PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of joint transition visits on quality of life in adolescents with inflammatory bowel diseases: a protocol for a prospective, randomised, multicentre, controlled trial (TRANS-IBD)
AUTHORS	Erős, Adrienn; Dohos, Dóra; Veres, Gábor; Tárnok, András; Vincze, Áron; Tészás, Alexandra; Zádori, Noémi; Gede, Noémi; hegyi, Péter; Sarlós, Patrícia

VERSION 1 – REVIEW

REVIEWER	Holger Muehlan University of Greifswald Department Health & Prevention Germany
REVIEW RETURNED	03-Apr-2020

GENERAL COMMENTS	The authors stated that empowerment is an important indicator of successfull transition - but I wonder it wasn't inclded in the list of secondary outcomes? This holds also true for patient activation. There are some very minor issues concerning orthograophy - please check once more for correct spelling (e.g. "three international consensus publication" ... plural? etc.)

REVIEWER	Jessica Philpott Cleveland Clinic Foundation, United States
REVIEW RETURNED	06-May-2020

GENERAL COMMENTS	It is important to attempt to provide evidence behind recommendation of ECCO and other groups that patients receive joint clinical visits. The difference between the two groups may be difficult to detect. It is important that clinical outcomes are included in this study. -Surgery seems to be listed on the review data collection sheets but in the text it is not listed as an outcome. -I would clarify what a "balanced appointment" is. Is it a clinical review without visit. -Are the physicians and locations the same for the intervention group and control group? When the two groups transition, will they go to the same adult gastroenterologists? IE how is it determined that there is no variation in therapy once two groups have transferred.

REVIEWER	Laura Hart Nationwide Children's Hospital / The Ohio State University College of Medicine, Columbus, OH, USA
REVIEW RETURNED	03-Jun-2020

GENERAL COMMENTS	Abstract: Clear and well-written. Introduction: The Delphi studies the authors cite in the "Transition Outcomes" section recognize a number of important outcomes (7 in 1 paper and 10 in the other). I think it would be more appropriate to say that the indicators that they select are "among the most important indicators," rather than "the most important indicators" since they chose to list a selection of the outcomes from these studies. Methods: The authors mention that joint visits are not currently the standard of care in the "study design" section of the methods, but do not describe the current standard of care until much later in the methods. It may be helpful to state they will describe this later. As a reader, I was expecting to see the description of the standard of care here. Alternatively, they could change the label of the "Study Design" section to something like "General Study Overview" so the reader knows that this part just gives the highlights. The authors state that 6 centres will be involved, but only list 5. Please clarify. The inclusion and exclusion criteria seem reasonable for the most part. I would appreciate the authors explaining why a BMI > 40 is an exclusion criterion. In the "balanced consultation" section, I would appreciate if the authors would state if this is the standard of care or not. In the description of the control group, the authors discuss that patients will get visits every 3 months. Is that the current standard of care for adolescents with IBD in Hungary? If the participants are all getting more than is currently the standard of care, which often happens in trials, it would be helpful for the authors to state so explicitly. For the disease activity outcome, who is deciding if a patient had a flare? Is that determined by the provider seeing the patient or is there an adjudication process? The authors are assessing transition readiness three ways: the STARx for adolescents and guardians and the TRAQ for adolescents. It would be helpful to hear why they chose to assess readiness in 3 ways. Regarding the drop out plan, if the study authors choose to remove those who miss visits, then the study is no longer intention-to-treat, it's really more per-protocol. This is reasonable, but should be stated as such. Regarding the dissemination and publication policy, it sounds like the authors plan to include additional authors based solely on recruitment. The ICMJE has clear guidance about authorship criteria, and recruitment alone is not sufficient. Please see the link from the ICMJE for details: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

REVIEWER	Dr Angharad Hurley University of Otago (Christchurch), New Zealand
REVIEW RETURNED	08-Jun-2020

