PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	PROTOCOL FOR A PILOT RANDOMISED CONTROLLED TRIAL OF MINDFULNESS BASED COGNITIVE THERAPY IN YOUTH WITH INFLAMMATORY BOWEL DISEASE AND DEPRESSION
AUTHORS	Ewais, Tatjana; Begun, Jake; Kenny, Maura; Chuang, Kai-Hsiang; Barclay, Johanna; Hay, Karen; Kisely, Steve

VERSION 1 - REVIEW

REVIEWER	Micol Artom King's College London, United Kingdom
REVIEW RETURNED	01-Aug-2018

GENERAL COMMENTS	- Introduction, page 4, line 19: specify which condition the meta-analysis was conducted in. Add page number after sentence in "". - If this is a pilot study, the feasibility outcomes should come first. - Methods, Page 5, line 46: specify which type of clinical interview will be conducted to determine a diagnosis of depression and who will conduct the interview. - Inclusion criteria: please specify whether you will include or exclude people with a diagnosis of IBD unclassified - Exclusion criteria: please specify what is meant by extremely severe levels of depression and how this will be assessed - If IBD patients in a flare will be excluded, are you only recruiting patients in remission? How will you measure that? - Due to the pilot nature of the study, the authors should conduct both intention to treat and per protocol analysis - Please double check issues with spacing throughout manuscript - The extensive number of questionnaires, the multiple follow-up times and procedures may make the study quite burdensome to participate in. Consider using questionnaires in electronic format and putting reminders in place. Also should consider allowing for higher drop out rates and longer recruitment times.

REVIEWER	Linda Cillessen Radboudumc Center for Mindfulness Nijmegen, the Netherlands
REVIEW RETURNED	06-Aug-2018

GENERAL COMMENTS	Comments for the authors: This protocol describes a pilot RCT of mindfulness-based cognitive therapy in adolescents and young adults with

	inflammatory bowel disease and depression. This pilot aims to recruit 64 participants. The primary outcome is depressive symptoms. A large number of secondary outcomes, including psychological measures, inflammatory measures and neuro-imaging measures are also included. Findings will inform about feasibility and efficacy of MBCT for this patient group. The protocol has several strengths. The authors are, to my best knowledge, the first to study a mindfulness-based intervention in youth with IBD and depression in a RCT. The study design presented in the protocol is clear and thorough. The authors have a large number of outcome measures that include, besides psychological measures, also inflammatory measures and neuro-imaging measures. There are some points that need to be addressed to further improve this manuscript. My suggestions for improvement are stated below. 1. The authors describe (various places in manuscript) that both feasibility and efficacy will be studied. However, the feasibility part is quite minor (including attendance and homework adherence) compared to the efficacy part. Details regarding the ease or difficulty with inclusion might be also important to learn more about feasibility. Furthermore, qualitative interviews could also provide a lot of information about feasibility, although it might be difficult to implement interviews, as inclusion of participants has already started. In case it is still possible to add more measures for feasibility, I would suggest to include them, to learn more about feasibility, especially in this young participant group. 2. The abstract does not describe the data analysis. I would suggest to add a sentence containing that information in the abstract, to be more thorough. 3. The introduction starts with a paragraph about IBD and depression in youth. I think it would be interesting to include the absolute percentage of IBD youth that suffer from depression, which is currently not described. 4. The definition of mindfulness (top page 3) does not include a reference to Kabat-Zinn. I would suggest to include this citation. Secondly, it is stated that mindfulness is a meditative practice. This description seems to refer more to the formal mindfulness exercises, that are indeed meditative practice, however, mindfulness is more, namely a particular state of attention that can arise outside meditative practice as well. I would suggest to improve clarity by rewriting this sentence. 5. The second hypothesis does include ‘medication adherence’ and ‘perceived health care empowerment’. I would suggest to add research findings of the relationship between mindfulness and these constructs in the introduction, to substantiate this hypothesis. 6. The third hypothesis describes the expected neurological changes. I would suggest to be a bit more specific regarding what changes are exactly expected, as the default mode and executive control networks involve many brain regions. 7. The second ‘specific aim’ discusses adapting the intervention and delivery fidelity. I am not sure how exactly adaptation relates to delivery fidelity. Secondly, I am not sure how delivery fidelity is measured, as this I could not find this in the manuscript. I would suggest to add information regarding treatment fidelity in the method section.

