PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a randomized, placebo-controlled pilot study for assessing feasibility and efficacy of fecal microbiota transplantation in a pediatric ulcerative colitis population: PediFETCh Trial
AUTHORS	Pai, Nikhil; Popov, Jelena

VERSION 1 - REVIEW

REVIEWER	Richard Kellermayer Section of Pediatric Gastroenterology, Baylor College of Medicine, Houston, TX, USA
REVIEW RETURNED	24-Mar-2017

GENERAL COMMENTS	I applaud the authors for initiating this trial!A generally well written protocol, but some major and minor changes should be considered for the manuscript. In sequence of the paper: 3-13: The control preparation of normal saline should be spelled out in the abstract. Additionally the Phase Ib, single blinded placebo controlled nature of the trial should also be spelled out. 3-29: The additional limitation of normal saline as technically (patients cannot blinded with NS compared to stool) and physiologically (auto-transplant is arguably a much better physiologic control/placebo) questionable control should be highlighted. 4-5: Significant underestimation of UC in North America. Recent epidemiology estimated 3.1 million IBD patients just in the US, close to 50% of whom had UC diagnosis in medical record. 4-8: “profound” growth impairment seems to be an overstatement for pediatric UC, without any reference to support it. 4-20: FMT is a consensus abbreviation for Fecal Microbiota Transplantation, not “fecal microbial transplant”. This should be corrected and from here on only the abbreviation of FMT used throughout the manuscript. The authors randomly switch between FMT and spelling out the abbreviation throughout the paper. 4-37: Of note, patient of reference 14 had colectomy within 1 year after the publication of the case (personal communication with authors). Also discuss: Failure of Fecal Microbiota Transplantation in a Three-Year-Old Child with Severe Refractory Ulcerative Colitis. Kumagai H, Yokoyama K, Imagawa T, Inoue S, Tulyeu J, Tanaka M, Yamagata T. Pediatr Gastroenterol Hepatol Nutr. 2016 Sep;19(3):214-220. 4-49: Incorrect statement: Patients in reference 11 received standardized anonymous donor stool preparations, and more FMT than planned in the protocol of this paper. 4-57: An overstatement, where reference 20 gave a p=0.04 with inappropriate placebo (water enema cannot be blinded compared to stool), whereas: Rossen NG, Fuentes S, van der Spek MJ, Tijssen

	JG, Hartman JH, Duflou A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings from a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology. 2015 Jul;149(1):110-118 had negative results with auto-transplantation as control. 5-4: Has the 1y disease duration observation been confirmed in independent trials? If not, then this conclusion should not be made. 5-43: Please provide estimate of pediatric UC cases in Canada with age limit for "pediatric" clearly stated. Table 1: Is there any evidence for the utility of MRE in assessing colonic mucosal healing? If yes, please give references in corresponding text. 6-52: Use of CRP as eligibility criteria is unusual in UC. Please give reference where this has been observed to be feasible in pediatric UC trials. 7-6: Age limits for eligibility should be clearly stated (i.e. maximum age). FDA/NIH uses 16y for drug trials. Show age criteria in Figure 1 as well. 8-12: Define "preserved cold-chain delivery". Enema product: volume and expected/required retention time not provided. This is very important in pediatric patients since capacity for enema retention is age dependent. 8-46: Rationale for MRE and reliability of the imaging modality in respect to mucosal healing should be clearly stated and supported with references. 8-56: Why Chi-square and not Fischer exact test? 9-6: Inaccurate statement: Significant worsening/flare of UC has been noted after FMT 9-17: By what method is VRE and MRSA screened?

REVIEWER	Patrizia K. Kump Div of Gastroenterology and Hepatology Dep of Internal Medicine Medical University Graz Austria
REVIEW RETURNED	05-Apr-2017

GENERAL COMMENTS	Pai N and Popov J present a protocol for a randomized, placebo controlled pilot study for assessing feasibility and efficacy of fecal microbiota transplantation (FMT) in a pediatric ulcerative colitis (UC) population: PediFetCh Trial. Methods follow a prior protocol of FMT, which had been successfully performed in adult UC patients. Major comments: 1. Eligibility criteria include "signs of disease activity" defined as a PUCAI score $\geq$ 10. As a PUCAI score of $\leq$ 10 already defines clinical remission, PUCAI score values for clinical activity have to be clearly separated from remission criteria. Following prior studies of pediatric UC and FMT (Kunde s. et al in 2013) or anti-TNF antibody therapy (Volonaki E et al. 2015), PUCAI score for clinical activity should be at least 15.

