PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1)
AUTHORS	Krause, Nicole; Riemann-Lorenz, Karin; Steffen, Tanja; Rahn, Anne; Pöttgen, Jana; Stellmann, Jan-Patrick; Koepke, Sascha; Friede, Tim; Icks, Andrea; Vomhof, Markus; Temmes, Herbert; van de Loo, Markus; Gold, Stefan M.; Heesen, Christoph

VERSION 1 – REVIEW

REVIEWER	Leigh Hale University of Otago, New Zealand
REVIEW RETURNED	27-Aug-2020

GENERAL COMMENTS	This very well written paper describes the protocol of a RCT to investigate the effectiveness of an intervention to reduce and change patient behaviour (behaviour of what? - be more explicit). An intervention to reduce inflammatory disease activity with proven effectiveness would be of considerable benefit and hugely and positively impact the lives of people living with MS. A robust rationale is made for the theory underpinning the intervention. On reading the study objectives (primary and secondary) I expected the study design to be purely one of a RCT. However, it is described as multiphase-mixed-methods-study, which begs different objectives, including that pertaining to the development and feasibility testing of the intervention. I was confused when I read on page 7 that the intervention was still to be developed and feasibility tested, and yet on page 14 you note that the recruitment for the trial began in July 2019. These aspects need to be clarified and revised either with revised objectives or reference to previous development of the intervention and this paper focusing purely on the protocol of the RCT. Regarding the intervention: it appears based on a lot of the theories and approaches yet doesn't explicitly state exactly what aspects of all these theories are being targeted and how, this needs to be unpicked more - what exactly will be done to address / deliver what? "Simulated dialogue" on its own is not particularly informative - what will happen / what are the interactive segments (with an example or two of these)? What will participants be reminded about? Are the topics delivered in the sequence listed in the paper? Is so, then, as optimising physical activity (for example) only comes 5th on the list, you will only expect a change in PA involvement after that? How will you individualise the approach? Given this intervention is aimed at "empowerment" and "autonomy", it seems paradoxical that patient "adherence" will be monitored. At the moment it still sounds like an intervention that teaches (albeit interactively) people what to do rather than works with them to enable empowerment (choice,

	control, self -efficacy, etc) and support their endeavours to change their lifestyles. I am sure that your intervention is not didactic or expert medical model based, but this needs to be articulated more clearly and in more detail. Patient and public involvement: more details are required here as to exactly how patient/public were involved in developing the intervention - as currently read it looks a bit tokenistic. I note on page 7 you talk of an "expert PwMS" - what makes one person with MS and expert and not another person with MS? Are they not each expert in how MS affects them individually? There are a huge number of secondary outcome measures in this trial, and I wondered what impact this would have for participants, especially people who usually say their fatigue is their main concern - are all these measures thus ethically justified? Data collection methods: I note that the results of the MRI scans will be sent on a CD via mail - how secure is this option, will you use a courier service (or whatever is the safest way to mail in Germany)? The rest of the methods section is good. Conclusion: the last sentence needs to be revised slightly for clarity. Throughout please change instances of "MS patient" to "patient with MS" or even better to "person/people/individual with MS".

REVIEWER	Elizabeth A Hubbard Berry College, Rome, GA, United States of America
REVIEW RETURNED	29-Aug-2020

GENERAL COMMENTS	OVERVIEW • I would like to thank the authors for this opportunity to evaluate their protocol. The POWER@MS1 behavioral lifestyle program is an evidence-based, theory-driven, and web-based behavior change program that has the capacity to change patient behavior and reduce inflammatory disease activity in the early stages of MS diagnosis. The objectives, statistical analyses, ethics, dissemination, appendices, and figures are well-defined and easy to read. The introduction and study design are well-written, but I would like some clarity on several points detailed below. ABSTRACT • The abstract is very thorough. • The abstract should also concisely describe the secondary aims, parallel process evaluation, and parallel health economic parameters. • Strengths and limitations: o Lines 42-44: Consider revising this sentence to be more concise and direct. INTRODUCTION • Lines 18-20: This sentence is confusing. I would suggest splitting it into two sentences, ending the first sentence after “PwMS.” In the second sentence, I would like some clarification on what the “potential of stress management and lifestyle measures” is “high” in? Based on the previous sentence, it would be information; however, it appears that you are referring more to its quality of life or disease progression potential. A clarification of this longer sentence would make this paragraph read smoother. • Lines 25-26: The authors describe exercise and nutrition information as important; However, they fail to reference the published article by Motl and colleagues, on the benefits of an internet-based, walking behavior change intervention in MS. o Motl RW, Hubbard EA, Bollaert RE, Adamson BC, Kinnett-Hopkins D, Balto JM, Sommer SK, Pilutti LA, McAuley E.