	8. In the method section 'Recruitment Strategies' is described that an interview is used to confirm the clinical diagnosis of depression. I am not sure whether a clinical diagnosis of depression (for instance measured with the SCID) always overlaps with a score of at least 10 on the DASS; it possible that some participants have a score of 10 or higher, without having a clinical diagnosis of depression, as the DASS measures severity, and a clinical interview is to determine whether there is a depressive episode or not. Therefore, I am a bit unsure whether the inclusion criteria is 'having a depressive episode' or 'having a severity of at least 10 on the DASS'. Maybe it is possible to rephrase this criteria, or to adjust how it is measured. Secondly, I am unsure what instrument will be used for the clinical interview. I would suggest to include that information. 9. In the method section 'Adapted MBCT Program' is not stated what the length of the program and the duration of the sessions is. I would suggest to include this information, which is useful for authors of future meta-analyses. Secondly, I would like to know what the background of the mindfulness trainer is, and especially, whether he or she is mental health professional. 10. Data is collected before and after the intervention, and at 20 weeks follow-up. In Figure 1, the post-measure and the follow-up measure are not separately described. I would suggest to make separate 'assessment' boxes for post-treatment and follow-up, to be more precise. 11. In the method section, 'Safety Considerations' is mentioned that Kuyken et al. (2016) did not report any adverse events. However, I think that Kuyken did report adverse events, but that is was concluded that these were not related to the treatment. Secondly, it is stated that there are no reports of significant adverse side effects. However, for instance Williams et al. (2014) do report 15 serious adverse events, of which 1 is a serious adverse reaction potentially related to MBCT. I would suggest to adjust the text accordingly. However, I still think the method of monitoring safety is adequate. 12. In the method section 'Outcomes' is stated that remission and recovery rates are calculated. If I understand correctly, that would create a variable with two levels, 'recovered' and 'not recovered'. However, I think you cannot analyze this data with ANCOVA, which is stated in the data-analysis section. Clarity regarding this issue would be useful. Furthermore, a bit more details regarding the analyses would benefit transparency. 13. The manuscript sometimes describes 'youth', and sometimes refers to 'AYA'. I would suggest to be more consistent in terminology, to facilitate clarity for readers. Related to that, it would help a reader to state the outcomes in the same order on all occasions they are discussed.

VERSION 1 – AUTHOR RESPONSE

Reviewer # 1

1) Introduction, page 4, line 19: specify which condition the meta-analysis was conducted in. Add page number after sentence in "".

 We thank the reviewer for bringing this omission to our attention. As requested, we specified the condition, which was the immune system parameters, and added the page number. See page 3, para 3.

2) If this is a pilot study, the feasibility outcomes should come first.

 We changed the order of outcomes to reflect the pilot nature of the study. See page 4, para 1.

3) Methods, Page 5, line 46: specify which type of clinical interview will be conducted to determine a diagnosis of depression and who will conduct the interview.

 As suggested, we specified the nature of the intake interview and who would conduct the interview. The intake interview is an unstructured, diagnostic clinical interview and it will be conducted by the study principal investigator. See page 5, para 2.

4) Inclusion criteria: please specify whether you will include or exclude people with a diagnosis of IBD unclassified. Exclusion criteria: please specify what is meant by extremely severe levels of depression and how this will be assessed. If IBD patients in a flare will be excluded, are you only recruiting patients in remission? How will you measure that?

 As suggested by the reviewer, we amended the inclusion criteria to state that all subtypes of IBD will be included. See page 5, box 1, line 5 (inclusion criteria). We defined the extreme levels of depression and also included a sentence referring to the evidence that MBCT showed larger effect size and further improvement over time in individuals with more severe depressive symptoms at baseline in the introduction and discussion. See page 6, box 2, line 4 (exclusion criteria), page 3, para 4, and page 10, para 3.