	2. The enema product of the placebo group contains polyethylene glycol (PEG) preservative and saline. PEG has a laxative effect and applied twice weekly might increase PUCAI score. To ensure equal conditions in the placebo group, the same amount of PEG should also be used preparing the product of the FMT group. Minor comments: 1. In the rational section the authors refer to a 67-100% clinical response. In fact the cited paper of Kellermayer et al. demonstrated the prolongation of a symptom free interval due to FMT in patients after withdrawal of immunotherapy. These patients presented already with a Mayo score of 0 and 1 respectively even before the first FMT had been performed. 2. The cited case report of Vendaplas Y et al in 2015 deals with serial FMT infusion in a 18month old UC patient but donors were not anonymous as written in the protocol by Pai N and Popov J but age related relatives. 3. Nylund L et al (BMC Microbiology 2013) demonstrated an association of a diverse and adult-type microbiota in early childhood with eczema; this raises the question, if donors for the younger patients should be matched for age to prevent possible side effects.

VERSION 1 – AUTHOR RESPONSE

丿3-13: The control preparation of normal saline should be spelled out in the abstract. Additionally, the Phase Ib, single blinded placebo controlled nature of the trial should also be spelled out.
Response to reviewer's comment:
Addressed.

丿4-5: Significant underestimation of UC in North America. Recent epidemiology estimated 3.1 million IBD patients just in the US, close to 50% of whom had UC diagnosis in medical record.
Response to reviewer's comment:
Addressed.

丿4-8: "profound" growth impairment seems to be an overstatement for pediatric UC, without any reference to support it.
Response to reviewer's comment:
Addressed: "A diagnosis of ulcerative colitis can be debilitating in childhood. Chronic diseases can have significant impacts on children, and ulcerative colitis may particularly affect childhood growth and development."

Please refer to:
El Mouzan MI, Al Mofarreh MA, Saadah OI, Al-Hussaini AA, Al-Saleem KA, Al Mehaidib AI. Impact of pediatric inflammatory bowel disease on linear gowth: data from a national cohort study in Saudi Arabia. Saudi J Gastroenterol, 2016; 22(2): 106-108
Sanderson IR. Growth problems in children with IBD. Nature Rev Gastroenterol Hepatol, 2014; doi: 10.1038/nrgastro.2014.102

丿4-20: FMT is a consensus abbreviation for Fecal Microbiota Transplantation, not “fecal microbial transplant”. This should be corrected and from here on only the abbreviation of FMT used throughout the manuscript. The authors randomly switch between FMT and spelling out the abbreviation throughout the paper.
Response to reviewer’s comment:
Addressed.

丿5-4: Has the 1y disease duration observation been confirmed in independent trials? If not, then this conclusion should not be made.
Response to reviewer’s comment:
Please refer to Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in Patients with Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology. 2015;149(1):102-109.e6.

丿5-43: Please provide estimate of pediatric UC cases in Canada with age limit for “pediatric” clearly stated.
Response to reviewer’s comment:
For Canadian UC prevalence, please refer to:
Rocchi A, Benchimol EI, Bernstein CN, Bitton A, Feagan B, Panaccione R, Glasgow KW, Fernandes A, Ghosh S. Inflammatory bowel disease: A Canadian burden of illness review. Can J Gastroenterol, 2012; 26(11):811-817
While extrapolations of incidence data from literature as recent as April, 2017 may be possible, the authors were unable to identify an accurate, recent Canadian pediatric UC prevalence estimate.

丿7-6: Age limits for eligibility should be clearly stated (i.e. maximum age). FDA/NIH uses 16y for drug trials. Show age criteria in Figure 1 as well.
Response to reviewer’s comment:
Addressed. 3-17yo.