	Randomized controlled trial of an e-learning designed behavioral intervention for increasing physical activity behavior in multiple sclerosis. Multiple Sclerosis Journal–Experimental, Translational and Clinical. 2017 Oct;3(4):2055217317734886. • Lines 30-32: I would like more clarification on the overall goal of the information provided. Is it to provide information on lifestyle-related matters, like exercise and nutrition, or to increase immunotherapy initiation? It seems like the immunotherapy initiation is not necessarily a lifestyle factor, but about making and keeping appointments in the clinic and adhering to prescribed medications/transfusions. • Lines 30-32: With regards to the phrase, “and consequently, better adherence and optimization of lifestyle habits,” lifestyle behaviors are typically not a consequence of immunotherapy initiation, but a separate behavior and goal altogether. Doing activities at home, like stress reduction breathing techniques or engaging in physical activity, may require different information and training than adhering to a drug regimen. If you are providing information on these other types of behaviors (which it is apparent within the study design that you are), the EBPI is also targeting those behaviors. The increase in immunotherapy initiation is not per se the reason why participants increase secondary behaviors. METHODS & ANALYSIS • Study Design o Development, Line 9: Please provide more details about the “simulated dialogues.” o Development, Line 10: I would suggest indicating the theoretical models used to develop the intervention (i.e., empowerment, cognitive behavioral therapy, self-determination theory, responsiveness, and content tailoring) here as well as under the intervention section later on in the manuscript. o Overall, I would like a better description and clarity on how patients were involved in the study design and what aspects of the study were included/modified because of participant involvement. • Feasibility o Line 17: Please provide more information/detail regarding the “think-aloud, teach-back” exercise. o Line 17-18: Please provide more detail regarding the “closed questions.” • Eligibility Criteria o Line 44: “Substantial cognitive deficit based on clinical impression” is a limitation of eligibility criteria. Considering the number of possible clinicians included, clinical impression could vary widely. I would suggest adding this to the limitations of the protocol. In future iterations of the study, the authors should consider excluding potential participants based on an objective measure of cognitive capacity, such as the Symbol Digit Modalities Test. This test can be given in the clinic within 3 minutes and has standardized cutoffs for normal performance and cognitive impairment. • Interventions o Line 18: How often will the IG program be monitored and “reacted on” (e.g., daily vs weekly vs monthly)? More details here would be helpful. • Patient and public involvement o This sentence is written in the past tense, suggesting that the intervention was already developed and piloted. However, in the study design section, it appears as if this is something that will be

	happening in the proposed protocol. Please clarify whether the study design occurred before or will be happening in this proposed protocol. Furthermore, if the design and piloting indeed occurred in the past, please respond to the question above regarding which aspects of the study were directly related to participant feedback and involvement. • Criteria for discontinuation and relevant concomitant care o Please clarify if immunotherapy type, use, and adherence rates be collected throughout the study. • Outcomes o Secondary Outcomes Lines 32-41: Please provide details regarding which “selected items” will be used from each questionnaire. The GLTEQ, BSA, and 24-hour dietary recall may be difficult for some individuals with MS, even if they are not to the level of clinical cognitive impairment. This should be mentioned within the limitations section of the article. Physical activity rates measured through accelerometry and a 3-day food journal would be more objective and accurate. These items could be mailed out to and received from participants using the standard postal system. Recruitment: Are participants remunerated in any way for study participation?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1.0: This very well written paper describes the protocol of a RCT to investigate the effectiveness of an intervention to reduce and change patient behaviour (behaviour of what? - be more explicit). An intervention to reduce inflammatory disease activity with proven effectiveness would be of considerable benefit and hugely and positively impact the lives of people living with MS. A robust rationale is made for the theory underpinning the intervention.
Reply 1.0: Thank you, we found your comments very helpful and have revised the manuscript accordingly. The intervention aims to address lifestyle behaviour, in particular coping, stress management, sleeping behaviour, physical activity and dietary behaviour. This is now clarified from the very beginning of the manuscript (see page 3), reading: “Moreover, the programme aims to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour.” Different techniques and targeted aspects implemented to address lifestyle behaviour are described in the following (see reply 1.3).

Comment 1.1: On reading the study objectives (primary and secondary) I expected the study design to be purely one of a RCT. However, it is described as multiphase-mixed-methods study, which begs different objectives, including that pertaining to the development and feasibility testing of the intervention.
Reply 1.1: We are sorry for being unclear with regard to the manuscript focus. To clarify, the present manuscript is focusing purely on the RCT. Development, feasibility and piloting of the programme will be part of a separate manuscript. This is now explicitly stated (see page 4 of the manuscript) and reads as follows: “Details with regard to the development and adaptation process will be reported in a separate publication.” “Results of feasibility testing and piloting, including revisions of the programme, will be published separately.” “This protocol is focusing purely on the RCT.”

Comment 1.2: I was confused when I read on page 7 that the intervention was still to be developed and feasibility tested, and yet on page 14 you note that the recruitment for the trial began in July 2019. These aspects need to be clarified and revised either with revised objectives or reference to

previous development of the intervention and this paper focusing purely on the protocol of the RCT.
Reply 1.2: We are sorry for the confusion. We now state in the manuscript (see page 3 and 4) that the developmental process has already taken place and that the intervention was already tested and piloted. Moreover, we specified the focus of this manuscript (see also reply 1.1).

Comment 1.3: Regarding the intervention: it appears based on a lot of the theories and approaches yet doesn't explicitly state exactly what aspects of all these theories are being targeted and how, this needs to be unpicked more - what exactly will be done to address / deliver what?
Reply 1.3: Our intervention indeed is based on a variety of behaviour change approaches, although CBT and acceptance oriented approaches are the main foundation. While neither a defined set of techniques nor one health psychological model have proven to be superior to others, we refer to the TDF as the main framework which tries to cover all possible behaviour change concepts. In fact, we chose as many as meaningful and possible of these approaches in the intervention development. This and examples of targeted aspects are now more explicitly mentioned in the text (see page 5 of the manuscript): “These techniques influence different theoretical domains as outlined in the theoretical domains framework (21) and thereby the participants' ability, motivation and opportunity to change their physical activity, stress management attitudes and dietary behaviour. For example, CBT techniques such as behavioural activation and identifying and refuting unhelpful automatic thoughts and cognitive distortions, goal setting, goal review, agreeing on behavioural contracts, setting graded tasks, planning social support, action planning, weighing of pros and cons, preparing for/dealing with setbacks, self-motivational statements, constructing if-then plans and formulating implementation intentions and positive emotion induction are incorporated throughout. Mental imagery exercises and mindfulness/acceptance exercises are integrated both in text format and as audio recording.” A detailed description of this approach is not feasible within the limits of this manuscript. However, a publication on an example chapter development is in preparation.