With regards to excluding patients who are currently experiencing a flare, this is assessed during the screening process by the gastroenterologist who is one of the trial investigators, on the basis of their clinical presentation. We understand that the concern of the reviewer might be that we are only including patients in remission and therefore won't be able to determine if there is any improvement in IBD after the intervention. However, we are excluding patients with a flare because they are likely to receive changes to their medical treatment which might confound any findings of the effect of the intervention or interfere with their ability to participate (e.g. if they end up hospitalised or undergoing surgery etc). Therefore, we are selecting patients who are on a stable medical regimen for their IBD and who are not expected to change medications over the course of the study.

5) Due to the pilot nature of the study, the authors should conduct both intention to treat and per protocol analysis

 We agree with the reviewer's comment that both intention to treat and per protocol analysis should be conducted due to the pilot nature of the study and have added the per protocol analysis to the methods section. See page 8, para 3.

6) Please double check issues with spacing throughout manuscript.

 We rectified the spacing issues in the manuscript.

7) The extensive number of questionnaires, the multiple follow-up times and procedures may make the study quite burdensome to participate in. Consider using questionnaires in electronic format and putting reminders in place. Also should consider allowing for higher dropout rates and longer recruitment times.

 We thank the reviewer for this valuable feedback. In order to minimise the burden to participants, we are offering the screening questionnaires in electronic format and have a system of email and text reminders sent to the participants by the research assistant. We provide transport and parking

vouchers to facilitate participants' access. We added a sentence referring to this process under the recruitment strategies. See page 5, para 2.

The protocol allows a longer recruitment period by recruiting the participants in groups of 16 in four separate time periods, twice per year, of approximately four to six months duration. See page 5, para 2. We considered the potential for higher dropout rates and have based our predictions on the past two years' experience of running groups in this particular centre which caters specifically for adolescents and young adults and has shown relatively small dropout rates.

Reviewer # 2

The protocol has several strengths. The authors are, to my best knowledge, the first to study a mindfulness-based intervention in youth with IBD and depression in a RCT. The study design presented in the protocol is clear and thorough. The authors have a large number of outcome measures that include, besides psychological measures, also inflammatory measures and neuro-imaging.

1) The authors describe (various places in manuscript) that both feasibility and efficacy will be studied. However, the feasibility part is quite minor (including attendance and homework adherence) compared to the efficacy part. Details regarding the ease or difficulty with inclusion might be also important to learn more about feasibility. Furthermore, qualitative interviews could also provide a lot of information about feasibility, although it might be difficult to implement interviews, as inclusion of participants has already started. In case it is still possible to add more measures for feasibility, I would suggest including them, to learn more about feasibility, especially in this young participant group.

 We thank the reviewer for this valuable feedback. We agree that the details regarding the ease or difficulty with recruitment are important in learning about the feasibility. We are currently recording the reasons for not enrolling those participants who expressed interest but were no recruited due to not meeting some of the inclusion criteria or having one of the exclusion criteria. A sentence referring to this is located in the Methods and Analysis section, under subheading Data Collection and Analysis. "Research assistant will complete a screening and recruitment sheet with details of all patients approached regarding the study, enrolled and excluded at each stage of the recruitment process and reasons for this". See page 8, para 2.

The protocol refers to measuring of the attendance and attrition rates in the Methods and Analysis section, under the subheading Data Collection and Analysis. "MBCT group facilitator will complete weekly attendance sheets to enable the calculation of attendance and attrition rates in the intervention group". See page 8, para 2. In light of the reviewer's comments, we also listed recruitment and attrition rates with the feasibility measures in the hypotheses and aims, and in the Methods and Analysis section. See page 4, para 1 and 3, and page 7, para 4.

We agree with the reviewer that qualitative investigation of young participants' experiences would add valuable information. We will be running focus groups to explore participants' MBCT group experiences. The manuscript has been an amended to include a sentence referring to this in the abstract, hypotheses and aims, and discussion. See page 1, para 2, page 4, para 1 and 3, and page 10, para 6.