丿8-12: Define “preserved cold-chain delivery”.
Response to reviewer’s comment:
Addressed: “Specifically, the samples are stored in -80°C freezers at Rebiotix®, Minnesota, with next-day, on-site delivery in styrofoam-insulated boxes containing ice packs. Frozen enemas are removed from the boxes and stored in the clinic fridge (4oC) for up to 3 days.”

丿Enema product: volume and expected/required retention time not provided. This is very important in pediatric patients since capacity for enema retention is age dependent.
Response to reviewer’s comment:
This was removed from the text as it could not be accurately controlled through the trial, due to varying ages, disease activity, and tolerance for the enema procedure. Standardizing retention times was not practical.

丿3-29: The additional limitation of normal saline as technically (patients cannot blinded with NS compared to stool) and physiologically (auto-transplant is arguably a much better physiologic control/placebo) questionable control should be highlighted.

Response to reviewer's comment:
The authors respectfully disagree with this comment.
The existing literature on fecal transplant trials has not established that autologous transplants are a better study control than normal saline enemas.
(1) Physiologically, normal saline enemas are inert and less likely to confer impact on the host. Autologous enemas may confer a unique therapeutic potential. This has been highlighted in rCDI studies where autologous transplants were used as a control, and patients experienced significant response rates (62.5% of autologous FMT group experienced clinical cure for CDI vs. 90.9% with heterologous FMT; Kelly CR, Khoruts A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent Clostridium difficile infection. Ann Intern Med 2016;165:609–16).
(2) The normal saline enema is also not technically inferior to the intervention enema. Patients who received the control enema do not have a reference for the consistency or odour of the intervention enema. The control enema is given a brown color. When the control enema is excreted after the procedure, it is excreted along with the patients' recto-sigmoid fecal contents, conferring an odor and sediment. Finally, from our experience with patients in our trial, they would frequently incorrectly guess their treatment arm proving that the integrity of the placebo was retained.

丿4-37: Of note, patient of reference 14 had colectomy within 1 year after the publication of the case (personal communication with authors). Also discuss: Failure of Fecal Microbiota Transplantation in a Three-Year-Old Child with Severe Refractory Ulcerative Colitis. Kumagai H, Yokoyama K, Imagawa T, Inoue S, Tulyeu J, Tanaka M, Yamagata T. Pediatr Gastroenterol Hepatol Nutr. 2016 Sep;19(3):214-220.
Response to reviewer's comment:
Given that this outcome was not reported, we will not be able to include this communication without citation. Thank you for drawing our attention to this 2016 Sep case report. We have discussed this in the revised version of our manuscript.

丿4-49: Incorrect statement: Patients in reference 11 received standardized anonymous donor stool preparations, and more FMT than planned in the protocol of this paper.
Response to reviewer's comment:
"Protocols and response rates varied across each study, but lower gastrointestinal tract administration yielded clinical response rates in 67-100% of patients10,11."
Please review the language used. The range of clinical responses was provided (67-100%), and stated as being based on varying protocols.

丿4-57: An overstatement, where reference 20 gave a p=0.04 with inappropriate placebo (water enema cannot be blinded compared to stool), whereas: Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings from a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology. 2015 Jul;149(1):110-118 had negative results with auto-transplantation as control.
Response to reviewer's comment:
As stated in response to the reviewer's previous comment, normal saline enemas are not physiologically nor technically inferior to autologous enemas. These two RCTs had differences in their study designs that extended well beyond their choice of placebo control, alone. For reference, these differences have been clearly described in the commentary that accompanied the publication of these two articles in the same issue of Gastroenterology where Moayyedi et al, and Rossen et al's RCTs were published.
Grinspan AM, Kelly CR. Fecal Microbiota Transplantation for Ulcerative Colitis: Not Just Yet. Gastroenterology. 2015;149(1):15-8.)

丿Table 1: Is there any evidence for the utility of MRE in assessing colonic mucosal healing? If yes,

please give references in corresponding text.
Response to reviewer's comment:
Use of the MRE has been removed from the protocol. This was originally described as an optional step in the protocol at the clinicians' discretion. No patients enrolled in the study thus far have actually had an actual end-of-study MRE performed, and the authors agree with the reviewers' comment that MRE findings have not been clearly established in the evaluation of (unprepped) colonic disease. .