Comment 1.4: "Simulated dialogue" on its own is not particularly informative - what will happen / what are the interactive segments (with an example or two of these)?
Reply1.4: We are sorry that the term was not clear enough. Information regarding the simulated dialogues has now been added to the manuscript (see page 5): “The programme is designed as a highly individualized, dialogue-based system that provides PwMS with narrative and coordinated information based on their existing health beliefs, interests, etc. Each text passage ends with a set of pre-programmed response options in multiple-choice format reflecting possible reader’s feedback, such as “Yes. That makes sense.” or “I do not quite understand this yet.” The participant is invited to tick the matching response and will be guided to the next page referring to the choice, e.g. “I'm glad that you can understand it.” or “No problem. Then let me explain it in a little more detail.”

Comment 1.5: What will participants be reminded about?
Reply 1.5: The purpose of the optional email and SMS reminders is to generate lifestyle-related stimuli (e.g. “Regular exercise and physical activity can help you stay mobile and fit for a long time. I will gladly support you in the implementation! Your EBBC programme”), to inform participants about newly activated modules as well as to remind participants about the programme. We now included information with regard to the reminders in the manuscript (see page 5): “An optional email and SMS reminder system (e.g. with lifestyle-related stimuli or reminders regarding programme usage and newly activated modules) aims to enhance involvement.”

Comment 1.6: Are the topics delivered in the sequence listed in the paper? If so, then, as optimising physical activity (for example) only comes 5th on the list, you will only expect a change in PA involvement after that?
Reply 1.6: The topics delivered in the “Interventions” section are not listed according to relevance. This has now been clarified in the manuscript (see page 5), reading: "The modules are not ordered by priority." However, in the setting of a more or less recent multiple sclerosis diagnosis we aimed to

structure the programme by beginning with factual information, followed by psychologically oriented information supporting coping. After this, psychologically oriented modules and modules focusing lifestyle (e.g. dietary behaviour and physical activity) are delivered in alternation. Overall, the programme contains two modules on physical activity as well as a booster session covering PA towards the end of the programme. In the modules and the session, participants are provided with MS-specific information on PA, they can define their personal PA type and individual PA goals and create as well as adjust an individual training plan. While the overall topics are men-tioned in the very beginning of the programme, the reviewer is right that formally any programme-induced change of PA will be only induced after the first PA was administered. We believe that a detailed description of the programme content is beyond the scope of this manuscript. As described above (see reply 1.1), this will be part of a separate publication focus-ing purely on the development process of the programme.

Comment 1.7: How will you individualise the approach?
Reply 1.7: The intervention is individualised by being conveyed in the form of interactive simu-lated dialogues. As mentioned above, we have now expanded the description of the “simulated dialogue” to clarify this (see also reply to comment 1.4). Thereby it is possible for participants to have some aspects studied more deeply than others, which is summarised as an individualised approach. Moreover, participants can create individual training and nutrition plans based on their needs and preferences. However, as this is computer-based and the number of combinations is restricted, this individualisation is limited.

Comment 1.8: Given this intervention is aimed at "empowerment" and "autonomy", it seems paradoxical that patient "adherence” will be monitored.
Reply 1.8: We are sorry for not being clear enough. However, we do not believe that adhering to this empowering intervention is in contrast to promoting autonomy. We believe that adhering to an educational process towards autonomy is very different from adhering, e.g. to a drug prescription schedule. Adherence to the tool is primarily monitored to identify any problems with the tool (e.g. issues regarding ease of use, appropriateness, user-friendliness etc.) as fast as possible or, considering the group of participants and the challenges of their everyday life (mainly young adults who are starting or are in the middle of professional/family life etc.), to remind them about tool usage with reasonable frequency. For this purpose, last usage date and number of days with activity within the last four weeks are monitored. Non-adherence is only reacted on in case of non-usage within the last four weeks. Module completion is not monitored and participants are free to decide how fast or slow they want to complete the modules. In addition, participants can pause the modules whenever wanted. However, regular tool usage (at least once a month) during the study is necessary to be able to prove a potential effect on our primary and secondary endpoints. Monitoring of adherence is now specified in the manuscript (see page 5), reading:
“Usage of the IG programme will be monitored biweekly and reacted on after four weeks of non-usage to ensure patient adherence.”

Comment 1.9: At the moment it still sounds like an intervention that teaches (albeit interactively) people what to do rather than works with them to enable empowerment (choice, control, self -efficacy, etc) and support their endeavours to change their lifestyles. I am sure that your intervention is not didactic or expert medical model based, but this needs to be articulated more clearly and in more detail.
Reply 1.9: As pointed out in the reply to comment 1.3, this protocol paper does not follow the aim (also due to the word limit) of giving a detailed description of the content and strategies in communicating lifestyle evidence and behaviour change. The programme aims to translate the evidence in the MS treatment and lifestyle management area, which means naming many uncertainties and thereby making clear that choices can be made. It follows the concept that every PwMS has to develop his or her own approach towards the disease, which might be early medication in one case and development of a sophisticated food concept in the other. This is now clarified in the

description of the intervention (see page 5 of the manuscript): “The programme aims to translate evidence in the MS treatment and lifestyle management area in order to illustrate that decisions can be made. It follows the concept that every PwMS can develop an individual approach towards the disease, which might be a targeted immunotherapy initiation in one case or the development of a sophisticated food concept in the other.”

