PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of a community-based multicomponent rehabilitation programme for patients with fibromyalgia: Protocol for a randomised controlled trial
AUTHORS	Haugmark, Trond; Hagen, Kåre Birger; Provan, Sella; Bærheim, Elisebeth; Zangi, Heidi

VERSION 1 – REVIEW

REVIEWER	Cecilie von Bülow The Parker Institute, Bispebjerg-Frederiksberg Hospital and Research Initiative for Activity Studies and Occupational Therapy, Research Unit of General Practice Universitiy of Sourthern Denmark
REVIEW RETURNED	16-Jan-2018

GENERAL COMMENTS	Peer Review of bmjopen-2017-021004 “Effects of a community-based multicomponent rehabilitation programme for patients with fibromyalgia: Protocol for a randomised controlled trial” General Comments: The overall aim of the study was to investigate the effects of a community-based multicomponent rehabilitation program comprising an acceptance- and mindfulness-based group intervention, the Vitality Training Programme (VTP), followed by tailored physical activity counselling. It is relevant to conduct non-pharmacological intervention programs for people with fibromyalgia, and also to evaluate outcome in an RCT design. Moreover, it is relevant that the authors have designed intervention programs that are graded and individualised. It has been interesting to read the protocol, however, there are some issues needed to be addressed. Overall judgement: Major revision In general, several terms are not used consistently and/or not explained, this make the protocol difficult to follow • In the abstract the term ’effect’ is used in the aim, while ’effectiveness’ is used in aim of the introduction. • In the introduction (page 6) the terms ’functional ability’ and ’physical fitness’ are used without explanations. Likewise, the term ‘physical activity’ is used in the aim. It is relevant to either explain the differences between these terms or use the same terms thought-out the paper. • Are multi-component rehabilitation and multi-faceted treatment the same or distinct? If distinct please explain how. • The use of the patients and participants are not used consistently.

	• In the description of the intervention the term 'graded physical activity' is used, whereas in the discussion 'graded physical exercises' is used – are the meaning the same? Introduction • The ability to work is an outcome in this RCT. Therefore, please provide knowledge about decreased functional ability within this population. Decreased functional ability, not only decrease the ability to work, but also the ability to perform familiar and relevant activities of daily living (ADL). • The introduction does not provide adequate information, as to why FM patients are in need of mindfulness- and acceptance training. • An argument for using mindfulness- and acceptance based training is that systematic reviews show improvements in quality of life (QoL), however the authors have not mention QoL as a problem within the population. • The main goals of the VTP programme is to "enhance participants' awareness of their health promoting resources and to strengthen their inner authority and abilities to make conscious choices in line with their personal values" and VTP has previously shown reduced emotional distress, improved pain coping and mental well-being. If this is the an argument for applying the program in FM, it seems relevant to illuminate that people with FM show these kinds of problems. This would improve the structure of the protocol. • Long disease duration is used as an explanation for not identifying improvements in the FM group. It would be relevant to define how many years a long disease duration is to be understood. E.g. more than 10 years? • Offering physical exercise to improve physical fitness seem relevant (if physical fitness it understood as strength, balance, condition etc?) (page 6). However, it is unclear if authors find that physical exercise improves functional ability (which could be understood within the context of activity and participation e.g. ability to work or perform ADL tasks?). That is, it is unclear if the authors suggest that exercise improves body capacity (i.e. physical fitness)? or functional ability (i.e. activity and participation)? Aim • The primary objective is to study if the intervention will improve self-perceived health, however primary outcome of the intervention is Patient Global Impression of Change (PGIC), which to my knowledge, is not an evaluation of health, but a surrogate of overall improvement. Is it fair to conclude that a possible improvement in PGIC is an improvement in health? That is, there might be a discrepancy between primary objective and primary outcome? Trial development and design • The study is described as a pragmatic parallel randomised controlled trial, how is it pragmatic? • The authors state that the rehabilitation program complex, I agree, however I find it relevant to unfold how it is complex? • Also that the program followed the new Medical Research Council guidance for Developing and evaluating complex interventions. How does the intervention follow the guidance? Materials Eligibility criteria • The authors write "Patients are eligible if they are aged between 20 and 50 years" and in the discussion the authors write that they "aim

