PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of faecal microbiota transplantation in patients with psoriatic arthritis: protocol for a 6-month, double-blind, randomised, placebo-controlled trial The FLORA trial
AUTHORS	Kragsnaes, Maja; Kjeldsen, Jens; Horn, Hans; Munk, Heidi; Pedersen, Finn; Holt, Hanne; Pedersen, Jens Kristian; Holm, Dorte; Glerup, Henning; Andersen, Vibeke; Fredberg, Ulrich; Kristiansen, Karsten; Christensen, Robin; Ellingsen, Torkell

VERSION 1 – REVIEW

REVIEWER	Dr Laura C Coates University of Oxford UK
REVIEW RETURNED	06-Sep-2017

GENERAL COMMENTS	Comments 1. Page 4 abstract - there is a typo with "God Clinical Practice" 2. Introduction - whilst MTX is the first line drug in most settings for PsA, it should be acknowledged that the evidence for MTX in PsA is poor. This isn't a criticism of design but I think I would acknowledge that up front. 3. Whilst the inclusion criteria are similar to many trial, I worry about recruitment if you want at least 3 swollen joints for a placebo controlled trial of a therapy with no prior evidence for 6 months. When is the alternative treatment strategy for non responder used? Is it if they are no better after 3 months? They already have active disease at baseline so they could be eligible for steroids/DMARDs immediately? 4. I think the outcome measures are reasonable but it might be nice to consider some newer more specific PsA measures such as DAPSA for peripheral joint disease or MDA for overall disease control. 5. Will PASI only be used in patients with significant levels of skin disease or all? It does not perform as well in those with low BSA.

REVIEWER	Matthew Stoll University of Alabama at Birmingham USA
REVIEW RETURNED	16-Sep-2017

GENERAL COMMENTS	This is a novel and important study. I have some concerns about the protocol, specifically whether a single transplantation from a single donor is going to last six months. In addition, despite all the

	clinical and histopathologic data the team will be collecting, the endpoint is subjective -- whether the treating physician has elected to alter the patient's therapy. Finally, if the sigmoidoscopy results are merely tertiary outcomes, why are the authors subjecting the patients to the risks and research costs associated with this procedure? Minor comments 1. Page 4, line 21: Howbeit is not a word. Either "however" or "albeit" are ok. 2. Page 5, evidenced based research. I performed the same search and identified 322 manuscripts. The authors have missed a few citations, including a RCT of probiotics in AS patients (Jenks, 2010) and other studies of probiotics in RA patients. 3. Page 10. The investigators list the screening tests for the potential donors. They should also pre-define the acceptable ranges, e.g. for albumin, WBC, etc. 4. Are rheumatologists performing the PASI? 5. There is very little information on the microbiota analysis. The investigators state that they will measure fecal bacteria composition and metabolism (page 12, line 34). How will metabolism be measured? Fecal water metabolomics? Imputed from PICRUST? Will the composition be measured with 16S or shotgun sequencing? Also, how will "changes" in fecal microbiota composition be assessed? 6. Why are the investigators only measuring changes in enthesitis, dactylitis, and psoriasis among those who have it at baseline? In so doing, they will miss subjects who develop it de novo. 7. Table 1 -- which intestinal permeability test will they do?

REVIEWER	Maxime Breban University of Versailles-St-Quentin, and Hospital Ambroise Paré, AP-HP, Boulogne-Billancourt, and Inserm UMR 1173, and Labex Inflamex, france
REVIEW RETURNED	27-Sep-2017

GENERAL COMMENTS	This is a very straightforward protocol, that is well presented and very complete. It would be important to describe the type of microbiota analyses that will be performed on the collected samples. It would also be interesting to explain what the sigmoidoscopy will be used for, and to justify this procedure that will be repeated, since it is a rather heavy procedure.