GENERAL COMMENTS	Congratulations to the authors of this protocol manuscript who are addressing a very important need: to provide scientific evidence of the benefit of transition clinics for children with IBD. The manuscript is well written and has merit but some factors need addressing and the following comments are to highlight where more transparency would be beneficial. While it is acknowledged that all researchers would design a trial differently, justification of certain aspects of the methodology is required. If the trial has already started then it would obviously not be possible to address the issues raised in the study protocol itself, in which case rationales need to be included in the manuscript. 1. Inclusion criteria: The age limit for inclusion of 16.75 to 17 years seems very rigid as it is my understanding that the transition process is generally considered for those with an appropriate level of development, even if younger or older than 16.75 years. The guidelines for transition are no doubt different in other countries so transparency would be beneficial - greater justification is needed as to why and how this limited age range was selected. 2. Data collection points of baseline, transfer, and twelve months post-transfer, risks missing vital benefits to outcomes that may be seen in the first 3, 6 or 9 months post-transfer (for example) that may not be retained until 12 months. Justification of why interim measures are not being collected is important. In relation to the next point – collecting fewer outcomes at more frequent intervals would have been advantageous. 3. The number of secondary outcome measures needing completion by participants represents a high respondent burden, which is known to increase study drop-out rates which you have stated are a secondary outcome. There is little justification as to why two transition questionnaires have been used, as well as a self-efficacy assessment, when all three contain a number of similar items and there is distinct cross-over. If this cannot be addressed in the protocol then there needs to be greater justification of why all of the specific outcome measures were included, and how they differ. 4. The protocol states that one of the secondary outcomes is disease specific knowledge but this is not actually measured. The STAR-X asks a small number of questions (only 3) relating to individual understanding of their own illness, but this is not the same as ‘disease specific knowledge’. The inclusion of a knowledge assessment tool such as the IBD-KID2 or CCKNOW would provide very useful information on where knowledge gaps exist and could be addressed with targeted teaching during the transfer process. Disease specific knowledge is integral to successful transition and would be another important way of testing efficacy of the transition process. The exclusion of formal disease specific knowledge assessment should be addressed or included in the protocol if possible. 5. Reference list: This does not contain the original citations pertaining to the development and validation of the assessment tools (MARS-5, TRAQ, IBD-SES [the development, not validation, paper has been cited]) and subsequent citations have been used instead. In addition, an updated factor structure for IMPACT III has been developed which should be considered. Original references should be used - I have attached those required. 6. Statistical analysis: HRQoL is known to be reduced in those with active disease so more information on whether this will be controlled

	for should be included. In addition, no analysis has been included for how the longitudinal change of HRQoL, or secondary outcome measures, will be addressed. Please include this in the manuscript. 7. Supplementary material: There seems little need for the repetition of the information sheets and CRF's for each visit - one of each should suffice. The inclusion of the outcome measures as supplementary material would be helpful but not essential. 8. The use of the word 'empowerment' in this manuscript implies that you are providing an intervention aimed specifically at empowering children with IBD who are transitioning to adult services. You are not measuring empowerment, you have included no literature to show that an intervention such as this improves empowerment, and are making the assumption that improved HRQoL, self-efficacy, and readiness for transition, equate to improved empowerment. Stick to the basic aims of improving HRQoL, and 'readiness for transition', for example, which will take away any confusion in this regard.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: Holger Muehlan
Institution and Country: University of Greifswald, Department Health & Prevention, Germany

-The authors stated that empowerment is an important indicator of successful transition - but I wonder it wasn't included in the list of secondary outcomes? This holds also true for patient activation.
Thank you for this comment. It is true, that we did not choose specific tools assess empowerment and patient activation, but some of the questionnaires we use, indirectly measure these parameters. For example, the STARx and TRAQ questionnaires include several questions about adolescents' disease specific knowledge and their attitude towards management of disease-related activities.
As the answers to these questions only indirectly reflect the level of empowerment and activation, we have removed the word 'empowerment' from the abstract and the main text to make it more accurate and consistent.

-There are some very minor issues concerning orthography - please check once more for correct spelling (e.g. "three international consensus publication" ... plural? etc.)
Thanks for this comment. We have carefully reviewed the text to find and correct any grammatical errors that may have remained in the article.

Reviewer: 2
Reviewer Name: Jessica Philpott
Institution and Country: Cleveland Clinic Foundation, United States

-It is important to attempt to provide evidence behind recommendation of ECCO and other groups that patients receive joint clinical visits. The difference between the two groups may be difficult to detect. It is important that clinical outcomes are included in this study.
Thank you for this comment.
-Surgery seems to be listed on the review data collection sheets but in the text it is not listed as an outcome.
Thanks for this comment. Surgery as an endpoint can be find below the outcome named as "Health care utilisation (measured in every three months)". It is mentioned as: (5) the number and type of surgical interventions.

-I would clarify what a "balanced appointment" is. Is it a clinical review without visit.
Thanks for this comment. We have added an explanatory sentence to make it clear what a "balanced appointment" is. At the end of the ‘Balanced consultation’ section of the text, the following sentence was added: “In summary, a balanced consultation is a clinical review between the two gastroenterologists without the presence of the adolescents involved.”
-Are the physicians and locations the same for the intervention group and control group? When the two groups transition, will they go to the same adult gastroenterologists? IE how is it determined that there is no variation in therapy once two groups have transferred.
Thanks for this comment. Based on your suggestion, we have added the following explanation to the ‘General study overview’ subchapter of the text:
“Patients in the intervention and control groups are treated by the same physician and under the same conditions in each recruiting centre. Adolescents in both study groups are transferred to the same adult gastroenterologist. Modifications of therapy are easy to track because names of currently taken IBD-related drugs and side effects are recorded on the case report form, which is completed at each clinical visit during the study.”