	at reaching patients at an early stage of their disease to prevent further development of disability and therefore we will include only patients of 50 years and below". The authors, wish to exclude people with a long disease duration (as referred to in the introduction), however setting a limit for maximum age will not exclude patients having the pain condition for a long period of time, e.g. > 10 years. If the authors want to exclude patients with a long disease duration, they may need to define a period of time in which the patients recall having the pain condition. The intervention programs • It would be relevant to provide a short description of every session, as this would make the intervention programs more transparent and possible to repeat. The intervention programs could be described in appendixes. • Have the authors considered how many sessions the participants need to have entered, in order to conclude that the participants may have gained from the programs? Eg. an attendance >25%? • Please refer to the study flow chart when describing the intervention, and describe where in the flow chart the intervention programs are situated. It is not obvious were the 6-months booster session is placed? • Will goals be defined on an 'activity and participation' level or on a body level in the physical activity program? Consider providing an example of a goal, and how the physical activity program could be designed to reach that goal. • It is not obvious how or which of the intervention programs that are expected to improve the participants' ability to work? Outcomes • Have the authors considered using observation-based instruments? Several studies show that self-report and observation provide complementing but distinct results • It is stated that scores of 6 and 7 are considered clinically relevant improvement in the PGIC, with a reference to Choy et al 2009. It´s positive that the authors consider how to interpretate clinically relevant improvements, however I cannot find that Choy et al, write how results in the PGIC can be interpreted in regard to clinically relevant improvements? • How will clinically relevant improvements be defined in the other instrument used to evaluate secondary outcomes? • Secondary outcomes will be collected at baseline, 3 and 12 months. Why these evaluation time-points? • It is not clear if the 12-months follow-up is 12 months from baseline or 12 months after end of treatment? If it is 12 months from baseline, please provide information about the time period from end of treatment to follow-up assesment? • I wonder how come the authors have not included instruments to evaluate functional ability, when they state that these population has high levels of disability (in the discussion)? Data collection • The authors write that participants who do not possess an electronic device will receive a paper version of the questionnaire. Have the authors considered if answered given on the electronic device provide similar answers to those given on paper? Maybe the authors will find the following study interesting, as similar comparison were done. Scand J Rheumatol 2015;44(6):503-10. 'Agreement between touch-screen and paper-based patient-reported outcomes for patients with fibromyalgia: a randomized cross-over reproducibility study'. Wæhrens EE et al.

	Study flow chart • It would make the figure easier to understand if the different intervention programs were entered into the flow chart. Statistical outcomes • Please describe which covariate the authors will adjust for in the ANCOVA analyses.

REVIEWER	Teresa Paolucci Sapienza University of Rome, UOC Physical Medicine and Rehabilitation-Policlinico Umberto I Hospital, Italy
REVIEW RETURNED	04-Feb-2018

GENERAL COMMENTS	Dear Authors the study design is well conducted and explained, I look forward to the final results Regards

VERSION 1 – AUTHOR RESPONSE

Comments from Editor	**Our response**	**Page number**
1. On page 13 you say "Self-reported harmful events will be assessed at 12 months." Can you elaborate on how adverse events will be collected and assessed?	We agree that this can be written more explicitly. More information on the collection and assessment of adverse events are now added to the Outcomes section. We have also attached the questionnaire as Online Supplementary file 3.	p. 14
2. Re SPIRIT Checklist Item 27: Please elaborate on how personal information about potential and enrolled participations will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.	We agree that this item needs a clearer explanation. A new paragraph is added under the Ethical approval section to elaborate on SPIRIT Checklist Item 27.	p. 16
3. Re SPIRIT Checklist Item 29: Please clarify the manuscript who will have access to the final trial dataset.	We agree that this item is important to clarify. This item is added under the Ethical approval section.	p. 16
Comments from reviewer 1	**Our response**	**Page number**