Comment 1.10: Patient and public involvement: more details are required here as to exactly how patient/public were involved in developing the intervention - as currently read it looks a bit tokenistic.
Reply 1.10: Thank you for pointing this out. Throughout the development process of the programme, we involved PwMS, expert PwMS (see reply to comment 1.11) and health professionals in order to critically appraise the programme as well as to increase practicability, user-friendliness and comprehensibility of the intervention. As suggested by the reviewer, we revised the patient and public involvement section (see page 6 of the manuscript), reading: “They were given access to the programme and invited to evaluate content, practicability, user-friendliness and comprehensibility of the programme, also considering the needs of newly diagnosed PwMS. The programme was revised based on the acquired feedback (e.g. technical adjustments, inclusion of more break possibilities and a progress bar in the modules). In addition, suggestions for prospective adjustments, which were not possible due to technical limitations, such as the embedding of video material, were gathered.”

Comment 1.11: I note on page 7 you talk of an "expert PwMS” – what makes one person with MS and expert and not another person with MS? Are they not each expert in how MS affects them individually?
Reply 1.11: We agree that every PwMS is expert of his or her individual disease. However, we believe that patients having the disease for a while and deeply involved in information strategies as well in exchange with other PwMS up to responsible roles in self-help organisations and advocacy roles can develop to advanced experts. This is now explained also in the text (see page 4 of the manuscript): “At an early stage of development, the intervention programme was presented to expert PwMS (e.g. PwMS who are deeply involved in information strategies or in exchange with other PwMS as well as PwMS who have responsible roles in self-help organisations or advocacy roles) and evaluated using qualitative methods (think-aloud, teach-back) and closed questions.”

Comment 1.12: There are a huge number of secondary outcome measures in this trial, and I wondered what impact this would have for participants, especially people who usually say their fatigue is their main concern - are all these measures thus ethically justified?
Reply 1.12: We appreciate this concern and in fact discussed a lot the set of outcome measures for this study. First, patients are in the first year of the disease and most of those who will ultimately be enrolled in the trial are thus unlikely to suffer from substantial fatigue. In addition, data collection including all secondary outcome measures was piloted with PwMS (see page 4 of the manuscript). Here, we received positive feedback regarding user-friendliness (e.g. time needed for completion) and comprehensibility. Furthermore, the number of secondary outcome measures was found acceptable by all Ethics Committees, including the lead Ethics Committee of the Hamburg Chamber of Physicians. As indicated in Table 1 of the manuscript, not all outcome measures have to be filled out during each of the visits. Based on the acquired feedback on data collection, the time needed for completion of the visit containing the highest number of secondary outcome measures (visit 1 and visit 4) was indicated in the informed consent form.

Comment 1.13: Data collection methods: I note that the results of the MRI scans will be sent on a CD via mail - how secure is this option, will you use a courier service (or whatever is the safest way to mail in Germany)?
Reply 1.13: Thank you for pointing this out. In medical practise CDs are send by regular mail in Germany. This procedure has been accepted by the responsible Ethics boards.

Comment 1.14: Conclusion: the last sentence needs to be revised slightly for clarity.
Reply 1.14: As suggested by the reviewer, we changed the last sentence to (see page 11 of the manuscript):
“If successful, POWER@MS1 has a paradigm shifting potential. If successful, the trial could give lifestyle management a label as putative disease-modifying. This can impact guideline development.”

Comment 1.15: Throughout please change instances of "MS patient" to "patient with MS" or even better to "person/people/individual with MS".
Reply 1.15: Thank you for this observation. We checked the manuscript carefully and corrected all instanced of "MS patient" to person with MS, abbreviated as PwMS.

Reviewer: 2

Comment 2.0: I would like to thank the authors for this opportunity to evaluate their protocol. The POWER@MS1 behavioral lifestyle program is an evidence-based, theory-driven, and web-based behavior change program that has the capacity to change patient behavior and reduce inflammatory disease activity in the early stages of MS diagnosis. The objectives, statistical analyses, ethics, dissemination, appendices, and figures are well-defined and easy to read. The introduction and study design are well-written, but I would like some clarity on several points detailed below.
Reply 2.0: Thank you for your valuable feedback. We are grateful for the insightful comments and have incorporated most of the suggestions.

Comment 2.1: The abstract should also concisely describe the secondary aims, parallel process evaluation, and parallel health economic parameters.
Reply 2.1: Thank you for pointing this out. If the editor agrees to an excess of the protocol abstract word count limit (see request above), we would suggest the following: “The secondary endpoints comprise patient autonomy and empowerment, quality of life, anxiety and depression, level of physical activity and dietary behaviour. The parallel process evaluation aims to assess the fit of the intervention with users and contextual factors. The parallel health economic evaluation will determine the efficiency of the intervention by comparing the cost and outcome of the intervention group to the control group.”

Comment 2.2: Strengths and limitations: Lines 42-44: Consider revising this sentence to be more concise and direct.
Reply 2.2: As suggested by the editor and the reviewer, we revised this sentence (see reply 0.2 and page 2 of the manuscript).

