PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A qualitative study of barriers to clinical trial retention in adults with recently diagnosed Type 1 Diabetes
AUTHORS	Henshall, Catherine; Narendran, P; Andrews, Robert; Daley, Amanda; Stokes, Keith; Kennedy, Amy; Greenfield, Sheila

VERSION 1 – REVIEW

REVIEWER	Ruozhi Zhao University of Manitoba, Canada
REVIEW RETURNED	06-Mar-2018

GENERAL COMMENTS	Type I diabetes patient (T1D) exercise therapy information is very rare, this topic is very interesting, is a good exploration. Look forward to future research: 1) increase the sample size; 2) increase the ethnic groups; 3) would like to know that whether exercise affects the development of T1D patients.

REVIEWER	Mette Due-Christensen King's College London, London UK
REVIEW RETURNED	07-Mar-2018

GENERAL COMMENTS	**Overall experiences of people with new onset type 1 diabetes involved in a physical activity study** Title I wonder, if stating clearly in the title, that this paper is about adults with new onset type 1 diabetes would be helpful for the reader. Abstract It would be helpful for the reader to know the age of the participants Keywords Please consider adding adults, new onset and/or diagnosis Introduction The introduction is well structured and informative. It would help the reader if it was specified that the meta-analysis referred to in line 49 included people with type 2 not type 1 diabetes.

	Methods The method section is well structured. I have a few suggestions that might help the reader to understand the method better: Setting, access and recruitment: Line 24: reference 13 should probably be 14? It would be helpful to add a little more information about the EXTOD study at this stage; e.g. the number of people who participated in each phase of the study, a brief description of the study and what was expected of the participants. Is the qualitative study in phase 1 published? Please could you explain the reason for selecting the specific 5 sites from the original 19? As age was a selection criteria I would suggest this is reported in the table instead of the study sites. Patient involvement Would it be possible to add more information about how the PPI was organised such as how many people were involved and if they were involved in i.e. developing the interview guide? Also I was wondering if the participants at the informal feedback evening had an opportunity to give feedback on the findings? Data collection Please could you comment on the interview guide – it contains many specific details and seem more structured than semi-structured? Data analysis Please could you elaborate on how the emerging data shaped the interview process? Also how did the predetermined themes in the interview guide influence the analysis? Did the three researchers

	independently develop themes and then agreed on the themes presented in the paper? Results I think the result section could benefit from some rethinking in terms of some of the themes. I wonder if "time" should be a theme in its own right describing the time related to conducting the activities of the intervention but also the length of the programme and the timing of the information? Some of these reflections are mentioned in the discussion but is not completely clear in the result section. The theme coming to terms with diagnosis of T1D is not mentioned as a theme in the abstract or mentioned in the discussion although it seems to be important? In addition, it would ease the reading of the paper if you provided information about age and sex after each quote instead of EXTOD and their # Discussion There is growing evidence that type 1 diabetes is diagnosed throughout adult life (see e.g. Thomas, N. J., Jones, S. E., Weedon, M. N., Shields, B. M., Oram, R. A., & Hattersley, A. T. (2017). Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. *Lancet Diabetes Endocrinol, 6*(2), 122-129. Thunander, M., Petersson, C., Jonzon, K., Fornander, J., Ossiansson, B., Torn, C., et al. (2008). Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. *Diabetes research and clinical practice, 82*(2), 247-255. Likewise, the age of onset of type 2 diabetes is getting younger. How does that influence your discussion and conclusion? Please could you reflect on these issues in the discussion and conclusion.