REVIEWER	Jose Scher Psoriatic Arthritis Center Microbiome Center for Rheumatology and Autoimmunity NYU Langone Health NY, USA
REVIEW RETURNED	09-Oct-2017

GENERAL COMMENTS	I read with great interest the Protocol for the FLORA trial by Kragsnaes MS, et al. They propose a randomized, placebo-controlled trial of FMT infused into the small intestine of PsA patients with active peripheral disease who are IR to sq MTX. The objective is to explore clinical aspects (efficacy and safety) associated with FMT in PsA patients. Primary endpoint is the proportion of patients who experience a

	treatment failure during the 6-month trial period vs placebo. Although FMT has been utilized with undisputed success for the treatment of C. diff. infectious colitis and to a certain degree for inflammatory bowel diseases, the effects such approach would have on systemic autoimmunity is unknown. This is therefore a novel and a priori well-designed RCT with potential for clinical-altering results. The premise is clear and the clinical/biomarker collections are delineated. In reading this protocol at length, however, several concerns arise that diminish my enthusiasm for this trial at this moment in time: 1- As pointed out by the authors, there are only a handful of studies in the literature that characterize a gut dysbiotic process in psoriatic diseases. These, including the one conducted by our group, require validation at local centers so that the overall premise of the study can be supported. Have the authors performed preliminary studies looking at what perturbations (if any) are present in their PsA population? This is vital, since presumably FMT would "restore" a homeostatic gut community. 2- The inclusion criteria is quite flexible in that it allows for any disease duration and prior use of other medications, including biologic therapy. The concern here is that there are many confounding variables that may significant reduce the interpretation of any potential benefit of the intervention. The authors describe this limitation based on UC literature, but decide to pursue a potentially less significant strategy. If the don't have access to that patient population, could they collaborate with other institutions that do? 3- Based on prior data on IBD, one FMT infusion appears to be insufficient. The three randomized trials differed of FMT efficacy in UC utilized several more infusions (one infusion every week for 6 weeks; or two infusions 3 weeks apart; or one FMT followed by enemas 5 days per week for 8 weeks). If this was the approach for the treatment of "local" autoimmunity, it follows that a therapeutic approach for systemic autoimmunity would at the very least be equal to the ones used for UC. The authors suggest that that will not be the case in PsA, but do not present any evidence to that end. Rather, they conclude that "we strongly believe that the FMT procedure in the present study will be sufficient to boost the effects of MTX". This is an intriguing hypothesis but not in line with their overall premise. Is there any preliminary data that suggest microbiota boosting MTX response? And if so, how would that occur with sq MTX use? 4- Sample size and power considerations appear overly optimistic. The assumption that twice as many PsA subjects in the sham group will be treatment failures is not based on any available evidence. A more realistic outcome is advised. 5- Donor selection is a challenge. Suggest they limit donors to no more than 4 (one oer 10 recipients) in an attempt to avoid errors in prior studies. 6- The investigators claim that "extensive bacteria taxonomic and metagenomic analyses will be performed on fecal samples before and after the FMT to get an indication of the functional capacity of the intestinal microbiota". However, no description on who and how this will be performed is lacking. Presumably, this will be performed by Dr. Kristiansen. Please, expand on this crucial aspect.

REVIEWER	Sameer Parpia

	McMaster University, Canada
REVIEW RETURNED	31-Oct-2017

GENERAL COMMENTS	The authors present a design paper for a proof-of concept double blind placebo-controlled trial to evaluate the efficacy and safety of faecal microbiota transplantation in patients with psoriatic arthritis. There are methodological and statistical concerns that need addressing. The major issue relates to the design of the trial given the lack of data pointed out my the authors 1. The authors state the lack of data for the intervention (its efficacy, feasibility etc), but much of the trial is designed as a phase III trial (even though they state its a proof of concept trial). A strong justification is needed for the proposed design over a feasibility/pilot design given the lack of data for the intervention in this setting? 2. The authors mention the limited data on the intervention, however, power the trial at 90% to detect a decrease in treatment failure from 70% to 35% - given that there is no data available, it is unclear how the authors have justified this treatment effect. In addition, the implication of not observing the hypothesized treatment effect is not discussed, for example, a reduction of 20%? 3. In the discussion, it is pointed out that feasibility data for FMTs in this setting are not available. However, no feasibility outcomes have been proposed. Please clarify? 4. Authors propose 11 secondary outcomes with no adjustment for multiple testing - the overall type I error will be inflated using this approach. An approach of estimation of treatment effect and its corresponding variance would be more suitable. 5. Missing data for the primary outcome will be treated as treatment failure. Assuming 20% attrition as stated, 9/40 (23%) per group will be considered treatment failures. This seems as a very conservative approach as the expected treatment failures by groups are 35% and 70%. 6. Multiple imputation is the standard for all missing data. Consider making MI analysis the primary analysis. 7. Page 14 Line 11 - "Categorical changes for dichotomous outcomes" - please clarify? 8. How will diff