Comment 2.3: Lines 18-20: This sentence is confusing. I would suggest splitting it into two sentences, ending the first sentence after “PwMS.” In the second sentence, I would like some clarification on what the “potential of stress management and lifestyle measures” is “high” in? Based on the previous sentence, it would be information; however, it appears that you are referring more to its quality of life or disease progression potential. A clarification of this longer sentence would make this paragraph read smoother.
Reply 2.3: Thank you for this suggestion. We indeed meant to refer to its potential regarding improved quality of life but also to the neurodegenerative process and reduced inflammatory disease activity. In fact, work, especially in dementia, has shown that lifestyle behaviour has the potential to influence disease evolution of a neurodegenerative disease. Here we cited the study published by Ngandu et al. 2015. In MS, Mohr et al. 2012 have shown that stress management influences inflammatory lesion evolution as a further indicator of the disease modifying potential of lifestyle behaviour, e.g. stress management techniques. The sentence is now split into two sentences and the potential of stress management and lifestyle measures is now specified (see pages 2-3 of the manuscript): “The existing

care structures cannot meet the complex information needs of PwMS." "There is a high potential of lifestyle management with regard to improved quality of life and a reduction of inflammatory disease activity as well as reduced neurodegeneration in MS (12, 13)."

Comment 2.4: Lines 25-26: The authors describe exercise and nutrition information as important; However, they fail to reference the published article by Motl and colleagues, on the benefits of an internet-based, walking behavior change intervention in MS. (Motl RW, Hubbard EA, Bollaert RE, Adamson BC, Kinnett-Hopkins D, Balto JM, Sommer SK, Pilutti LA, McAuley E. Randomized controlled trial of an e-learning designed behavioral intervention for increasing physical activity behavior in multiple sclerosis. Multiple Sclerosis Journal–Experimental, Translational and Clinical. 2017 Oct;3(4):2055217317734886.
Reply 2.4: Thank you, we appreciate the reviewer's suggestion and now cite the reference as recommended (see page 3 of the manuscript), reading: "Despite few examples on change of physical activity behaviour in MS, such as Motl et al. (15), online interventions in MS have mainly been investigated for the management of symptoms such as depression and fatigue (16, 17) but not for change of overall lifestyle behaviour."

Comment 2.5: Lines 30-32: I would like more clarification on the overall goal of the information provided. Is it to provide information on lifestyle-related matters, like exercise and nutri-tion, or to increase immunotherapy initiation? It seems like the immunotherapy initiation is not necessarily a lifestyle factor, but about making and keeping appointments in the clinic and adhering to prescribed medications/transfusions.
Reply 2.5: We are sorry of not having been clear enough on the content and goals. As pointed out in comment 1.9 and added to the text, the programme aims to stimulate PwMS to find their own MS approach. In fact, immunotherapy is only addressed in a short sequence. However, as the programme was designed for newly diagnosed PwMS and considering the high number of available immunotherapies, immunotherapy initiation is an important topic that was needed to be addressed shortly in the programme. While we summarize the limited efficacy, we underline that PwMS need to make a decision about early treatment. For further details they are encouraged to contact their neurologists and other information sources. This is now clarified in the manuscript (see page 5 and reply 2.6): "The programme does not provide drug specific information about available immunotherapies."

Comment 2.6: Lines 30-32: With regards to the phrase, "and consequently, better adherence and optimization of lifestyle habits," lifestyle behaviors are typically not a consequence of immunotherapy initiation, but a separate behavior and goal altogether. Doing activities at home, like stress reduction breathing techniques or engaging in physical activity, may require different information and training than adhering to a drug regimen. If you are providing information on these other types of behaviors (which it is apparent within the study design that you are), the EBPI is also targeting those behaviors. The increase in immunotherapy initiation is not per se the reason why participants increase secondary behaviors.
Reply 2.6: We agree with the reviewer's assessment and are sorry for the confusing sentence. We did not mean to put immunotherapy initiation and adherence into context with optimised lifestyle behaviours and therefore reworded the sentence for clarification, reading (see page 3 of the manuscript): "The goal of this programme is a more targeted immunotherapy initiation. Moreover, the programme aims to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour."

Comment 2.7: Development, Line 9: Please provide more details about the "simulated dialogues."
Reply 2.7: As also suggested by reviewer 1, more details regarding the simulated dialogues were added to the "Study design" section (see reply to comment 1.4 and page 5 of the manuscript).

Comment 2.8: Development, Line 10: I would suggest indicating the theoretical models used to develop the intervention (i.e., empowerment, cognitive behavioral therapy, self-determination theory, responsiveness, and content tailoring) here as well as under the intervention section later on in the manuscript.
Reply 2.8: Thank you for this suggestion. In order to avoid repetition while considering the limited word count, we now included a sentence referring to the “Interventions” section, reading (see page 3 of the manuscript): “The theoretical models used to develop the intervention are shortly outlined in the “Interventions” section.”

Comment 2.9: Overall, I would like a better description and clarity on how patients were involved in the study design and what aspects of the study were included/modified because of participant involvement.
Reply 2.9: The “Patient and public involvement” section is now filled with details in order to address their input with regard to the revision of the intervention (see reply to comment 1.10 and page 6 of the manuscript). A detailed description will be provided in a separate publication solely on the development, feasibility and pilot testing phase.

Comment 2.10: Line 17: Please provide more information/detail regarding the “think-aloud, teach-back” exercise.
Reply 2.10: As described above, development, feasibility and pilot testing (including methods and results) are beyond the scope of the RCT protocol and will be communicated in a separate publication (see also reply to comment 1.1).