1. In the abstract the term “effect” is used in the aim, while “effectiveness” is used in aim of the introduction.	Our aim is to evaluate effects of the multicomponent rehabilitation programme. We have now used ‘effects’ consistently throughout the manuscript.	p. 8
2. In the introduction (page 6) the term “functional ability” and “physical fitness” are used without explanations. Likewise, the term “physical activity” is used in the aim. It is relevant to either explain the differences between the terms or use the same terms through-out the paper.	Thank you very much for this comment. We have carefully reconsidered our use of concepts and aim at using the concepts consistently throughout the manuscript. We have clarified and defined our use of “physical activity” and “physical exercise” in the Introduction. This has resulted in replacing “physical activity” by “physical exercise” in the description of the Healthy Life Center (HLC) intervention. The aim of this intervention is to increase FM patients’ physical activity through participation in the VTP and physical exercise at the HLC. We have removed the term functional ability because this was not included in the aim of our intervention.	p. 6 ff.
3. Are multi-component rehabilitation and multi-faceted treatment the same or distinct? If distinct, please explain how.	These two terms are used as synonyms. We have now consequently used the term “multicomponent rehabilitation programme”.	p. 7
4. The use of the patients and participants are not used consistently.	We have now used “patients” when referring to people with FM who are included in the trial and “participants” when we refer to those who participate in the multicomponent rehabilitation programme.	p. 4 ff.
5. In the description of the intervention the term “graded physical activity” is used, whereas in the discussion “graded physical exercises” is used – are the meaning the same?	We have now used the term “graded physical exercise” in the description of the intervention. Please, see our response to comment 2 above.	p. 4
6. **Introduction:** The ability to work is an outcome in this RCT. Therefore, please provide knowledge about decreased functional ability within this population. Decreased functional ability, not only decrease the ability to work, but also the ability to perform familiar and relevant activities of daily living (ADL).	The reason for including work ability as an outcome measure in this trial was that it is well-documented that chronic widespread pain, such as FM, is a common cause of sick leave and use of disability benefit in Norway. To increase work ability (and reduce sick leave) is an expressed aim in the Norwegian society. We have now added two more references to support this in the first sentence in the introduction. We have removed the term functional ability because this was not included in our aims (see comment 2 above), and we have not included any outcome measures that explicitly measures functional ability. However, we measure aspects that may be related to functional ability, such as psychological distress, physical activity and health-related quality of life. Moreover, the WPAI is not only a measure of work ability, but also include ability to perform other daily activities.	p. 4

7. The introduction does not provide adequate information, as to why FM patients are in need of mindfulness- and acceptance training.	There are several systematic reviews analysing effects of mindfulness- and acceptance training for FM patients. However, we acknowledge that the basis for these interventions needs some elaboration. We have now included more knowledge about FM patients' emotion regulation styles and related this to mindfulness- and acceptance-based training.	p. 5
8. An argument for using mindfulness- and acceptance based training is that systematic reviews show improvements in quality of life (QoL), however the authors have not mention QoL as a problem within the population.	In the 2016 update of the EULAR recommendations for management of fibromyalgia, Macfarlane et al state that reduced QoL is a common problem. This reference is now added to the introduction.	p. 4
9. The main goal of the VTP programme is to "enhance participants` awareness of their health promoting resources and to strengthen their inner authority and abilities to make conscious choices in line with their personal values" and VTP have previously shown reduced emotional distress, improved pain coping and mental well-being. If this is the argument for applying the programme in FM, it seems relevant to illuminate that people with FM show these kinds of problems. This would improve the structure of the protocol.	This has now been addressed in the manuscript. In the ACR 2010 preliminary diagnosis criteria mental distress, such as problems with concentration and thinking clearly (memory) and depression are included (Wolfe, et al 2010). We have reformulated "emotional distress" to "psychological distress" which is a more correct term of the included outcome measure (GHQ-12). This concept includes symptoms of depression and anxiety. Mental well-being is perceived as reduction of mental distress.	p. 6
10. Long disease duration is used as an explanation for not identify improvements in the FM group. It would be relevant to define how many years a long duration is to be understood. E.g. more than 10 years?	We agree that this is relevant. The FM patients in the cited study had a mean disease duration of 14 years and had on average experienced pain symptoms more than 10 years before they were diagnosed with FM.	p. 6
11. Offering physical exercise to improve physical fitness seem relevant (if physical fitness is understood as strength, balance, condition etc.?) (Page 6). However, it is unclear if authors exercise improves functional ability (which could be understood within the context of activity and participation e.g. ability to work or perform ADL tasks?). That is, it is unclear if the authors suggest that exercise	We agree on this comment. We have removed the term "functional ability", and aimed to clarify the relationship between physical exercise and physical activity. Please see comment 2 above. As described in aims of the study (page 7) we will investigate if the community based multicomponent programme will increase FM patients' physical activity. The purpose of the physical activity counselling is to help participants find exercises that can be easily continued in their everyday life and gradually increase their levels of physical activity (page 11). By increasing physical activity	p. 8+11