	I think Dr Karin Johansson's work on falling ill with diabetes (Johansson, K., Ekebergh, M., & Dahlberg, K. (2009). A lifeworld phenomenological study of the experience of falling ill with diabetes. *International Journal of Nursing Studies, 46*(2), 197-203) along with other qualitative studies/meta-syntheses could inform your discussion in relation to the theme "coming to terms with diagnosis of T1D". General comment: the terms "patients" and "people with diabetes" are used interchangeably and so are T1D and T1DM– please consider more consistency

REVIEWER	Johan Wadén 1Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki, Finland., 2Abdominal Center Nephrology, University of Helsinki and Helsinki University Hospital, Finland.
REVIEW RETURNED	06-May-2018

GENERAL COMMENTS	Henshall et al, "Overall experiences of people with New Onset Type 1 Diabetes involved in a physical activity study" Reviewer´s comments: This paper written by Henshall et al deals with the topic of experiences and potential barriers to engage in physical activity in patients with chronic disease, in this case newly diagnosed type 1 diabetes. The patients (N=20) are between 19 and 55 years of age (men/women: 11/9). Physical activity in patients with type 1 diabetes is an important topic which clearly needs more extensive research, especially when there is a large body of evidence of numerous benefits of regular physical activity for patients with type 2 diabetes. This is a cross-sectional, qualitative study involving 20 patients. The present study is part of the EXTOD (Exercise to preserve beta cell function in recent-onset type 1 diabetes mellitus) Study. The present study mentions briefly the EXTOD study protocol and directs to reference 13 for more detailed information. However, reference 13 is a meta-analysis for strategies for adherence to RCT:s, and the needed clarifying information regarding the EXTOD Study was found in reference 14. I would like the authors to comment on this confusing matter. The patient selection was somewhat unclear, especially the size of the sampling population has to mentioned in the paper and a flow-chart of the patient selection process would be informative. Patient selection and especially reasons for non-selection into such a study is critical for the interpretation of the results. It seems the EXTOD study according to reference 14 comprises 60 patients with now-onset T1D, and the number of patients in the present study is one third thereof. Also the number of participating study centers in EXTOD is 19, and the patients in the present study came from five study centers. The possibility of both patient- and study center-derived sampling bias needs to be clarified. The introduction section should be more focused on the topic of the present paper. Beta-cell function is not investigated in the present

	paper. The results are presented as selected excerptions from interviews. The data are of qualitative nature, with many questions and a low number of patients, which have implications on statistical power. How well can we generalise the results for type 1 diabetic patients? The results section can be shortened down. The authors discuss differences between type 1 and type 2 diabetes with respect to barriers to engage in physical activity, and in this discussion I was surprised that no effort was made to discuss the pathophysiological differences between type 1 and type 2 diabetes. It is important to realise that there is a big difference in the risk for exercise-related hypoglycaemia (high in type 1 diabetes, low in type 2 diabetes treated with oral non-sulfonylurea agents) have which have implications for fear and safety matters during physical activity. Overall: this is an important study topic but the present study has problems, a small sample size and the recruitment of the study population is somewhat unclear.

VERSION 1 – AUTHOR RESPONSE

Responses to reviewers' comments

Thank you for your helpful comments relating to Manuscript ID bmjopen-2018-022353 "Overall experiences of people with New Onset Type 1 Diabetes involved in a physical activity study". We have carefully considered each comment, have responded to them in the table below and amended the manuscript accordingly. We look forward to hearing your thoughts.

Reviewer's comment	**Authors' response**
Editorial Requests	
Please revise your title to indicate the research question, study design, and setting. This is the preferred format of the journal.	Thank you for this clarification. We have revised the title which now reads *'A qualitative study of barriers to clinical trial retention in adults with recently diagnosed Type 1 Diabetes'*
Please reduce the number of strengths in the 'Strengths and limitations' section on page 3 and include some limitations. This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods or design of the study reported (see: http://bmjopen.bmj.com/site/about/guidelines.xhtml#articletypes).	A limitation has been added to the 'Strengths and Limitations' section (page 3) and a strength removed, so that five bulleted points remain. The limitation is documented below: *'Ethnicity excluded as a purposive sampling criterion resulting in only White participants being represented.'*
Reviewer 2	
Title I wonder, if stating clearly in the title, that this paper is about adults with new onset type 1 diabetes would be helpful for the reader.	Thank you for this comment. The title has been amended in line with the comment from the editor above and now states that the paper is about adults with recently diagnosed Type 1 Diabetes.