丿8-46: Rationale for MRE and reliability of the imaging modality in respect to mucosal healing should be clearly stated and supported with references.
Response to reviewer's comment:
Removed.

丿6-52: Use of CRP as eligibility criteria is unusual in UC. Please reference where this has been observed to be feasible in pediatric UC trials.
Response to reviewer's comment:
Please refer to:
Turner D, Mack DR, Hyams J, LeLeiko N, Otley A, Markowitz J, Kasirer Y, Muise A, Seow CH, Silverberg MS, Crandall W, Griffiths AM. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? A systematic evaluation in pediatric ulcerative colitis. Journal of Crohn's and Colitis, 2011; 5(5):423-429
Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012;55(3):340-61

丿8-56: Why Chi-square and not Fischer exact test?
Response to reviewer's comment:
Statistical analysis was informed through the expertise of a clinical statistician affiliated with our research team. As recommended by our statistician, Fischer exact test has statistical superiority for smaller sample sizes (n<20), but as our sample size will exceed this (n=50), we were recommended to use Chi-square.

丿9-6: Inaccurate statement: Significant worsening/flare of UC has been noted after FMT
Response to reviewer's comment:
Addressed.

丿9-17: By what method is VRE and MRSA screened?
Response to reviewer's comment:
VRE is tested by enzyme immunoassay, and MRSA is screened by assessing growth on oxacillin-salt screening agar. We did not chose to state this in the protocol, as 19 other pathogens were listed in the same section and all were analyzed using standardized screens.

Major comments:
1. Eligibility criteria include "signs of disease activity" defined as a PUCAI score > 10. As a PUCAI score of < 10 already defines clinical remission, PUCAI score values for clinical activity have to be clearly separated from remission criteria. Following prior studies of pediatric UC and FMT (Kunde s. et al in 2013) or anti-TNF antibody therapy (Volonaki E et al. 2015), PUCAI score for clinical activity should be at least 15.
Modified the eligibility criteria to PUCAI ≥15. Although Volonaki never specifically set a number for activity in his/her protocol, PUCAI 15 coincided with the lowest PUCAI score of all patients at time of enrollment.

2. The enema product of the placebo group contains polyethylene glycol (PEG) preservative and saline. PEG has a laxative effect and applied twice weekly might increase PUCAI score. To ensure

equal conditions in the placebo group, the same amount of PEG should also be used preparing the product of the FMT group.
The protocol was modified to explain in greater detail the contents of the placebo, which do in fact include equal amounts of PEG.
“25 patients will be randomized to receive normal saline enemas (control; saline/polyethylene glycol 3350) and 25 patients to receive a FMT enema (intervention; 50g/150ml, 107 microbes/mL of suspension in saline/polyethylene glycol 3350)”.

Minor comments:
1. In the rationale section the authors refer to a 67-100% clinical response. In fact the cited paper of Kellermayer et al. demonstrated the prolongation of a symptom free interval due to FMT in patients after withdrawal of immunotherapy. These patients presented already with a Mayo score of 0 and 1 respectively even before the first FMT had been performed.
“Protocols and response rates varied across each study, but lower gastrointestinal tract administration yielded clinical response rates in 67-100% of patients10,11.”
We do not agree with this being an inaccurate statement. In comparison to the other study mentioned in the same sentence used only 5 enemas. The response range was cleared stated (67-100%), based on varying protocols.

2. The cited case report of Vendaplas Y et al in 2015 deals with serial FMT infusion in a 18month old UC patient but donors were not anonymous as written in the protocol by Pai N and Popov J but age related relatives.
This comment has been corrected, to clarify that donors were an age-matched niece and older brother donors.

3. Nylund L et al (BMC Microbiology 2013) demonstrated an association of a diverse and adult-type microbiota in early childhood with eczema; this raises the question, if donors for the younger patients should be matched for age to prevent possible side effects.
Several publications have now described age-specific differences in microbial composition, including differences in core microbial genera that vary beyond age 5yo to early adolescence. This literature would posit that age-matched microbiota should be prioritized for not only younger patients, but several broad age groups of childhood. While the authors agree that age-matched donors would be ideal, this was simply impractical through any private or public stool bank for our study. This would be a desirable future direction.