improves body capacity (i.e. physical fitness)? Or functional ability (i.e. activity and participation)?	we suggest that the patients will improve their overall health status.	
12. **Aim:** The primary objective is to study if the intervention will improve self-perceived health, however primary outcome of the intervention is Patient Global Impression of Change (PGIC), which to my knowledge, is not an evaluation of health, but a surrogate of overall improvement. Is it fair to conclude that a possible improvement in PGIC is an improvement in health? That is, there might be a discrepancy between primary objective and primary outcome?	Rampakakis et al 2015 states that "the PGIC evaluates overall health status as perceived by the patient" and represents a clinically relevant tool to assess perceived impact of disease management in FM. The PGIC evaluates overall health status as perceived by the patient in a seven-point single-item scale The formulation of the question is: "Since the start of the study, my overall health status is…" Thus, we consider that the PGIC measure change in patients' self-perceived health status.	p. 12
13. **Trial development and design:** The study is described as a pragmatic parallel randomized controlled trial, how is it pragmatic?	The trial is conducted in a real life community setting and thus considered as a pragmatic trial, ref. the definition by MacPherson H. Pragmatic clinical trials. Complementary Therapies in Medicine 2004;**12**(2):136-40: "*Pragmatic trials are designed to find out about how effective a treatment actually is in routine, everyday practice"*.	p. 8
14. The authors state that the rehabilitation program complex, I agree, however I find it relevant to unfold how it is complex?	We have now added a sentence to clarify this term by describing shortly that this study is designed with several interacting components.	p. 8
15. Also that the program followed the new Medical Research Council guidance for Developing and evaluating complex intervention. How does the intervention follow the guidance?	We have added a sentence to clarify that the study follow the guidance and complex interventions by e.g. having several phases such as the education for both groups, a number of interaction components within the intervention group such as a group intervention and a tailored physical activity counselling, a variability of outcomes, a degree of flexibility and tailoring of the intervention, etc. Craig, 2008.	p. 8
16. **Materials:** Eligibility criteria; The authors write "Patients are eligible if they are aged between 20 and 50 years" and in the discussion the authors write that they "aim at reaching patients at an early stage of their disease to prevent further development of disability and therefore we will include only patients of 50 years and below". The	We agree with the reviewer that there is no linear relationship between age and disease duration. The limitations and exclusion criteria were extensively discussed in the project group. It was agreed that patients' recall of when the pain started is an uncertain measure because the condition often develops gradually starting as single site pain not associated with FM. To include patients at an early stage of their disease, we therefore ended up with setting an age limit for participation. Another aim of the intervention is to prevent sick leave and	P. 10

authors, wish to exclude people with a long disease duration (as referred to in the introduction), however setting a limit for maximum age will not exclude patients having the pain condition for a long period of time, e.g. >10 years. If the authors want to exclude patients with a long disease duration, they may need to define a period of time in which the patients recall having the pain condition.	in the long-run, disability retirements. Hence, patients will be excluded if they have been out of work for more than two years due to their pain condition.	
17. **The intervention programs:** It would be relevant to provide a short description of every session, as this would make the intervention programs more transparent and possible to repeat. The intervention programs could be described in appendixes.	We have attached a description of one of the session 6 'Anger' (Online Supplementary file 2). All the sessions follow the same structure with methods and exercises adapted to the particular topic. The description of the HCL intervention has been amplified in the manuscript.	Online Suppl. 2
18. Have the authors considered how many sessions the participants need to have entered, in order to conclude that the participants may have gained from the programs? E.g. an attendance > 25%?	Based on a previous RCT (Zangi et al 2012) we have decided that the participants need to attend ≥ 50 % of the sessions to expect effects of the VTP. We have not set any attendance rate for the HLC intervention, but adherence will be reported.	p. 11
19. Please refer to the study flow chart when describing the intervention, and describe where in the flow chart the intervention programs are situated. It is not obvious were the 6-months booster session is placed?	This has now been addressed and the interventions are added in the Study Flow chart, Figure 1.	p. 15
20. Will goals be defined on an "activity and participation" level or on a body level in the physical activity program? Consider providing an example of a goal, and how the physical activity program could be designed to reach the goal.	Goals for the physical exercise at the HLC will be defined at an activity and participation level. The goals will be defined by the participant in collaboration with a physiotherapist. A common goal may be to reduce pain. An activity plan may be to perform strengthening and aerobic exercises, for example cycling or Nordic walking three times a week. Another aim is to learn the balance between activity and rest and find the right dosage of the exercises. This has been added to the text.	p. 11
21. It is not obvious how or which of the intervention programs that are to improve the "participants`" ability to work?	In this trial we do not intend to evaluate effects of the single intervention components, but in a pragmatic trial to evaluate the effects of the complete multicomponent rehabilitation programme. However, we will also collect data after the VTP (3 months) to evaluate if any of the outcomes are changed in either direction after completion.	