Reviewer: 3
Reviewer Name: Laura Hart
Institution and Country: Nationwide Children's Hospital / The Ohio State University College of Medicine, Columbus, OH, USA

-Abstract: Clear and well-written. Thanks for this comment.
-Introduction: The Delphi studies the authors cite in the "Transition Outcomes" section recognize a number of important outcomes (7 in 1 paper and 10 in the other). I think it would be more appropriate to say that the indicators that they select are "among the most important indicators," rather than "the most important indicators" since they chose to list a selection of the outcomes from these studies.
Thanks for this valuable comment. Based on your advice, we have modified the ‘Transition outcomes’ section of the Introduction as follows: “According to the data of non-disease-specific studies, patients not lost to follow-up, health-related quality of life (HRQoL), self-management and disease-specific knowledge are among the most important indicators of a successful transition. 4 5”

- Methods: The authors mention that joint visits are not currently the standard of care in the "study design" section of the methods, but do not describe the current standard of care until much later in the methods. It may be helpful to state they will describe this later. As a reader, I was expecting to see the description of the standard of care here. Alternatively, they could change the label of the "Study Design" section to something like "General Study Overview" so the reader knows that this part just gives the highlights.
Thanks for this comment. The label for the ‘Study Design’ section has been changed to ‘General Study Overview’. We have amended the ‘Study design’ section as follows to emphasize that the control arm corresponds to the standard of care currently applied in Hungary:
“Patients in the intervention arm receive usual medical care plus a transition intervention for one year consisting of four joint sessions of experts including PGE and AGE. Transitional care with joint visits is not standard in the Hungarian medical care system. In the control arm, which corresponds to the standard of care in Hungary, participants follow their usual medical care without the presence of AGE at outpatient consultations. The intervention period lasts between the ages of 17 and 18 (visits 1-4; V1-4); at the age of 18 transfer to adult gastroenterology is obligatory.”

-The authors state that 6 centres will be involved, but only list 5. Please clarify.
The six participating tertiary pediatric care centres in Hungary will be: University of Pécs, Debrecen and Szeged, Central Hospital of Borsod-Abaúj-Zemplén County, Semmelweis University Budapest and Heim Pál Children’s Hospital. The adult gastroenterology sites are the corresponding tertiary centres in Hungary, namely Pécs, Debrecen, Szeged, Miskolc, and two additional centres from

Budapest. In the text, the amendment to the ‘Participating centres’ section is highlighted in red.
-The inclusion and exclusion criteria seem reasonable for the most part. I would appreciate the authors explaining why a BMI > 40 is an exclusion criterion.
Thanks for this comment. We have chosen BMI > 40 as an exclusion criterion because we believe that with this degree of obesity, many comorbidities are more likely to appear (e.g., type II diabetes, joint damage). These conditions greatly affect the quality of life, which is the primary outcome of our trial. Therefore, BMI > 40 was chosen as an exclusion criterion to eliminate the effect of these comorbidities on our primary endpoint. Accordingly, the ‘exclusion criteria’ section was amended as follows: “ (5) BMI ≥ 40; to eliminate the impact of potential comorbidities on our primary outcome;”

-In the "balanced consultation" section, I would appreciate if the authors would state if this is the standard of care or not.
Thanks for this comment. Balanced consultation is not a standard of care in Hungary. We have added this information to the ‘Balanced consultation’ section as follows: “The aim of this study is to assess the effect of the interaction between the AGE and the adolescent. Balanced consultations are carried out to eliminate the bias caused by the physician-physician interaction, which are not currently part of the standard clinical care in Hungary.”

-In the description of the control group, the authors discuss that patients will get visits every 3 months. Is that the current standard of care for adolescents with IBD in Hungary? If the participants are all getting more than is currently the standard of care, which often happens in trials, it would be helpful for the authors to state so explicitly.
Thanks for this comment. The current standard of care for adolescents with IBD in Hungary is that patients visit their pediatric gastroenterologist every three months. It is pointed out in the first sentence of the ‘Control group (usual care)’ section as follows: “Patients in the control group are given standard of care and visit their PGE every three months between their 17 and 18 years of age.”

