impact, resources and recommendations. Health Expect. 2020;23(1):125-36.
45. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-7.
46. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Dore C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43.

Figure 1: The MS exercise-specific PICOTS model. The research question and study design of future MS exercise studies are encouraged to be specified and developed on the basis of deliberate choices considering the different elements (and their interdependence) of the MS exercise-specific PICOTS model. To facilitate replication and implementation future MS exercise studies should also ensure detailed reporting according to relevant international guidelines and checklists. Abbreviations: RCT=randomised controlled trial, SPIRIT= standard protocol items: recommendations for interventional trials, CERT= consensus on exercise reporting template, TIDieR= template for intervention description and replication, CONSORT= consolidated standards of reporting trials