22. **Outcomes:** Have the authors considered using observation-based instruments? Several studies show that self-report and observation provide complementing but distinct results.	Our selection of outcome measures based on The Fibromyalgia responder index defined by OMERACT (Mease et al 2011). Moreover, the ACR 2010 diagnostic criteria for FM are based on self-reported symptoms burden. We have therefore prioritized self-reported outcome measures.	p. 12
23. It is stated that scores of 6 and 7 are considered clinically relevant improvement in the PGIC, with a reference to Choy et al 2009. It`s positive that the authors consider how to interpretate clinically relevant improvements, however, I cannot find that Choy et al, write how results in the PGIC can be interpreted in regard to clinically relevant improvements?	Thank you very much for this observation. The reference was incorrect and we have now replaced it with the correct one, which is McBeth et al 2012.	p. 12
24. How will clinically relevant improvements be defined in the other instrument used to evaluate secondary outcomes?	The secondary outcomes other will be analysed as continuous variables and effect sizes will be calculated. The change in PGIC will be used as an anchor for defining clinical relevant improvements in these outcomes.	p. 12
25. Secondary outcomes will be collected at baseline, 3 and 12 months. Why these evaluating time-points?	The 3-month data collection is conducted after completion of the VTP, which makes it possible to evaluate direct effects of this programme before the participants start the HLC intervention. The 12 months data collection intends to evaluate effects of the complete multicomponent rehabilitation programme. Collecting data 12 months from baseline also means that baseline data follow-up data are collected at the same time of the year. This will reduce confounding by seasonal fluctuations of the disease, which are relevant in a Norwegian context.	p. 15
26. It is not clear if the 12-months follow-ups is 12-months from baseline or 12-months after end of treatment? If it is 12-months from baseline, please provide information about the time period from end of treatment to follow-up assessments?	The 12-monts follow-up is 12 months from baseline. This has now been changed in the manuscript.	p. 15
27. I wonder how come the authors have not included instruments to evaluate functional ability, when they state that this population has high levels of disability (in the discussion)?	As described above we have decided to remove the term ‘functional ability’. Please see our response to comment 2.	
28. **Data collection:** The authors write that participants who do not possess an electronic device will receive a paper	Thank you for this question and for making us aware of the interesting article by Wæhrens et al. Taking into account that participants in this trial is ≤ 50 years, we expect that the majority of the patients have access to a computer, a	p. 15

version of the questionnaire. Have the authors considered if answers given on the electronic device provide similar answers to those given on paper?	tablet or mobile phone and will prefer using the electronic solution to answer the questionnaires.	
29. **Study flow chart:** It would make the figure easier to understand if the different intervention programs were entered into the flow chart.	The interventions have now been added to the flow chart.	p. 15
30. **Statistical outcomes:** Please describe which covariate the authors will adjust for in the ANCOVA analyses.	We will adjust for the baseline values in the ANVOVA analyses.	p. 16
Comments from reviewer 2		
The study design is well conducted and explained, I look forward to the final results	Thank you for this comment.	

VERSION 2 – REVIEW

REVIEWER	Cecilie von Bülow The Parker Insitute, Bispebjerg-Frederiksberg Hospital and The Research Initiative for Actoivoty Studies and Occupational Therapy, General Practice, University of Southern Denmark, Denmark
REVIEW RETURNED	09-Apr-2018

GENERAL COMMENTS	I would like to thank the authors for having considered and answered my questions. I find that the protocol has improved significantly, and I suggest that the protocol is to be accepted without further revisions.