- For the disease activity outcome, who is deciding if a patient had a flare? Is that determined by the provider seeing the patient or is there an adjudication process?
Flare-up is determined by the provider seeing the patient. The provider should decide whether the patient has a flare-up based on clinical symptoms, calculated activity indexes, inflammatory laboratory markers and the need for therapy escalation. We have given the definition of a flare-up in the text as follows: “Flare-ups are defined as clinical symptoms suggesting disease activity, accompanied with biochemical (e.g., stool calprotectin, CRP), endoscopic, or imaging evidence of inflammation. Intensifying disease symptoms resulting in dose escalation or initiation of a new drug aiming to achieve remission are also considered as flare-ups.”

-The authors are assessing transition readiness three ways: the STARx for adolescents and guardians and the TRAQ for adolescents. It would be helpful to hear why they chose to assess readiness in 3 ways.
Thanks for this comment. Although both the STARx and TRAQ questionnaires assess adolescents’ transition readiness, and some of their questions are almost the same, it should be noted that certain areas of transition readiness occur only in one of the two questionnaires. For example, only TRAQ asks questions about documenting health tasks, while STARx do not ask this topic. On the other hand, STARx examines disease-specific knowledge in more detail (in Section 2).
We plan to use the adolescent and parent version of STARx because we would like to compare how adolescents themselves and their parents judge participants’ transition readiness.
-Regarding the drop out plan, if the study authors choose to remove those who miss visits, then the study is no longer intention-to-treat, it's really more per-protocol. This is reasonable, but should be stated as such.
Thanks for this comment. We have added the following sentence in the ‘Drop-out’ section: “Data from patients who complete the study according to the requirements of the study protocol will be analysed

in a per-protocol analysis."

-Regarding the dissemination and publication policy, it sounds like the authors plan to include additional authors based solely on recruitment. The ICMJE has clear guidance about authorship criteria, and recruitment alone is not sufficient. Please see the link from the ICMJE for details: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html
Thanks for highlighting this important issue. We have examined the ICMJE guidance on authorship and modified the 'Dissemination and publication policy' section as follows:
"Centres can add one or more authors to the authorship list if they: (1) make a substantial contribution to the acquisition of the data (recruiting at least 25 participants) and; (2) ensure that questions related to the conduction of the investigation are appropriately investigated and resolved and ; (3) take part in the critical review of the draft version of the work and; (4) give their final approval of the version to be published."

Reviewer: 4
Reviewer Name: Dr Angharad Hurley
Institution and Country: University of Otago (Christchurch), New Zealand

-Congratulations to the authors of this protocol manuscript who are addressing a very important need: to provide scientific evidence of the benefit of transition clinics for children with IBD. The manuscript is well written and has merit but some factors need addressing and the following comments are to highlight where more transparency would be beneficial. While it is acknowledged that all researchers would design a trial differently, justification of certain aspects of the methodology is required. If the trial has already started then it would obviously not be possible to address the issues raised in the study protocol itself, in which case rationales need to be included in the manuscript. Thanks for this comment.

1. Inclusion criteria: The age limit for inclusion of 16.75 to 17 years seems very rigid as it is my understanding that the transition process is generally considered for those with an appropriate level of development, even if younger or older than 16.75 years. The guidelines for transition are no doubt different in other countries so transparency would be beneficial - greater justification is needed as to why and how this limited age range was selected.
Thanks for this comment. As explained in the 'Study protocol development' section, two different study plans were put together at the beginning of the planning phase. One had a two-year intervention period and the current version has a one-year long intervention period. Since the majority of adolescents surveyed, voted for the current version of the protocol, we ultimately chose this version of the trial.
The aim of our study protocol was to ensure continuity of health care. We believe that this is best achieved if the intervention period is in the time interval right before the transfer, while the follow-up period falls in the period immediately after the transfer. We have decided the intervention period should start at the age of 17, as the official time for the transfer of a patient to the adult health care system in Hungary is 18 years. Additionally, we did not want the interval used as an inclusion criterion to last too long, so we set it within three months.
We are aware of the fact that recommendations suggest that it is advisable to start transition process in early adolescent hood, even at the age of 12 years (White,2018). On the other hand, it is also true that psychosocial maturity should be considered more important than chronological age for the beginning of the transition process. However, based on the above considerations, we had to set clear and precise intervals for the study to be feasible.
2. Data collection points of baseline, transfer, and twelve months post-transfer, risks missing vital benefits to outcomes that may be seen in the first 3, 6 or 9 months post-transfer (for example) that may not be retained until 12 months. Justification of why interim measures are not being collected is