Abstract It would be helpful for the reader to know the age of the participants	The age range of the participants (19-55yrs) has been added to the abstract on page 2.
Keywords Please consider adding adults, new onset and/or diagnosis	'Adults' and 'Diagnosis' have been added as additional keywords (page 3).
Introduction The introduction is well structured and informative. It would help the reader if it was specified that the meta-analysis referred to in line 49 included people with type 2 not type 1 diabetes.	It has been clarified that this meta-analysis refers to people with type 2 diabetes (page 5, line 95).
Methods The method section is well structured. I have a few suggestions that might help the reader to understand the method better: Setting, access and recruitment: Line 24: reference 13 should probably be 14?	Apologies for this error. We have altered this citation from 13 to 14 in the manuscript.
It would be helpful to add a little more information about the EXTOD study at this stage; e.g. the number of people who participated in each phase of the study, a brief description of the study and what was expected of the participants.	We have added some information (page 5, line 113-16) about the aim and the hypothesis being tested by the EXTOD study: *'The EXTOD study explored the barriers and benefits of exercise in adults with newly diagnosed T1D. The hypothesis being tested by the EXTOD study was that exercise preserved beta cell function in adults recently diagnosed with T1D.'*
Is the qualitative study in phase 1 published?	The qualitative study is now published and the reference is provided (page 5, line 107 and line 117).
Please could you explain the reason for selecting the specific 5 sites from the original 19?	This information has now been provided (page 6, lines 127-29): '*Similarly the sites were selected to allow a purposeful sampling of geographical areas participating in the EXTOD study (teaching*

	hospitals versus district general hospitals).'
As age was a selection criteria I would suggest this is reported in the table instead of the study sites.	Unfortunately we do not have access to the data relating to the individual ages of the participants. However, the age range of participants (19-55 years) is reported in the manuscript (page 10, line 193).
Patient involvement Would it be possible to add more information about how the PPI was organised such as how many people were involved and if they were involved in i.e. developing the interview guide?	The numbers involved have now been included in the manuscript (page 7, lines 147-52).
Also I was wondering if the participants at the informal feedback evening had an opportunity to give feedback on the findings?	The feedback evening was organised for phase 2 of the study – not the subject of this manuscript. We have clarified this (page 7, lines 152-55).
Data collection Please could you comment on the interview guide – it contains many specific details and seem more structured than semi-structured?	Thank you for this comment. We have removed the word 'semi' from 'semi-structured' to reflect the fact that this topic guide was a structured topic guide (page 7, line 163).
Data analysis Please could you elaborate on how the emerging data shaped the interview process? Also how did the predetermined themes in the interview guide influence the analysis? Did the three researchers independently develop themes and then agreed on the themes presented in the paper?	We have added an example of how the emerging data shaped the interview process on Page 9, lines 175-78 onwards. This reads: *'For example, some participants in the early interviews spoke of how they had struggled to come to terms with their new T1D diagnosis. As a result subsequent interviews explored this area in more depth, focusing on the impact this had on their experience of participating in the EXTOD study.'* Detail has now also been added to this section to explain how the topic guide areas influenced the data analysis (page 9, lines 179-82)*:* *'The pre-determined topic areas set out in the topic guide (Table 1) such as 'health professional support' and 'recruitment and follow-up' guided the analysis process as much of the data collected focused on these topic areas, enabling the researchers to elicit information that was relevant*