VERSION 2 – REVIEW

REVIEWER	Richard Kellermayer BCM, USA
REVIEW RETURNED	28-May-2017

GENERAL COMMENTS	The authors did a great job with incorporating the recommendations. In the meantime, a few corrections would still be highly feasible to improve the quality of the final work. 1. Correction to Ref 19 description in text is recommended: The authors of the reference concluded that mild and not “severe” UC as stated in the current text, may be more amenable to FMT: “Therefore, any pediatric patient with UC who has achieved remission through conventional medical therapy, or who has mild disease, might be a better candidate for FMT.”. Please correct “severe” to mild. 2. I would like to repeatedly emphasize that “previous fecal transplant trials have also used protocols that delivered transplants

	infrequently", and "No pediatric study has ever measured response after FMT from an anonymous donor." statements are incorrect. Ref 14 used frozen-thawed preparations from standardized "anonymous" donors, and delivered more treatments that the ongoing study in question. Therefore, please correct the text accordingly. 3. I would like to repeatedly emphasize that unless the duration of disease affecting FMT outcomes in UC has been validated in an independent study from reference 20, the statement "there are differences in response between patients with duration of disease ≤1 year versus >1 year20." should modified in order to highlight that this is a possibility, which has not been validated, therefore not a given fact. 4. The significant limitation of the employed enema treatment in the pediatric population should be described, since it is "retention" and "large volume" (250-500ml) FMT enemas, which have been shown to provide success in rCDI. Less than 10 year old patients are highly unlikely to be able to achieve retention of large volume FMT, which will probably result in significant age dependent technical variation. 5. I sincerely disagree about the inert nature of NS enema in the background of UC (see Steinhart AH, et al.: Treatment of left-sided… where 47% of patients had therapeutic response to saline). The argument of the Kelly et al. rCDI trial is weak, since the results of that were VERY significantly affected by center bias (i.e. more than likely inappropriate recipient selection or massive placebo effect at one of the recruiting sites). I strongly recommend a lengthy discussion about the pro/con of NS vs. autotransplant. It is within this discussion that Paramsothy, et al. Lancet. 2017 Mar 25;389(10075):1218-1228 should be conversed (where odorant was also added to the NS placebo). Additionally, the paper should be adjusted to incorporate this new reference/trial in the introduction as well. I understand that it appeared in press after the submission of this manuscript, but ongoing revisions of yet unaccepted manuscripts should incorporate the accumulating knowledge up to their acceptance.

REVIEWER	Patrizia Kump Division of Gastroenterology and Hepatology Department of Internal Medicine Medical University of Graz Austria
REVIEW RETURNED	30-May-2017

GENERAL COMMENTS	Congratulations on a comprehensive and high-quality protocol, which has been greatly improved by the revision. You are adressing a very important question as the demand for fecal microbiota transplantation not only in adult but also in pediatric ulcerative colitis is increasing.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Richard Kellermayer
Institution and Country: BCM, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The authors did a great job with incorporating the recommendations. In the meantime, a few corrections would still be highly feasible to improve the quality of the final work.
1. Correction to Ref 19 description in text is recommended: The authors of the reference concluded that mild and not "severe" UC as stated in the current text, may be more amenable to FMT: "Therefore, any pediatric patient with UC who has achieved remission through conventional medical therapy, or who has mild disease, might be a better candidate for FMT.". Please correct "severe" to mild.
Response: This has been addressed.

2. I would like to repeatedly emphasize that "previous fecal transplant trials have also used protocols that delivered transplants infrequently", and "No pediatric study has ever measured response after FMT from an anonymous donor." statements are incorrect. Ref 14 used frozen-thawed preparations from standardized "anonymous" donors, and delivered more treatments that the ongoing study in question. Therefore, please correct the text accordingly.
Response: This has been addressed.

3. I would like to repeatedly emphasize that unless the duration of disease affecting FMT outcomes in UC has been validated in an independent study from reference 20, the statement "there are differences in response between patients with duration of disease ≤1 year versus >1 year 20." should modified in order to highlight that this is a possibility, which has not been validated, therefore not a given fact.
Response: This has been addressed. Changed to "there may be differences in response between patients with duration of disease ≤1 year versus >1 year".