2) The abstract does not describe the data analysis. I would suggest adding a sentence containing that information in the abstract, to be more thorough.

 As suggested, a sentence about data analysis has been added to the abstract. See page 1, para 2.

3) The introduction starts with a paragraph about IBD and depression in youth. I think it would be interesting to include the absolute percentage of IBD youth that suffer from depression, which is currently not described.

 As requested, we have included the percentage of youth with IBD suffering from depression. See page 2, para 2.

4) The definition of mindfulness (top page 3) does not include a reference to Kabat-Zinn. I would suggest including this citation. Secondly, it is stated that mindfulness is a meditative practice. This description seems to refer more to the formal mindfulness exercises, that are indeed meditative practice, however, mindfulness is more, namely a particular state of attention that can arise outside meditative practice as well. I would suggest improving clarity by rewriting this sentence.

 As suggested, we amended this sentence and provided the operational definition of mindfulness given by Jon Kabat Zin with the reference to his book. See page 3, para 2.

5) The second hypothesis does include 'medication adherence' and 'perceived health care empowerment'. I would suggest adding research findings of the relationship between mindfulness and these constructs in the introduction, to substantiate this hypothesis.

 The improvements in treatment adherence and health care empowerment result from attenuating depression and anxiety which have been shown to be predictors of treatment non-adherence and have negative effect on health care empowerment. A sentence referring to this mechanism has been added to the introduction. See page 3, para 2.

6) The third hypothesis describes the expected neurological changes. I would suggest to be a bit more specific regarding what changes are exactly expected, as the default mode and executive control networks involve many brain regions.

 We added most commonly affected brain regions to the third hypotheses. See page 2, para 1 (hypothesis 5).

7) The second 'specific aim' discusses adapting the intervention and delivery fidelity. I am not sure how exactly adaptation relates to delivery fidelity. Secondly, I am not sure how delivery fidelity is measured, as this I could not find this in the manuscript. I would suggest to add information regarding treatment fidelity in the method section.

 We thank the reviewer for their comment regarding fidelity and program adaptation. The relationship between the MBCT manual adaptation and treatment fidelity is related to potential impact of the manual adaptations to the fidelity of the intervention (i.e. extensive adaptations can endanger the intervention fidelity). The fidelity is measured by the MBCT supervisor reviewing the video recordings of MBCT sessions and discussing the MBCT delivery in regular supervision sessions. The fidelity monitoring is currently described in the protocol in the Methods and Analysis section, under the subheading Adapted MBCT Program. "Fidelity of the delivered intervention will be appraised by assessing video-recordings of the sessions by the study MBCT supervisor and discussing the adherence to session content and delivery in supervision". See page 7, para 4.

8) In the method section 'Recruitment Strategies' is described that an interview is used to confirm the clinical diagnosis of depression. I am not sure whether a clinical diagnosis of depression (for instance measured with the SCID) always overlaps with a score of at least 10 on the DASS; it possible that some participants have a score of 10 or higher, without having a clinical diagnosis of depression, as the DASS measures severity, and a clinical interview is to determine whether there is a depressive episode or not. Therefore, I am a bit unsure whether the inclusion criteria is 'having a depressive episode' or 'having a severity of at least 10 on the DASS'. Maybe it is possible to rephrase this

criteria, or to adjust how it is measured. Secondly, I am unsure what instrument will be used for the clinical interview. I would suggest to include that information.

 As the reviewer rightly noted, there is a difference between the dimensional assessment offered by the DASS and diagnostic assessment which is categorical in nature. The DASS therefore has no direct implications for the allocations of patients to diagnostic category of depression, and the recommended DASS cut-offs of severity do not always correspond to the diagnostic and severity qualifiers in the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) which is a classificatory categorical system. The DASS is used in this trial as a screening tool prior to the diagnostic assessment interview.