	to the study question.' It has been clarified on page 10 (lines 184-86) that the themes were developed by CH and these were then discussed and agreed on during discussions with research team members.
Results I think the result section could benefit from some rethinking in terms of some of the themes. I wonder if "time" should be a theme in its own right describing the time related to conducting the activities of the intervention but also the length of the programme and the timing of the information? Some of these reflections are mentioned in the discussion but is not completely clear in the result section.	Thank you for this comment. Whilst we appreciate that issues relating to time are prominent throughout the findings section, these time related issues are applicable within a number of the current themes, adding context to the issues that are being explored. Therefore we feel that rather than adding a new theme "time" it is best to leave the themes as they are in their current form so that the reader can understand how time feeds into many of the considerations that people with newly diagnosed T1D face with regard to trial related issues. In addition, the remaining reviewers are happy with the themes structured in this original format.
The theme coming to terms with diagnosis of T1D is not mentioned as a theme in the abstract or mentioned in the discussion although it seems to be important?	Thank you for pointing this out. The theme 'coming to terms with a diagnosis of T1D' has now been added to the abstract (page 2, line 42) and the Discussion section (page 16, lines 324-25).
In addition, it would ease the reading of the paper if you provided information about age and sex after each quote instead of EXTOD and their #	Unfortunately we do not have access to the data relating to the ages of the individual participants. However, the sex of each participant and their participating centre has been added after each quote, to add context to the findings.
Discussion There is growing evidence that type 1 diabetes is diagnosed throughout adult life (see e.g. Thomas, N. J., Jones, S. E., Weedon, M. N., Shields, B. M., Oram, R. A., & Hattersley, A. T. (2017). Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes Endocrinol, 6(2), 122-129.	Thank you for the provision of these useful references. The issues relating to the age of onset of adults with T1D and T2D has been reflected on in the Discussion (page 19, lines 379-89) and Conclusion (page 20, lines 426-27) sections and both references have been added to verify these reflections.

Thunander, M., Petersson, C., Jonzon, K., Fornander, J., Ossiansson, B., Torn, C., et al. (2008). Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. Diabetes research and clinical practice, 82(2), 247-255. Likewise, the age of onset of type 2 diabetes is getting younger. How does that influence your discussion and conclusion? Please could you reflect on these issues in the discussion and conclusion.	
I think Dr Karin Johansson's work on falling ill with diabetes (Johansson, K., Ekebergh, M., & Dahlberg, K. (2009). A lifeworld phenomenological study of the experience of falling ill with diabetes. International Journal of Nursing Studies, 46(2), 197-203) along with other qualitative studies/meta-syntheses could inform your discussion in relation to the theme "coming to terms with diagnosis of T1D".	Thank you for signposting us towards this insightful reference. We have used it, alongside another qualitative study, to inform our Discussion in relation to the theme 'coming to terms with diagnosis of T1D' as suggested (page 16-17, lines 325-29).
General comment: the terms "patients" and "people with diabetes" are used interchangeably and so are T1D and T1DM– please consider more consistency	The manuscript has been carefully checked to ensure that the term 'T1D' is used consistently, rather than 'T1DM'. In addition, the term 'patients' has been replaced with 'people with T1D' throughout the manuscript.
Reviewer 3	
The present study mentions briefly the EXTOD study protocol and directs to reference 13 for more detailed information. However, reference 13 is a meta-analysis for strategies for adherence to RCT:s, and the needed clarifying information regarding the EXTOD Study was found in reference 14. I would like the authors to comment on this confusing matter.	Apologies for this error, which was also noted by reviewer 2. We have altered this citation from 13 to 14 in the manuscript.
The patient selection was somewhat unclear, especially the size of the sampling population has to mentioned in the paper and a flow-chart of the patient selection process would be informative. Patient selection and especially	We are sorry that you found details of the sampling process unclear. As identified on page 6 of the manuscript, purposive sampling was used to select participants based on the characteristics age, gender, study arm (intervention/control) and