4. The significant limitation of the employed enema treatment in the pediatric population should be described, since it is "retention" and "large volume" (250-500ml) FMT enemas, which have been shown to provide success in rCDI. Less than 10 year old patients are highly unlikely to be able to achieve retention of large volume FMT, which will probably result in significant age dependent technical variation.
Response: In the authors' experience with our 150mL FMT enema (not 250-500mL), the enema actually has been retained for >1hr on average (with the vast majority of patients reporting they did not stool until "several hours" after the FMT). While the concerns are certainly acknowledged about inadequate retention times, our observations across ~200 enemas have not demonstrated that retention time is limited. This was even noted in our youngest patients (two male patients, age 3, and age 5) who most often retained their enemas for several hours over their 12 treatments.

5. I sincerely disagree about the inert nature of NS enema in the background of UC (see Steinhart AH, et al.: Treatment of left-sided… where 47% of patients had therapeutic response to saline). The argument of the Kelly et al. rCDI trial is weak, since the results of that were VERY significantly affected by center bias (i.e. more than likely inappropriate recipient selection or massive placebo effect at one of the recruiting sites).
I strongly recommend a lengthy discussion about the pro/con of NS vs. autotransplant. It is within this discussion that Paramsothy, et al. Lancet. 2017 Mar 25;389(10075):1218-1228 should be conversed (where odorant was also added to the NS placebo). Additionally, the paper should be adjusted to incorporate this new reference/trial in the introduction as well. I understand that it appeared in press

after the submission of this manuscript, but ongoing revisions of yet unaccepted manuscripts should incorporate the accumulating knowledge up to their acceptance.
Response: The authors thank the reviewer for noting the Paramsothy et al paper. We will incorporate a reference to this study in our discussion, given the paucity of published FMT IBD RCTs.
Given the debate over the choice of autologous versus normal saline as a control, we will state the following in our limitations section: “The strengths and limitations of normal saline versus autologous stool as placebo are unclear, with previous investigators having used both in studies of FMT for recurrent Clostridium difficile colitis, and FMT for the treatment of inflammatory bowel disease.”
However, the authors will respectfully refrain from making any further statements about the superiority of NS versus autologous enema therapy as a non-physiology placebo control. There continues to be little evidence that NS enemas have limitations. We respectfully offer the following responses to our reviewer’s feedback to our earlier comments:
- The authors note that the Paramsothy et al paper showed a 27% vs. 8% response of FMT vs. NS placebo. An 8% normal placebo response is ostensibly low, as could be expected for an inert treatment.
- The Steinhart et al study does not demonstrate flaws of normal saline enema placebo therapy:
o methodologically, the sample size of this study was small.
o ascribing the study’s failure to show difference between the placebo and the butyrate enema to an exaggerated placebo response is a presumption of the therapeutic value of SCFA enemas. The few studies that have been performed on SCFA enema therapy for IBD have also not shown significant benefit.
o High placebo response rates have always been seen in IBD studies, including in large, well-designed pharmacologic IBD RCTs. As just one example, ACT 1, assessing IFX 5mg/kg vs. IFX 10mg/kg vs. placebo showed a staggering 37% placebo response rate. This likely reflects the cyclic nature of this disease more than true therapeutic benefit of the placebo intervention
Further to the Paramsothy et al paper, the authors carefully reviewed the methodology of the investigators. We do not endorse the need for odorant to be added to the normal saline enema. Again, from our methodology, the FMT and NS enemas are odorless upon administration to the patient (odor is concealed by the airtight bag and tubing). Upon instillation, and presumed defecation by the patient at a later time, the odor of fecal contents is provided by the patient regardless of what they were administered. Further, details of the “odorant” added to the normal saline enema was not described by Paramsothy et al. The authors could only speculate how this odorant would be captured in a reproducible study design.

We sincerely thank the editors and reviewers for their invaluable input and support in the development of this manuscript.

VERSION 3 – REVIEW

REVIEWER	Richard Kellermayer Baylor College of Medicine, USA
REVIEW RETURNED	29-Jun-2017

GENERAL COMMENTS	My concerns have adequately been addressed.