Comment 2.11: Line 17-18: Please provide more detail regarding the “closed questions.”
Reply 2.11: Closed questions meant a defined set of questions with predefined answering formats with multiple choice or Likert formatted items. While we appreciate the reviewer’s assessment, as stated above (see reply 2.10) methodological details within the context of development, feasibility testing and piloting will be communicated separately.

Comment 2.12: Line 44: “Substantial cognitive deficit based on clinical impression” is a limitation of eligibility criteria. Considering the number of possible clinicians included, clinical im-pression could vary widely. I would suggest adding this to the limitations of the protocol. In future iterations of the study, the authors should consider excluding potential participants based on an objective measure of cognitive capacity, such as the Symbol Digit Modalities Test. This test can be given in the clinic within 3 minutes and has standardized cutoffs for normal performance and cognitive impairment.
Reply 2.12: We appreciate the critical reflection about cognitive deficits. In fact, in this study we refer to RRMS patients within the first year after diagnosis. We believe that nearly no patient will be excluded based on this criterion. While SDMT is a quick test, it is far from implemented in routine clinical care settings where this study takes place. Furthermore, we would be very hesitant to argue that a SDMT below 1.5 SD of a reference population leads to inability to handle the programme. And a cut-off as beyond 3.0 would be hardly reached by anyone. Clinical judgement for cognition was applied as a criterion in many of our studies and we believe it is a pragmatic approach. However, when moving this programme to more advanced PwMS, it might be very helpful to have e.g. an online SDMT to do subgroup analysis.

Comment 2.13: Line 18: How often will the IG program be monitored and “reacted on” (e.g., daily vs weekly vs monthly)? More details here would be helpful.
Reply 2.13: Thank you for pointing this out. Usage of the programmes (intervention as well as control group programme) will be monitored biweekly. However, programme usage will only be reacted on after 4 weeks without any activity (e.g. no logging in). Further information regarding monitoring and related reactions is now integrated (see reply 1.8 and page 5 of the manuscript), reading: “Usage of the IG programme will be monitored biweekly and reacted on after four weeks of non-usage to ensure

patient adherence."

Comment 2.14: This sentence is written in the past tense, suggesting that the intervention was already developed and piloted. However, in the study design section, it appears as if this is something that will be happening in the proposed protocol. Please clarify whether the study design occurred before or will be happening in this proposed protocol. Furthermore, if the design and piloting indeed occurred in the past, please respond to the question above regarding which aspects of the study were directly related to participant feedback and involvement.
Reply 2.14: We are sorry for the confusion. As stated above (see reply 1.1 and 1.2) you are right that the intervention was already developed, tested and piloted. As a crucial step of the overall multiphase-mixed-methods study, this manuscript is purely focusing on the RCT. In fact, patient and public feedback lead to some but no major changes of the intervention. However, these details will be communicated in a separate publication. This is now revised accordingly and we now additionally included information about the dissemination of results related to participant feedback in the "Patient and public involvement" section (see page 6 of the manuscript): "Details regarding the feedback and resulting programme changes will be communicated in a separate publication."

Comment 2.15: Please clarify if immunotherapy type, use, and adherence rates be collected throughout the study.
Reply 2.15: Data on immunotherapy type, use, and adherence rates is in fact collected throughout the study (during the clinical visits) and is now added in the "Criteria for discontinuation and relevant concomitant care" section of the manuscript (see page 6): "Immunotherapy type, use, and adherence rates will be collected during the clinical visits throughout the study."

Comment 2.16: Lines 32-41: Please provide details regarding which "selected items" will be used from each questionnaire.
Reply 2.16: We are sorry, that the information was not clear enough. Information about the selected items is now included for each questionnaire. We revised the paragraph on page 8 for clarity to: "[…] the coping capability, based on two items (item 10 and 24) of the coping self-efficacy scale, CSES (36) will be measured. In addition, patient expectancies based on items 1-3 of the credibility/expectancy questionnaire (37) will be assessed. Based on principles of the Health Action Process Approach, HAPA (38), readiness to change (39) will be estimated in order to determine the interventions impact on willingness to change lifestyle habits. Moreover, changes in perceived empowerment (based on (40), items 1, 3 and 4) will be measured."

Comment 2.17: The GLTEQ, BSA, and 24-hour dietary recall may be difficult for some individuals with MS, even if they are not to the level of clinical cognitive impairment. This should be mentioned within the limitations section of the article. Physical activity rates measured through accelerometry and a 3-day food journal would be more objective and accurate. These items could be mailed out to and received from participants using the standard postal system.
Reply 2.17: We agree that accelerometry and a 3 day food intake tool might be a more valid measure. However, this study is a pragmatic trial aiming to take place in private practises and clinics with limited resources of case payment as given by the German innovation fund. Aiming to keep patient and administrative burden low, we decided for the chosen tools. Moreover, the primary endpoint is relapse occurrence and inflammatory activity on MRI. Assessment of all outcome measures were piloted with five PwMS, indicating good practicability and acceptance. Nevertheless, we now added to the "Strengths and limitations" section (see page 2 of the manuscript): "Designing a pragmatic trial, we chose predominantly patient reported secondary clinical outcomes while more sophisticated instruments, as e.g. accelerometry, might yield more accurate estimates."