important. In relation to the next point – collecting fewer outcomes at more frequent intervals would have been advantageous.
Thanks for this comment. In the literature, the timing of measurement of transition outcomes varies widely between IBD transition studies. (Eros A, Soos A, Hegyi P, et al. Spotlight on Transition in Patients With Inflammatory Bowel Disease: A Systematic Review. Inflamm Bowel Dis 2019) In most studies, outcomes are measured six and twelve months after transfer.
Based on the recommendation of a recently conducted multinational Delphi study on the transition care of adolescent with IBD, HRQoL should be assessed with IMPACT-III questionnaire at one year post-transfer. (van den Brink G, van Gaalen MAC, de Ridder L, et al. Health Care Transition Outcomes in Inflammatory Bowel Disease: A Multinational Delphi Study. J Crohns Colitis 2019;13(9):1163-72.) Taking all this into account and in order not to increase the burden on patients, the timing of the primary endpoint measurement was determined to be at one year.
3. The number of secondary outcome measures needing completion by participants represents a high respondent burden, which is known to increase study drop-out rates which you have stated are a secondary outcome. There is little justification as to why two transition questionnaires have been used, as well as a self-efficacy assessment, when all three contain a number of similar items and there is distinct cross-over. If this cannot be addressed in the protocol then there needs to be greater justification of why all of the specific outcome measures were included, and how they differ.
Thanks for this comment.
Although both the STARx and TRAQ questionnaires assess adolescents' transition readiness, and some of their questions are almost the same, it should be noted that certain areas of transition readiness occur only in one of the two questionnaires. For example, only TRAQ asks questions about documenting health tasks, while STARx do not ask this topic. On the other hand, STARx examines disease-specific knowledge in more detail (in Section 2).
We plan to use the adolescent and parent version of STARx because we would like to compare how adolescents themselves and their parents judge participants' transition readiness."

4. The protocol states that one of the secondary outcomes is disease specific knowledge but this is not actually measured. The STAR-X asks a small number of questions (only 3) relating to individual understanding of their own illness, but this is not the same as 'disease specific knowledge'. The inclusion of a knowledge assessment tool such as the IBD-KID2 or CCKNOW would provide very useful information on where knowledge gaps exist and could be addressed with targeted teaching during the transfer process. Disease specific knowledge is integral to successful transition and would be another important way of testing efficacy of the transition process. The exclusion of formal disease specific knowledge assessment should be addressed or included in the protocol if possible.
Thanks for this comment.
Although disease specific knowledge is important for a successful transition, our study does not currently aim to examine the impact of a targeted, knowledge-focused education in the process. Furthermore, according to a recently published Delphi study involving experts and patients with IBD, disease specific knowledge was not even ranked among the top ten transition outcomes. (van den Brink G, van Gaalen MAC, de Ridder L, et al. Health Care Transition Outcomes in Inflammatory Bowel Disease: A Multinational Delphi Study. J Crohns Colitis 2019;13(9):1163-72.)
Based on these considerations, we have amended the main text and removed 'disease specific knowledge', to make it more accurate and consistent.

5. Reference list: This does not contain the original citations pertaining to the development and validation of the assessment tools (MARS-5, TRAQ, IBD-SES [the development, not validation, paper has been cited]) and subsequent citations have been used instead. In addition, an updated factor structure for IMPACT III has been developed which should be considered. Original references should be used - I have attached those required.
Thanks for this comment. Based on your advice, we have added references that contain the validation of this three questionnaires (MARS-5, TRAQ, IBD-SES). These are the references numbered 46, 50,

53.
Thank you for drawing our attention to the updated factor structure of the IMPACT-III questionnaire, which showed reliable and valid domains, demonstrated better model fit and higher reliability than the original IMPACT domain structure, and showed construct validity with PROMIS instruments. However, to the best of our knowledge, the new version of IMPACT-III has so far been only mentioned in a conference abstract (in the version you have attached), but the full-text version of the questionnaire has not been published. Additionally, the original version of the questionnaire has already been adapted in Hungary. Based on these facts, we decided to use the original version of IMPACT-III.