REVIEWER	Lynda Cochrane Clinical Statistics Consultants Scotland
REVIEW RETURNED	06-Nov-2017

GENERAL COMMENTS	This is a well-thought through study design. Please could the authors provide evidence for the assumptions of 35% and 70% treatment failures for the FMT-active / -sham groups? Although this is a proof-of-concept trial, it would be interesting to

	have a comparison of FMT-active / -sham groups at baseline. There are a few minor typographic errors. For example, Page 14, Line 13 "lists was" should read "lists were", there are missing words in Lines 1 and 8 of Page 15.

VERSION 1 – AUTHOR RESPONSE

Regarding the editorial Requirements:

Dear Editor,

Thank you for your insightful and relevant comments.

1. Please complete and include a SPIRIT check-list, ensuring that all points are included and state the page numbers where each item can be found: the check-list can be downloaded from here: http://www.spirit-statement.org/
Answer: A SPIRIT check-list has been uploaded.

2. Please revise the Strengths and Limitations section (after the abstract) to focus on the methodological strengths and limitations of your study rather than discussing the results.
Answer: In the "Strengths and Limitations" section, the 4th bullet point "Associated microbiome analyses can reveal novel insight into the PsA pathogenesis" has been replaced by "No feasibility data regarding FMT in rheumatic patients were available when the trial was designed." (page 2 line 34-35).

3. Please ensure the manuscript is correctly formatted as per our guidelines for protocol articles: http://bmjopen.bmj.com/pages/authors/ For example, please remove the Conclusions section.
Answer: The "Conclusions" section has been removed and the final paragraph in the "Discussion" section has been rephrased (page 22 line 13-17).

Authors' response to reviewers' comments:

Reviewer: 1

Dear Dr Laura C Coates

Thank you for your insightful and relevant comments.

1. Page 4 abstract - there is a typo with "God Clinical Practice"
Answer: The typo has been corrected to "Good Clinical Practice".

2. Introduction - whilst MTX is the first line drug in most settings for PsA, it should be acknowledged that the evidence for MTX in PsA is poor. This isn't a criticism of design but I think I would acknowledge that up front.
Answer: In the Introduction section, we have added that "the evidence for MTX in PsA is poor" (page 3 line 18).

3A. Whilst the inclusion criteria are similar to many trial, I worry about recruitment if you want at least 3 swollen joints for a placebo controlled trial of a therapy with no prior evidence for 6 months.

Answer: We are well aware that the majority of PsA patients do not have three (or more) swollen joints, but when deciding on the study population, we found it important that only patients with severe arthritis could participate in this first rheumatological FMT trial. Fortunately, we have succeeded in recruiting 13 patients from our local area (Fune) since May, and now we are starting to recruit from other Danish departments (outpatient clinics) of rheumatology.

3B. When is the alternative treatment strategy for non responder used? Is it if they are no better after 3 months? They already have active disease at baseline so they could be eligible for steroids/DMARDs immediately?
Answer: The alternative treatment strategy for non-responders will be offered throughout the study. The patients can contact the department due to unacceptable diseases activity whenever needed, and will be seen by the treating rheumatologist as soon as possible. So far, 1 patient out of 13 included has received this alternative treatment strategy after just 1 month. However, if the patients do not report unacceptable disease activity, they will first be considered for other interventions if they are not better after three months. Patients who at the pre-study screening visit have active spine involvement or in other ways due to high disease activity will be candidates for immediate biological treatment, will not be considered eligible for the study. This is now clearly stated in the "Exclusion criteria" section (page 8 line 24-25) and in the "Treatment strategy for non-responders" section (page 10 line 19-20).