reasons for non-selection into such a study is critical for the interpretation of the results. It seems the EXTOD study according to reference 14 comprises 60 patients with now-onset T1D, and the number of patients in the present study is one third thereof. Also the number of participating study centers in EXTOD is 19, and the patients in the present study came from five study centers. The possibility of both patient- and study center-derived sampling bias needs to be clarified.	study status (completed/withdrawn). The wording of the manuscript has been amended to clarify that this was done to increase *diversity* in the sampling process and to ensure that an even spread of participants across the key characteristics were sampled. In addition, page 6 now states the original size of the sampling population was 60 and that of these, 20 were selected for the present study (page 6, lines 122-23). Qualitative sampling processes differ from quantitative sampling processes. In qualitative studies a sample size of 20 is considered fairly large and the researchers did not see any merit in interviewing the full sample population of 60 as data saturation had been achieved after interviewing the 20 participants included in the study (i.e. no new themes were emerging from the dataset). Of the 19 centres in the main EXTOD study, five participating centres were chosen in a purposeful way to represent both district general hospitals and teaching hospitals. This has been clarified in the text (page 6, lines 127-29).
The introduction section should be more focused on the topic of the present paper. Beta-cell function is not investigated in the present paper.	Thank you for this comment; we have now made these changes. We have reduced the introductory text to explaining the background to the EXTOD study, and focussed more on the need for a qualitative study of barriers to retention in clinical trials for this population,
The results are presented as selected excerptions from interviews. The data are of qualitative nature, with many questions and a low number of patients, which have implications on statistical power. How well can we generalise the results for type 1 diabetic patients?	As stated above, a sample size of twenty is considered more than sufficient in qualitative research to elicit rich data findings using interview methods. The quotes used to illustrate the themes identified are considered the most transparent and rigorous way to present data findings in qualitative research. Statistical power is not a consideration in qualitative research; rather the numbers sampled are based on how many interviews are likely to be required to achieve data saturation (where no new themes emerge from the data). Using this qualitative methodology, we cannot presume that the findings are generalizable to *all* people who are newly diagnosed with T1D; rather these findings provide us with rich, detailed insights about the experiences of people with newly diagnosed T1D involved in clinical trials. These

	insights allow us to build theories and develop ideas and constructs relating to the types of considerations that must be thought through when designing clinical trials for this particular population group.
The results section can be shortened down.	We feel that the information contained within the Results section is necessary to provide the reader with context and aid their understanding in relation to the quotes presented. We are therefore reluctant to shorten the Results section as we feel this might result in the true meaning of the findings being lost or misconstrued. We are however happy to do so if the Editor agrees and feels it is possible to reduce content without losing significant meaning.
The authors discuss differences between type 1 and type 2 diabetes with respect to barriers to engage in physical activity, and in this discussion I was surprised that no effort was made to discuss the pathophysiological differences between type 1 and type 2 diabetes. It is important to realise that there is a big difference in the risk for exercise-related hypoglycaemia (high in type 1 diabetes, low in type 2 diabetes treated with oral non-sulfonylurea agents) have which have implications for fear and safety matters during physical activity.	Thank you for this comment. Whilst we fully agree with the reviewer on this important difference in susceptibility to hypoglycaemia between the T1D and T2D populations, we have refrained from expanding on this in the paper because this work relates to barriers to retention in clinical trials rather than barriers to exercise. I hope the reason for this choice is clear.
Overall: this is an important study topic but the present study has problems, a small sample size and the recruitment of the study population is somewhat unclear.	Thank you for acknowledging that this is an important topic. As discussed above, a sample size of 20 is considered more than sufficient for a qualitative interview study. In addition, details relating to the recruitment/sampling of the study population have now been addressed in previous comments.

VERSION 2 – REVIEW

REVIEWER	Mette Due-Christensen King's College London, London UK
REVIEW RETURNED	04-Jun-2018

GENERAL COMMENTS	Thank you for the opportunity to review a revision of your paper on a very important subject in an under researched population. In relation to the changes you have made based on my request in relation to providing age and sex after each quote I would like you to reconsider adding the participating centre as this could potentially be a breach to the anonymity of the participants. Also, you do not make any comparison between the centres so the information is not

	necessary. Other than that your revisions have improved the paper and I recommed acceptance.