In light of the reviewer's feedback, we have amended the inclusion criteria wording by replacing the word "correspond" with "and". See page 5, line 6 in the Box 1 (inclusion criteria). Additionally, an ethics amendment has been approved to remove the upper range of the DASS score from the inclusion criteria as high DASS scores do not always correspond to diagnostic qualifiers-the inclusion criteria have been amended to reflect this. See page 5, lines 6 and 7 in the box 1 (inclusion criteria). Furthermore, the DASS does not contain questions related to suicidal ideas, delusions and other psychotic symptoms that can be associated with severe depression, and these will be explored and recorded in the clinical interview. We added these symptoms to the exclusions criteria in order to specify which symptoms of severe depression would constitute reasons for exclusion. See page 6, box 2 (exclusion criteria), lines 4 and 5. We also added a sentence describing the intake clinical interview which is unstructured diagnostic clinical interview. See page 5, para 2.

9) In the method section 'Adapted MBCT Program' is not stated what the length of the program and the duration of the sessions is. I would suggest to include this information, which is useful for authors of future meta-analyses. Secondly, I would like to know what the background of the mindfulness trainer is, and especially, whether he or she is mental health professional.

 The protocol currently states that the "MBCT program which will be used in this trial closely follows the original MBCT curriculum designed by Segal, Williams and Teasdale". See page 7, para 3. In light of reviewer's feedback, we specified the length of the adapted MBCT program, sessions' duration and frequency, and the background of the mindfulness facilitator who is a mental health professional. See page 7, para 3.

10) Data is collected before and after the intervention, and at 20 weeks follow-up. In Figure 1, the post-measure and the follow-up measure are not separately described. I would suggest to make separate 'assessment' boxes for post-treatment and follow-up, to be more precise.

 We have separated the post intervention and 20 weeks follow up assessments in figure 1 but kept them in the assessment box in keeping with the recommendations from the CONSORT extension for pilot and feasibility trials flow chart guidelines. See figure 1.

11) In the method section, 'Safety Considerations' is mentioned that Kuyken et al. (2016) did not report any adverse events. However, I think that Kuyken did report adverse events, but that is was concluded that these were not related to the treatment. Secondly, it is stated that there are no reports of significant adverse side effects. However, for instance Williams et al. (2014) do report 15 serious adverse events, of which 1 is a serious adverse reaction potentially related to MBCT. I would suggest to adjust the text accordingly. However, I still think the method of monitoring safety is adequate.

 The sentence in the Safety Considerations part of the Methods and Analysis sections states that "there have been no reports of significant adverse side effects of MBCT in literature" and the second part of the same sentence intended to convey that this was confirmed in the Kuyken et al. (2016) meta-analysis. In order to clarify that that we were referring to the MBCT-related side-effects, we

added the wording “MBCT-related” to adverse events in the second part of the same sentence. See page 8, para 5.

As the reviewer pointed, the Williams et al (2014) article reported 15 adverse events, five in the MBCT group and 10 in the cognitive psychological education (CPE) group. The authors reported that they “adjudged only one to be a serious adverse reaction—an episode of serious suicidal ideation following discussion of different coping responses to low mood in CPE group”. Therefore, the serious adverse reaction was related to the CPE and not to MBCT.

12) In the method section ‘Outcomes’ is stated that remission and recovery rates are calculated. If I understand correctly, that would create a variable with two levels, ‘recovered’ and ‘not recovered’. However, I think you cannot analyze this data with ANCOVA, which is stated in the data-analysis section. Clarity regarding this issue would be useful. Furthermore, a bit more details regarding the analyses would benefit transparency.

 The primary outcome measure is depression subscale score, which is a continuous measure. We have removed the sentence about remission and recovery rates to improve clarity. We have updated the Data Collection and Analysis section to clarify the methods to be used. We will be using linear mixed effects models (rather than ANCOVA) to analyse the continuous outcome measures because these methods are better suited to analysing data with repeated measures where there is attrition. See page 8, para 3.

13) The manuscript sometimes describes ‘youth’, and sometimes refers to ‘AYA’. I would suggest to be more consistent in terminology, to facilitate clarity for readers. Related to that, it would help a reader to state the outcomes in the same order on all occasions they are discussed.

 We rectified this by referring to the study population in the article as adolescents and young adults (AYAs) throughout the article and have listed the outcomes in the same order in the hypotheses, aims and outcomes sections.