Comment 2.18: Are participants remunerated in any way for study participation?
Reply 2.18: No, participants are not remunerated for study participation. This is now mentioned in the

paper (see page 11 of the manuscript): “A financial compensation for participation in this study cannot be granted.” Only PwMS who participated in the developmental process (piloting) and evaluated the intervention programme were compensated financially for their efforts. Nevertheless, participants of the RCT receive the programme and a closer clinical supervision, as the number of clinical visits and MRI scans exceeds standard care in Germany. The study-related burden in contrast seems low. We believe that we developed a very patient-centred study that has a lot to offer for newly diagnosed PwMS.

VERSION 2 – REVIEW

REVIEWER	Leigh Hale University of Otago New Zealand
REVIEW RETURNED	26-Oct-2020

GENERAL COMMENTS	The authors have addressed some of the comments I made in my previous review, which has aided understanding somewhat but the protocol remains confusing. In the abstract the authors state “This randomised controlled trial (RCT) investigates the hypothesis that such a programme can change patient behaviour and reduce inflammatory disease activity in PwMS.” And then in the next line state “Methods and analysis: A multiphase mixed methods study will be conducted.” So is it as RCT or a mixed methods study? My suggestion is that the authors state that “This randomised controlled trial (RCT) with an embedded process evaluation investigates the efficacy and cost-effectiveness of a web-based behavioural lifestyle programme to change lifestyle behaviour and reduce inflammatory disease activity in PwMS.” Strength and limitations: “• Designing a pragmatic trial, we chose predominantly patient reported secondary clinical outcomes while more sophisticated instruments, as e.g. accelerometry, might yield more accurate estimates”. This sentence is incomplete – it needs an added explanation at the end to justify the use of the word “while” Introduction “There is a high potential of lifestyle management with regard to improved quality of life and a reduction of inflammatory disease activity as well as reduced neurodegeneration in MS” – this corrected sentence does not make sense – please consider revising. “Despite few examples on change of physical activity behaviour in MS, such as Motl et al. (15),” – explain which PA behaviour change example of Motl et al. you are referring to and is it effective or not? “The goal of this programme” – which programme? “The goal of this programme is a more targeted immunotherapy initiation. Moreover, the programme aims to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour.” I suggest that this sentence would make more sense if written as follows “The goal of this programme is to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour, thereby initiating a targeted immunotherapy response.” As mentioned above – the authors are still confusing this manuscript’s design. If this manuscript is to describe the

	evaluation of the programme (efficiency, process evaluation, cost-effectiveness), then the development and feasibility must be described in the introduction. Description of the EBBP programme: whilst this is a more informative than the prior manuscript version, especially in explaining the underpinning theories, it does not explain what the person with MS has to do. What actually happens? Do they log-on and start a dialogue – with who – and get an automated response? How often are the supposed to be on the website and for how long, who provides the advice or support? Or are the interactive learning modules the person makes their way through? Sorry, you can see my confusion, this need to be explicitly described. I note that you did not respond to my query regarding the security of sending MRI scans via mail in Germany?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Comment 1.0: The authors have addressed some of the comments I made in my previous review, which has aided understanding somewhat but the protocol remains confusing.
Reply 1.0: We have revised the manuscript for more clarity according to your comments. We have now removed the developmental parts from the methods section and are now simply referring to the framework of complex interventions as the underlying concept for the project.

Comment 1.1: In the abstract the authors state “This randomised controlled trial (RCT) investigates the hypothesis that such a programme can change patient behaviour and reduce inflammatory disease activity in PwMS.” And then in the next line state “Methods and analysis: A multiphase mixed methods study will be conducted.” So is it as RCT or a mixed methods study? My suggestion is that the authors state that “This randomised controlled trial (RCT) with an embedded process evaluation investigates the efficacy and cost-effectiveness of a web-based behavioural lifestyle programme to change lifestyle behaviour and reduce inflammatory disease activity in PwMS.”
Reply 1.1: Thank you, we have revised the abstract as suggested (see page 1 of the manuscript):
“This randomised controlled trial (RCT) with an embedded process evaluation investigates the efficacy and cost-effectiveness of a web-based behavioural lifestyle programme to change lifestyle behaviour and reduce inflammatory disease activity in PwMS.”

Comment 1.2: Strength and limitations: “Designing a pragmatic trial, we chose predominantly pa-tient reported secondary clinical outcomes while more sophisticated instruments, as e.g. accelerome-try, might yield more accurate estimates”. This sentence is incomplete – it needs an added explana-tion at the end to justify the use of the word “while”.
Reply 1.2: We aimed to provide an example of more accurate outcome measures for physical activity as one of our secondary endpoints and now specified this sentence accordingly (see page 2 of the manuscript), reading:
“We aimed to design a patient-centred pragmatic trial and thus selected patient reported outcomes as secondary endpoints, however, objective measures, as e.g. accelerometry, are not included.“

Comment 1.3: Introduction: “There is a high potential of lifestyle management with regard to im-proved quality of life and a reduction of inflammatory disease activity as well as reduced neuro-degeneration in MS” – this corrected sentence does not make sense – please consider revising.
Reply 1.3: We tried to clarify and now changed as (see page 3 of the manuscript):
“Experimental research as well as several clinical studies have suggested that improved lifestyle

management may have the potential to impact inflammatory and neurodegenerative processes in MS (12, 13)."