4. I think the outcome measures are reasonable but it might be nice to consider some newer more specific PsA measures such as DAPSA for peripheral joint disease or MDA for overall disease control.
Answer: We have chosen to use the more traditional PsA outcome measures as secondary outcomes to supplement our primary outcome "Treatment failure based on shared decision making" which by some colleagues may be considered a "soft" endpoint. However, we acknowledge that other newer composite outcome measures such as DAPSA and MDA could be relevant when designing future trials. In the current study, we assess most (all) of the domains included in these scores.

5. Will PASI only be used in patients with significant levels of skin disease or all? It does not perform as well in those with low BSA.
Answer: We do use PASI in all participants although most of them have low BSA due to current s.c. MTX. We acknowledge, that no firm conclusions on FMT treatment effects on psoriatic skin involvement can be drawn from this study.

Reviewer: 2

Dear Matthew Stoll

Thank you for your insightful and relevant comments.

A. This is a novel and important study. I have some concerns about the protocol, specifically whether a single transplantation from a single donor is going to last six months.
Answer: We have chosen to perform only one transplantation in each patient as this is the first FMT trial evaluating rheumatic patients. Hence, we would like to evaluate the safety of the procedure in this patient group before testing any dose-response relationship. A previous study where FMT was performed on metabolic syndrome patients reported extensive coexistence of donor and recipient strains, persisting 3 months after treatment following one FMT (Li SS, Zhu A, Benes V et al. Durable coexistence of donor and recipient strains after fecal microbiota transplantation. Science. 2016;352:586-589). Consequently, we believe that one FMT has the potential to change the recipient's microbiota, and will, at least for a period, be able to affect bacteria that could be

responsible for disease promoting effects in the gut. Little (nothing) is known about bacteria type, dose and administration frequency to obtain long-lasting effects in rheumatic patients. If this study provides indications of positive effects in PsA patients, a new study testing how the treatment strategy could be optimized should be instigated. Your concerns are addressed in the “Discussion” section (page 19 line 13-31 and page 21 line 25-40).

B. In addition, despite all the clinical and histopathologic data the team will be collecting, the endpoint is subjective -- whether the treating physician has elected to alter the patient's therapy.
Answer: “Shared decision making between patient and physician” may be considered a “soft” primary endpoint, however, this overarching principle is used in everyday clinical practice and has recently been appreciated by an international taskforce. As both patients and the treating rheumatologists are blinded to the randomised intervention, the shared decision will be unaffected by intervention type. These considerations are now implemented in the “Discussion” section (page 19 line 38 to page 20 line 2).

C. Finally, if the sigmoidoscopy results are merely tertiary outcomes, why are the authors subjecting the patients to the risks and research costs associated with this procedure?
Answer: In Denmark, the risk of a sigmoidoscopy and the associated biopsy procedure is considered relatively low. Regarding the costs, in the current study the sigmoidoscopy at baseline is performed immediately before the FMT-procedure and lasts less than ten minutes, which limits the extra costs related to this procedure. Also, as the Dept. of Gastroenterology is part of our academic collaboration, the costs are limited. As the intestinal permeability test evaluates potential functional abnormalities of the small intestine, we found it relevant to assess whether gut pathology could be present at the more distal parts of the gastrointestinal tract.

Minor comments
1. Page 4, line 21: Howbeit is not a word. Either "however" or "albeit" are ok.
Answer: “Howbeit” has been replaced by “Still” (page 3 line 21).

2. Page 5, evidenced based research. I performed the same search and identified 322 manuscripts. The authors have missed a few citations, including a RCT of probiotics in AS patients (Jenks, 2010) and other studies of probiotics in RA patients.
Answer: In our database search, we only identified 122 manuscripts. We appreciate you thorough search and have now cited the extra RCT’s on probiotics (page 4, line 28-37).

3. Page 10. The investigators list the screening tests for the potential donors. They should also pre-define the acceptable ranges, e.g. for albumin, WBC, etc.
Answer: We have now pre-defined the acceptable ranges (page 9, line 15-18).

4. Are rheumatologists performing the PASI?
Answer: Yes, rheumatologists perform the PASI. They have had a one-hour brush-up training session in PASI supervised by a dermatologist within a month before the study commenced. However, we acknowledge that no firm conclusions on FMT treatment effects on psoriatic skin involvement can be drawn from this study.