6. Statistical analysis: HRQoL is known to be reduced in those with active disease so more information on whether this will be controlled for should be included. In addition, no analysis has been included for how the longitudinal change of HRQoL, or secondary outcome measures, will be addressed. Please include this in the manuscript.
Thanks for this comment. Based on your suggestions, the following details of the statistical analysis was added to the 'Statistical analyses' subchapter:
"The primary outcome HRQoL will be analysed with ANCOVA, taking into account disease activity as an influencing factor. For the longitudinal analysis of HRQoL, a mixed model with a proper covariate matrix will be performed. As for the secondary outcomes: the relative risk will be calculated for dichotomous variables and the T-test will be performed for continuous variables."
7. Supplementary material: There seems little need for the repetition of the information sheets and CRF's for each visit - one of each should suffice. The inclusion of the outcome measures as supplementary material would be helpful but not essential.
Thanks for this comment.
The most detailed CRF is constructed for V1, the V5 and V9 forms are completely the same. The V2-4, V6-8 CRFs are again the same. Based on your suggestion, we have shortened this part of the supplementary material and included only the four different CRFs and indicated at which visit the form should be completed.
Although the first part of the information sheets (basic viewpoints during the transitional visit) are the same, the second part of these sheets (patient education) are different. That is why we uploaded all four sheets.
We have summarized the specific outcomes and tools used for measurement in Figure 1 Schedule of enrolment, interventions, and assessments.

8. The use of the word 'empowerment' in this manuscript implies that you are providing an intervention aimed specifically at empowering children with IBD who are transitioning to adult services. You are not measuring empowerment, you have included no literature to show that an intervention such as this improves empowerment, and are making the assumption that improved HRQoL, self-efficacy, and readiness for transition, equate to improved empowerment. Stick to the basic aims of improving HRQoL, and 'readiness for transition', for example, which will take away any confusion in this regard.
Thanks for this comment. It is true, that we did not choose specific tools assess empowerment and patient activation, but some of the questionnaires we use, indirectly measure these parameters. For example, the STARx and TRAQ questionnaires include several questions about adolescents' disease specific knowledge and their attitude towards management of disease-related activities.
As the answers to these questions only indirectly reflect the level of empowerment and activation, we have removed the word 'empowerment' from the abstract and the main text, as to be more accurate and consistent.

VERSION 2 – REVIEW

REVIEWER	Holger Muehlan University of Greifswald Institute of Psychology Department Health & Prevention Robert Blum-Str. 13 17487 Greifswald Germany
REVIEW RETURNED	25-Jul-2020

GENERAL COMMENTS	The revsion improved the study protocol substantially. I Hvae no further comments to declare.

REVIEWER	Laura Hart Nationwide Children's Hospital / The Ohio State University College of Medicine, Columbus, OH, USA
REVIEW RETURNED	09-Jul-2020

GENERAL COMMENTS	I thank the authors for their clear reply and diligent work to respond to the reviewers. I have a few points that I believe require further revision. I had previously asked the authors to clarify if 5 or 6 centers are involved. In looking at their revision, it appears that my confusion was an issue of grammar. The sentence that I think needs to be corrected this one: "Study participants are recruited from six tertiary pediatric care centres in Hungary (University of Pécs, Debrecen and Szeged, Central Hospital of Borsod-Abaúj-Zemplén County, Semmelweis University Budapest and Heim Pál Children's Hospital)." If Debrecen and Szeged are separate centers (which it appears they are based on the adult center list), then the "and" between Debrecen and Szeged should be removed and replaced with a comma. I appreciate the authors' reasoning on including multiple transition readiness assessments. The manuscript would be improved by including this information in there as well. I also would suggest the authors cite the reference for the factor structure for the parent STARx scale, since they intend to use it in their study. Here is the reference: Nazareth M, Hart L, Ferris M, Rak E, Hooper S, van Tilburg MAL. A Parental Report of Youth Transition Readiness: The Parent STARx Questionnaire (STARx-P) and Re-evaluation of the STARx Child Report. Journal of pediatric nursing. 2018;38:122-126. Regarding the authors' addition to the Drop Out section, I appreciate them adding a mention of a per-protocol analysis. It still appears that they intend to do something other than intention-to-treat, and yet kept the term in the paper. In an intention-to-treat analysis, all participants who are randomized are included, even if they violate the protocol or have missing data. If they authors plan to remove those who violate the protocol, then they are doing a per-protocol analysis. As I stated previously, given the nuances of the intervention, that is reasonable. It is, important, however, to be accurate on this point.

REVIEWER	Angharad Hurley University of Otago, New Zealand
REVIEW RETURNED	16-Jul-2020