Comment 1.4: Introduction: "Despite few examples on change of physical activity behaviour in MS, such as Motl et al. (15)," – explain which PA behaviour change example of Motl et al. you are referring to and is it effective or not?
Reply1.4: We included this citation upon request of Reviewer 2. As suggested, we now added information regarding the behaviour change domain (walking behaviour) and efficacy in the manuscript (see page 3), reading:
"There are only very few examples for interventions that effectively change physical activity behaviour in MS. Motl et al. (15) have demonstrated in a pilot study that an internet-based intervention may change walking behaviour as assessed by self-report. However, online interventions in MS have mainly been investigated for the management of symptoms such as depression and fatigue (16, 17), but not for change of overall lifestyle behaviour."

Comment 1.5: Introduction: "The goal of this programme" – which programme?
Reply 1.5: We are sorry for being unclear. With this sentence we referred to the EBBC programme that is evaluated in this RCT. We now specified this in the manuscript (see page 3), reading:
"The goal of the web-based behavioural lifestyle programme evaluated in this RCT is…"

Comment 1.6: "The goal of this programme is a more targeted immunotherapy initiation. Moreover, the programme aims to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour." I suggest that this sentence would make more sense if written as follows "The goal of this programme is to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour, thereby initiating a targeted immunotherapy response."
Reply 1.6: Thank you, we have revised the sentence according to your suggestions. In addition, we have outlined in more detail how this may contribute to a more targeted immunotherapy initiation. The respective section now reads (see page 3 of the manuscript):
"The goal of the web-based behavioural lifestyle programme evaluated in this RCT is to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour. This may lead to decreased disease activity and lower distress to make an early treatment decision. Together with the careful MRI monitoring of the disease dynamics in the study, this procedure might enable a more targeted immunotherapy initiation."

Comment 1.7: As mentioned above – the authors are still confusing this manuscript's design. If this manuscript is to describe the evaluation of the programme (efficiency, process evaluation, cost-effectiveness), then the development and feasibility must be described in the introduction.
Reply 1.7:We now removed the developmental steps as indicated in reply to comment 1.0 (see page 4 of the manuscript), reading:
"Based on developmental work following the Medical Research Council (MRC) Framework for the development and evaluation of complex interventions (18), a web-based behavioural intervention programme on lifestyle adaptation in MS was developed (for details see below)."

Comment 1.8: Description of the EBBP programme: whilst this is a more informative than the prior manuscript version, especially in explaining the underpinning theories, it does not explain what the person with MS has to do. What actually happens? Do they log-on and start a dialogue – with who – and get an automated response? How often are they supposed to be on the website and for how long, who provides the advice or support? Or are the interactive learning modules the person makes their way through? Sorry, you can see my confusion, this needs to be explicitly described.
Reply 1.8: We are sorry for not having been clear. After randomisation, the participating person with MS receives login details/access data for either the intervention or the control group. After the first log

in, the participant is welcomed with a short introduction and has access to the first module. All other modules are activated sequentially, meaning they are only activated and accessible for the participant after completing the respective previous module. The program uses a fully automated feature called “simulated dialogue” with the computer programme. Here, the programme presents relevant educational content in each module. After each screen, the participants are provided with several response options (multiple choice). These typically include the option to get more detailed information, ask for concrete examples, indicate that the specific topic does not feel particularly relevant for the participant, or a general approval (e.g. “yes, that makes sense, let’s move on”). Based on the option selected, the programme will then present subsequent content that matches the participant’s choice. The participants are free to decide how often and for how long they want to log in.
This is now adapted in the description of the intervention in the manuscript (see page 5-6), reading: “The programme is designed as a highly individualised system that provides PwMS with narrative and coordinated information based on their existing health beliefs, interests, etc. Each text passage ends with a set of pre-programmed response options in multiple-choice format reflecting possible reader’s feedback, such as “Yes. That makes sense.” or “I do not quite understand this yet.” The participant is invited to tick the matching response and will be guided to the next page referring to the choice, e.g. “I'm glad that you can understand it.” or “No problem. Then let me explain it in a little more detail.” These simulated dialogues lead to a highly individualised way through the inter-vention, while on the other hand, the programme makes sure that every important area is touched.”

Comment 1.9: I note that you did not respond to my query regarding the security of sending MRI scans via mail in Germany?
Reply 1.9: As detailed in our previous point-by-point response, it is in accordance with current pro-cedures in medical practise in Germany to send CDs by regular mail. Moreover, this procedure has been reviewed and accepted by all responsible Ethics committees and is in compliance with current data protection rules and regulations. A sentence explicitly stating this has been added to the manu-script (see page 10):
„In accordance with current procedures implemented in medical practice, CDs with MRI data will be sent to the study centre in sealed envelopes via regular mail. This has been reviewed and accept-ed by the reviewing ethics committees and is in compliance with current data protection rules and regulations in Germany.“

VERSION 3 – REVIEW

REVIEWER	Leigh Hale University of Otago, New Zealand
REVIEW RETURNED	07-Jan-2021

GENERAL COMMENTS	Thank you for addressing all my concerns from the previous review. I have only 3 further suggested minor amendments: - At the end of page 2 (Introduction): "Nevertheless, early therapy directly after MS diagnosis is recommended (7), while adherence to immunotherapy in the first two years may be as low as 30-50% (8)." I suggest this sentence, indeed your whole rationale for the intervention, will make more sense if the word "while" was changed to "however". - Page 3, end of Introduction: "This may lead to decreased disease activity and lower distress to make an early treatment decision." Suggest you alter to "This may lead to decreased disease activity and lower distress to make an early treatment decision regarding use of immunotherapies." As PwMS may make decisions about other early treatment options.

	- Add a comma after the first bullet point on page 3 ("Strengthen patient autonomy and empowerment")