5. There is very little information on the microbiota analysis. The investigators state that they will measure fecal bacteria composition and metabolism (page 12, line 34). How will metabolism be measured? Fecal water metabolomics? Imputed from PICRUST? Will the composition be measured with 16S or shotgun sequencing? Also, how will "changes" in fecal microbiota composition be assessed?

Answer: We have written two extra paragraphs on this crucial topic in the “Methods and analysis” section (page 10 line 34 to page 11 line 6) and in the “Statistical methods” section (page 16 line 20-30).

6. Why are the investigators only measuring changes in enthesitis, dactylitis, and psoriasis among those who have it at baseline? In so doing, they will miss subjects who develop it de novo.
Answer: We measure enthesitis, dactylitis and psoriasis in all patients at every clinical visit, however, changes (de novo development) in patients not having activity in these domains at baseline will be reported separately as potential side effects.

7. Table 1 -- which intestinal permeability test will they do?
Answer: A lactulose/mannitol sugar test will be performed. We have written an extra paragraph regarding the intestinal permeability test procedure (page 11 line 8-14).

Reviewer: 3

Dear Maxime Breban

Thank you for your insightful and relevant comments.

A. This is a very straightforward protocol, that is well presented and very complete. It would be important to describe the type of microbiota analyses that will be performed on the collected samples.
Answer: We have written two extra paragraphs on this crucial topic in the “Methods and analysis” section (page 10 line 34 to page 11 line 6) and in the “Statistical methods” section (page 16 line 20-30).

B. It would also be interesting to explain what the sigmoidoscopy will be used for, and to justify this procedure that will be repeated, since it is a rather heavy procedure.
Answer: In Denmark, the risk of a sigmoidoscopy and the associated biopsy procedure is considered low, and due to our close academic collaboration with the Dept. of Gastroenterology, the costs are limited. As the intestinal permeability test evaluates potential functional abnormalities of the small intestine, we found it relevant to assess whether gut pathology could be present at the more distal parts of the gastrointestinal tract. The biopsies will be examined for presence of inflammation.

Reviewer: 4

Dear Jose Scher

Thank you for your insightful and relevant comments.

1. As pointed out by the authors, there are only a handful of studies in the literature that characterize a gut dysbiotic process in psoriatic diseases. These, including the one conducted by our group, require validation at local centers so that the overall premise of the study can be supported. Have the authors performed preliminary studies looking at what perturbations (if any) are present in their PsA population? This is vital, since presumably FMT would “restore” a homeostatic gut community.
Answer: We have not performed preliminary studies looking at what perturbations are present in the Danish PsA population. Nevertheless, we assume that changes like the ones previously published in the literature, including patients from the USA, also will be present in our patient population. Our collection of faecal samples will allow us to demine the patients’ gut bacteria composition before the

intervention. This will enable us to exam whether any variance in FMT treatment effect can be due to an unexpected initial "normal" gut microbiota in individual subjects.

2. The inclusion criteria is quite flexible in that it allows for any disease duration and prior use of other medications, including biologic therapy. The concern here is that there are many confounding variables that may significant reduce the interpretation of any potential benefit of the intervention. The authors describe this limitation based on UC literature, but decide to pursue a potentially less significant strategy. If the don't have access to that patient population, could they collaborate with other institutions that do?
Answer: We acknowledge that PsA patients constitutes a very heterogenous group which could limit our overall results. However, this study will be able to evaluate the safety of the FMT procedure in this patient group. Also, if the main disease promotor can be targeted by FMT, this procedure will likely provide positive effects for all PsA patients – regardless of their clinical characteristics. If the study only reveals effects in a subgroup of PsA patients, we hope to be able to identify clinical baseline characteristics associated with the beneficial effects of FMT ("Statistical methods" section; page 16 line 15-17). In future studies, we will be open for collaboration with other departments resided outside of Denmark if more strict study criteria are required.