GENERAL COMMENTS	Page 8 of 90, lines 7-12. This sentence needs to be changed, it is too long and you can't claim your own trial is 'well-designed'. Suggest changing to: This RCT aims to establish evidence on whether joint transition visits for adolescents with IBD are superior to standard care. Page 8 of 90, line 17. This first sentence stating the aim ('Our RCT aims to prove the superiority of joint visits compared to standard transitional care in improving HRQoL of adolescents with IBD in order to provide strong scientific evidence') implies lack of research equipoise and contains the assumption that you will prove superiority. Suggest changing to: This RCT aims to establish whether joint visits are superior to standard transitional care at improving the HRQoL for adolescents with IBD. Page 11 of 90, baseline assessments. This paragraph contains a lot of information that may not be necessary. Can you not summarise as 'standard laboratory parameters (haematology, biochemistry and inflammatory markers)'. Table 1. There is so much information in here, and in the legend, and shows a huge degree of repetition with the section 'baseline assessments'. Again, is it all necessary? Can visits 2-4 and 6-8 not be condensed as they are identical? And the legend reduced substantially? My initial comments regarding assessment of HRQoL at baseline, transition, and 12 months being too infrequent remain a concern. While I accept that the Delphi study cited recommends an assessment at 12 months, this is for clinical use and not research. In addition, in the cited paper by van Den Brink et al, the HRQoL assessment at 12 months was the only option given (not the option of a 6 or 12 month assessment, for example), so this should not be read as there being no benefit at 6 months, or that it shouldn't be measured. It is still my strong opinion that you may miss vital improvements in domains in the interim period that may have been lost at 12 months. It is stated that participants are not lost to follow up if they attend at least three of the five planned AGE visits following transition. Does that mean that if they miss the final visit, and therefore completion of all the final questionnaires, they are still included even though you are unable to assess the study outcomes?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Holger Muehlan Institution and Country: University of Greifswald Institute of Psychology Department Health & Prevention Robert Blum-Str. 13 17487 Greifswald, Germany

The revision improved the study protocol substantially. I Have no further comments to declare. Thanks for this comment.

Reviewer: 3

Reviewer Name: Laura Hart Institution and Country: Nationwide Children's Hospital / The Ohio State University College of Medicine, Columbus, OH, USA

I thank the authors for their clear reply and diligent work to respond to the reviewers. I have a few points that I believe require further revision. Thanks for this comment.

I had previously asked the authors to clarify if 5 or 6 centers are involved. In looking at their revision, it appears that my confusion was an issue of grammar. The sentence that I think needs to be corrected this one: "Study participants are recruited from six tertiary pediatric care centres in Hungary (University of Pécs, Debrecen and Szeged, Central Hospital of Borsod-Abaúj-Zemplén County, Semmelweis University Budapest and Heim Pál Children's Hospital)." If Debrecen and Szeged are separate centers (which it appears they are based on the adult center list), then the "and" between Debrecen and Szeged should be removed and replaced with a comma.

Thanks for this comment. We have corrected the text based on your recommendation. Debrecen and Szeged are separate centres, therefore the "and" between Debrecen and Szeged was removed and replaced by a comma.

I appreciate the authors' reasoning on including multiple transition readiness assessments. The manuscript would be improved by including this information in there as well.

Thanks for this comment. Based on your suggestion, we have provided additional information on why we include multiple transition readiness assessments. The following data was added to the 'Transition readiness' section of the main text:

"Since we would like to compare how adolescents themselves and their parents judge participants' transition readiness, STARx is also filled out by participating adolescents and their legal guardians. (Ferris M 2015; Nazareth M 2018)"

"Although both questionnaires assess adolescents' transition readiness, and some of their questions are almost the same, it should be noted that certain areas of transition readiness occur only in one of the two questionnaires. For example, only TRAQ asks questions about documenting health tasks, while STARx do not ask this topic. (Ferris M 2015; Anelli CG 2019) On the other hand, STARx examines disease-specific knowledge in more detail. (Ferris M 2015)"

I also would suggest the authors cite the reference for the factor structure for the parent STARx scale, since they intend to use it in their study. Here is the reference: Nazareth M, Hart L, Ferris M, Rak E, Hooper S, van Tilburg MAL. A Parental Report of Youth Transition Readiness: The Parent STARx Questionnaire (STARx-P) and Re-evaluation of the STARx Child Report. Journal of pediatric nursing. 2018;38:122-126.

Thanks for this comment. We have cited this article under the reference number 52.

Regarding the authors' addition to the Drop Out section, I appreciate them adding a mention of a per-protocol analysis. It still appears that they intend to do something other than intention-to-treat, and yet kept the term in the paper. In an intention-to-treat analysis, all participants who are randomized are

included, even if they violate the protocol or have missing data. If they authors plan to remove those who violate the protocol, then they are doing a per-protocol analysis. As I stated previously, given the nuances of the intervention, that is reasonable. It is, important, however, to be accurate on this point.

Thanks for this comment. We have clarified this section as follows:

“The collected data will be analysed separately for the intention-to-treat and the per-protocol study populations. The intention-to-treat analysis will include data from all participants randomized in the study, even if they violate the protocol or have missing data. The per-protocol analysis will include data from patients who complete the study according to the requirements of the study protocol. Patients automatically drop out from the per-protocol analysis if: (1) at least one joint visit is missed; or (2) any of the data considering the primary endpoints cannot be obtained from the participant.”