3. Based on prior data on IBD, one FMT infusion appears to be insufficient. The three randomized trials differed of FMT efficacy in UC utilized several more infusions (one infusion every week for 6 weeks; or two infusions 3 weeks apart; or one FMT followed by enemas 5 days per week for 8 weeks). If this was the approach for the treatment of "local" autoimmunity, it follows that a therapeutic approach for systemic autoimmunity would at the very least be equal to the ones used for UC. The authors suggest that that will not be the case in PsA, but do not present any evidence to that end. Rather, they conclude that "we strongly believe that the FMT procedure in the present study will be sufficient to boost the effects of MTX". This is an intriguing hypothesis but not in line with their overall premise. Is there any preliminary data that suggest microbiota boosting MTX response? And if so, how would that occur with sq MTX use?
Answer: We acknowledge that our statement is unclear. By "MTX boosting" we suggest that the hypothesised anti-inflammatory effect of the FMT procedure will assist the anti-inflammatory effects of MTX and thereby provide a sufficient clinical MTX response in a population of MTX-nonresponders. In the" Discussion" section, we have rephrased our statement: "We hope that the FMT procedure in the present study will be sufficient to boost the effects of MTX" (page 19 line 28).

4. Sample size and power considerations appear overly optimistic. The assumption that twice as many PsA subjects in the sham group will be treatment failures is not based on any available evidence. A more realistic outcome is advised.
Answer: We acknowledge that our assumption that twice as many PsA subjects in the sham group will be treatment failures is optimistic. However, when designing the study, we believed that if rheumatic patients would be willing to receive FMT as a future standardised treatment, the procedure should at least provide a moderate effect. Our total sample size of 80 assuming a balanced design has a power of 0.819 to detect a standardised mean difference of 0.65 (i.e. Cohen's effect size). We have added these considerations in the "Sample size and power considerations section" (page 13 line 32-37) and in the "Discussion section" (page 19 line 40 to page 20 line 2).

5. Donor selection is a challenge. Suggest they limit donors to no more than 4 (one oer 10 recipients) in an attempt to avoid errors in prior studies.
Answer: We have limited the number of donors to 4.

6. The investigators claim that "extensive bacteria taxonomic and metagenomic analyses will be performed on fecal samples before and after the FMT to get an indication of the functional capacity of

the intestinal microbiota". However, no description on who and how this will be performed is lacking. Presumably, this will be performed by Dr. Kristiansen. Please, expand on this crucial aspect.
Answer: We have written two extra paragraphs on this crucial topic in the "Methods and analysis" section (page 10 line 34 to page 11 line 6) and in the "Statistical methods" section (page 16 line 20-30).

Reviewer: 5

Dear Sameer Parpia

Thank you for your insightful and relevant comments.

1. The authors state the lack of data for the intervention (its efficacy, feasibility etc), but much of the trial is designed as a phase III trial (even though they state its a proof of concept trial). A strong justification is needed for the proposed design over a feasibility/pilot design given the lack of data for the intervention in this setting:
Answer: We acknowledge that our study is not designed as a simple feasibility study, rather, the study could be considered a phase II clinical study primarily aiming to evaluate short-term side effects and exploring whether FMT could have any disease modifying effects in PsA patients. Establishing a new FMT centre that fulfils the requirements laid down in the Danish Tissue Law is, of course, time consuming, but the practicability of this setup has been proven in other hospital settings worldwide. Secondly, when we designed the study, our patient partners found the intervention acceptable and they did not foresee recruitment problems due to the FMT procedure. Also, from early on both the Danish authorities and investors have supported the study without asking for preliminary feasibility data. Consequently, as the FMT procedure is now well-established at our primary study site (Odense) and the intervention has been well-tolerated by the first 13 PsA patients, we think that including another 67 patients is very feasible and will reveal more in-depth results compared to a smaller scale study. The lack of feasibility data prior to this RCT trial is now stressed in the "Strengths and limitations" section (page 2 line 34-35).

2. The authors mention the limited data on the intervention, however, power the trial at 90% to detect a decrease in treatment failure from 70% to 35% - given that there is no data available, it is unclear how the authors have justified this treatment effect. In addition, the implication of not observing the hypothesized treatment effect is not discussed, for example, a reduction of 20%?
Answer: We have added our considerations regarding the expected treatment effect in the "Sample size and power considerations" section (page 13 line 32-37) and in the "Discussion" section (page 19 line 38 to page 20 line 2).

3. In the discussion, it is pointed out that feasibility data for FMTs in this setting are not available. However, no feasibility outcomes have been proposed. Please clarify?
Answer: We have no predefined feasibility outcomes. However, following the FMT procedure, we do ask our patients about whether they would say "yes" to another FMT intervention – to clarify whether the procedure could be accepted as a future treatment in this population.