Reviewer: 4

Reviewer Name: Angharad Hurley Institution and Country: University of Otago, New Zealand

Page 8 of 90, lines 7-12. This sentence needs to be changed, it is too long and you can’t claim your own trial is ‘well-designed’. Suggest changing to: This RCT aims to establish evidence on whether joint transition visits for adolescents with IBD are superior to standard care.

Thanks for this comment. We have corrected the above mentioned sentence of the main text according to your suggestion.

Page 8 of 90, line 17. This first sentence stating the aim (‘Our RCT aims to prove the superiority of joint visits compared to standard transitional care in improving HRQoL of adolescents with IBD in order to provide strong scientific evidence’) implies lack of research equipoise and contains the assumption that you will prove superiority. Suggest changing to: This RCT aims to establish whether joint visits are superior to standard transitional care at improving the HRQoL for adolescents with IBD.

Thanks for this comment. We have corrected the above mentioned sentence of the main text according to your suggestion.

Page 11 of 90, baseline assessments. This paragraph contains a lot of information that may not be necessary. Can you not summarise as ‘standard laboratory parameters (haematology, biochemistry and inflammatory markers)’.

Thanks for this comment. Based on your advice, we have shortened this part of the text according to your suggestion.

Table 1. There is so much information in here, and in the legend, and shows a huge degree of repetition with the section ‘baseline assessments’. Again, is it all necessary? Can visits 2-4 and 6-8 not be condensed as they are identical? And the legend reduced substantially?

Thanks for this comment. Based on your advice, we have modified Table 1 as to make it more transparent, compact and to avoid data duplication. Additionally, the legend of the table was also shortened. The modified version of Table 1 and the shortened Legend were embedded to the Main text.

My initial comments regarding assessment of HRQoL at baseline, transition, and 12 months being too infrequent remain a concern. While I accept that the Delphi study cited recommends an assessment at 12 months, this is for clinical use and not research. In addition, in the cited paper by van Den Brink et al, the HRQoL assessment at 12 months was the only option given (not the option of a 6 or 12 month assessment, for example), so this should not be read as there being no benefit at 6 months, or that it shouldn't be measured. It is still my strong opinion that you may miss vital improvements in domains in the interim period that may have been lost at 12 months.

Thanks for this comment. You are right, that we may miss vital improvements in domains in the interim period if we only assess HRQoL only at the end of the follow-up period (at 12 months after transfer). However, we think that the burden caused by the participation is already quite high, as the filling out of the several questionnaires takes relatively long time for the adolescents and their parents.

Taking all these aspects into account, we have decided, that from all the endpoints measured with questionnaires, we are going to assess only the primary outcome (HRQoL) of the trial at the middle of the follow-up period (exactly on the seventh visit).

Therefore, we have modified the following part of the main text:

"The longitudinal change of patient reported HRQoL during the trial

HRQoL will be measured at baseline, at the beginning (visit 5), in the middle (visit7) and at the end (visit 9) of the follow-up period."

Additionally, the measurement of HRQoL was added to Table 1.

It is stated that participants are not lost to follow up if they attend at least three of the five planned AGE visits following transition. Does that mean that if they miss the final visit, and therefore completion of all the final questionnaires, they are still included even though you are unable to assess the study outcomes?

Thanks for this comment. The definition mentioned above was defined to be able to measure one of our secondary endpoints, namely: 'The number of patients not lost to follow-up'. This outcome reflects the continuity of care. Patients who miss the final visit will be excluded from the per-protocol analysis, but their data will be analysed as the part of the intention-to-treat study population. We plan to terminate the study when we are able to examine the complete data set of 160 participants (80 from each study group) in the per-protocol analysis.

VERSION 3 – REVIEW

REVIEWER	Laura Hart Nationwide Children's Hospital / The Ohio State University College of Medicine, Columbus, OH, USA
REVIEW RETURNED	17-Aug-2020

GENERAL COMMENTS	The authors have addressed my concerns. I have no other comments or suggestions for this manuscript.

REVIEWER	Angharad Hurley University of Otago, New Zealand
REVIEW RETURNED	19-Aug-2020

GENERAL COMMENTS	I am satisfied that my previous concerns have been addressed, many thanks. The legend for the table is still very busy and could be reduced (HCU outcomes 1-7 could be removed for example), but that is the decision of the journal on whether there are word limits for table legends. I wish you luck with this very interesting research project.