4. Authors propose 11 secondary outcomes with no adjustment for multiple testing - the overall type I error will be inflated using this approach. An approach of estimation of treatment effect and its corresponding variance would be more suitable.
Answer: We have decided not to adjust for multiple testing for the secondary outcomes, however, our final conclusions when interpreting these results, will take the multiple testing into account. Future studies will be needed to confirm our results. This is now stated in the "Statistical methods" section (page 16 line 8-10).

5. Missing data for the primary outcome will be treated as treatment failure. Assuming 20% attrition as stated, 9/40 (23%) per group will be considered treatment failures. This seems as a very conservative approach as the expected treatment failures by groups are 35% and 70%.
Answer: Our strategy for intention-to-treat (ITT) analysis with incomplete observations is now described in more details in the “Statistical methods” section (page 15 line 21-28).

6. Multiple imputation is the standard for all missing data. Consider making MI analysis the primary analysis.
Answer: MI analysis will be performed as a sensitivity analysis (if we can assume “Missing at Random”) to assess the robustness of the primary analyses (page 15 line 29-38).

7. Page 14 Line 11 - "Categorical changes for dichotomous outcomes" - please clarify?
Answer: “Categorical changes” has now been corrected to “categorical data” (e.g. ACR20) (page 15 line 39).

8. How will difference in simple proportions (e.g achieving PsARC) between groups be analyzed or summarized?
Answer: Categorical data for dichotomous end points will be analysed with the use of logistic regression with the model including treatment and centre as class effects. “Statistical methods” section (page 15 line 39-40).

Reviewer: 6

Dear Lynda Cochrane

Thank you for your insightful and relevant comments.

A. Please could the authors provide evidence for the assumptions of 35% and 70% treatment failures for the FMT-active / -sham groups?
Answer: We have no evidence for our assumption of 35% and 70% treatment failures for the FMT-active / -sham groups. We acknowledge that our assumption that twice as many PsA patients in the sham group will be treatment failure is optimistic, however, when designing the study, we believed that if rheumatic patients would be willing to receive FMT as a future standardised treatment, the procedure should at least provide a moderate effect. Our total sample size of 80 assuming a balanced design has a power of 0.819 to detect a standardised mean difference of 0.65 (i.e. Cohen's effect size). We have added our considerations regarding the expected treatment effect in the “Sample size and power considerations” section (page 13 line 32-37) and in the “Discussion” section (page 19 line 38 to page 20 line 2).

B. Although this is a proof-of-concept trial, it would be interesting to have a comparison of FMT-active / -sham groups at baseline.
Answer: Randomised trials aim to compare groups of participants that differ only with respect to the intervention (treatment). Although proper random assignment prevents selection bias, it does not guarantee that the groups are equivalent at baseline. Any differences in baseline characteristics are, however, the result of chance rather than bias. Still, we will explore whether our randomisation seems to have succeeded in providing comparable patient characteristics in the two groups. This is now clearly stated in the “Statistical method” section (page 15 line 14-20).

VERSION 2 – REVIEW

REVIEWER	Laura Coates University of Oxford, UK
REVIEW RETURNED	20-Dec-2017

GENERAL COMMENTS	No further comments

REVIEWER	Matthew Stoll University of Alabama at Birmingham USA
REVIEW RETURNED	21-Dec-2017

GENERAL COMMENTS	The authors have addressed all the reviewer comments. Best of luck with the study.

REVIEWER	Sameer Parpia McMaster University, Canada
REVIEW RETURNED	17-Jan-2018

GENERAL COMMENTS	The authors have addressed my concerns adequately.

VERSION 2 – AUTHOR RESPONSE

Dear Editor,

Thank you for an inspiring and insightful review process.

The only change made to the previous submitted manuscript is that the funding statement has been updated (page 21).

The updated manuscript (version 04) has been uploaded.

In addition, attached you will find the English translation of our patient consent form. The Danish version is approved by the health research ethics committee system in Denmark. The patient and the trial investigator sign the consent form before patient inclusion.

Sincerely,

Torkell Ellingsen and Maja Skov Kragsnæs