# PEER REVIEW HISTORY

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# **ARTICLE DETAILS**

TITLE (PROVISIONAL)	Living with Crohn's Disease: An exploratory cross-sectional qualitative study into decision-making and expectations in relation to Autologous Haematopoietic Stem Cell Treatment (The DECIDES study)
AUTHORS	Cooper, Joanne; Blake, Iszara; Lindsay, James; Hawkey, Christopher

# **VERSION 1 - REVIEW**

REVIEWER	MILTON ARTUR RUIZ ASSOCIAÇÃO PORTUGUESA DE BENEFICENCIA DE SJ RIO PRETO. SP. BRAZIL
REVIEW RETURNED	19-Dec-2016

GENERAL COMMENTS	The idea of this paper is very interesting and the proposition to report what the patients with Crohn's disease think about aspects related to the treatment with HSCT. In my opinion the number of patients should contain all or a greater number of participants of the ASTIC trial, not only 5 sites, and an additional group of patients who where not part or any involvement in the work of ASTIC, which leads
	to a lack of interpretation.

REVIEWER	Dr Karen Kemp
	University of Manchester / Manchester Royal Infirmary
	UK
REVIEW RETURNED	17-Feb-2017

GENERAL COMMENTS	This is a well written and important piece of qualitative research, supporting the international ASTIC trial. Real patient experience of trials can only be captured by qualitative methods and it is good to
	see this work presented.
	There is a good overview of Framework methodology, detailing rigour and validity and nvivo quotes to support the themes. The themes are in keeping with previous literature, using terminology such as 'battle' and 'fighting'.  This paper offers guidance for future trials in terms of individualised communication plans, how to help patients through periods of uncertainty during trials, patients who are not eligible for the trial itself, and being very clear with the patient why the trial is being
	undertaken.  There is no mention of limitations, which requires a few sentences.

REVIEWER	Sofía García-Sanjuán
	University of Alicante
	Spain
REVIEW RETURNED	20-Feb-2017

## **GENERAL COMMENTS**

The way authors have exposed the "aims" and the "objectives" is confusing. I would recommend clarifying which the main aim/objective is and then which the specific ones are. In the "Introduction" there is a lack of information and literature references that could justify why Spanish and British samples have been used in this study and which the cultural and social implications are for this study and according to other authors. For instance, any previous study regarding Crohn's Disease about Spanish Population? What about Social Support? Is it understood the same in both cultures?

Authors did not even mention the context description for each case, which is important when talking about "experiences" and "expectations" in Qualitative research. Moreover, the Crohn's Disease Organization and Management within the British and Spanish Health Systems are completely different and this situation is crucial to understand about the "expectations", "lived experiences" and "decisions made along the process".

The social and cultural approach of this study has not been exposed throughout the whole manuscript and not even in the "objectives" while this is one the manuscript's cores. The phenomenon studied seems to be the same or homogeneous in both cultures and this is an important flaw in Qualitative research.

About the identification of the theoretical framework, you said that they were based on other studies to start their own subjects, but they are no named or referred.

The schedule and structure that authors used in this manuscript seems to be the one usually implemented within quantitative research tradition. I would recommend authors to review especially the "Methods" section and the way the objectives have been exposed.

The Qualitative Method used in this study has not been explained and this is a key point for this sort of manuscript. Authors only say they used Qualitative Methodology and this is not enough. About the topics discussed, it is not clear that it includes all the subjects of the study in the same line. I think topics 1-2 are general, however 3, 4 and 5 are subtopics or even main themes for new lines of studies. It looks like topics 1-2 encompass all participants, while others only involve a part of the sample. I would recommend that you revisit the topics and sub-themes with the intention of clarify their priority.

There is no talk about any piloting about the interviews. Data collection its no clear. At the beginning there were three investigators in charge conducting interviews, but later he only two of them conducted the interviews. Clould you clarify this?. I have serious doubts about ensuring the validity of the interview method. I think the three contexts (home, hospital and Skype) seem adequate, but not at the same study, because there are external influences not collected that are very important when a qualitative interview is conducted.

With regard to the sub- theme of the sense of risk, only seems to give importance to the subject of the fertility sou you should renamed the sub-theme.

The sub-theme Self-management strategies and Strategies for coping and support are very similar so they could be merged

although I know that could be impossible with different groups. Because oh that I still think you should rephrase the topics There is not any specification about the way both cultural samples' data have been analysed. There is not any specification about the theoretical and/or conceptual approach of this qualitative manuscript.

Topic 5 states that it was on the part of a small group, what does this mean? It was two, three ...

Discussion stated that the factors affecting decision-making are shown, but this is not clear in the results. Also, at the discussion section, it is exposed that there are studies where the influence of being clear the objective of the treatment when deciding is studied, but I could find that at the results in no moment or referred to if this was taken into account when the analysis of the relats.

Some bibliographical references are obsolete. Number 4 and 5 have more than twenty years. I would suggest reviewing literature again to update and collect more recent studies of the same subject and objective.

You also alludes at the discussion how important language is when communicating a treatment, but in your study the language used to communicate it to the interviewees is not shown at any moment, reason why this affirmation can not be valued.

Although more factors appear in their results, it assures in the discussion that the only factor to choose the participation in the study was that they had no other option of treatment therefore that would be the only factor of decision making. Does not match results In my opinion you should redo the text and focus much and better on the goal, and ensure consistency between results and discussion.

REVIEWER	Lisa Kidd Robert Gordon University, Aberdeen
REVIEW RETURNED	20-Feb-2017

## **GENERAL COMMENTS**

I thought this was an interesting manuscript that aimed to explore the decision making perspectives and experiences of people with severe Cohn's disease participating in the ASTIC trial which for some, involved undergoing HSCT.

#### Overall:

Having read the full manuscript, I feel a little confused as to whether the main message in the manuscript was around the factors that influenced an individuals' decision to participate in the trial and subsequently, the need to balance participants' and researchers' perspectives (and intentions) in relation to clinical trial participation and to offer future recommendations around 'good practice' for involving people in trials who are at a potentially vulnerable crossroads in their lives. Or whether the main message was how participants decided upon, and experienced, undergoing HSCT and to offer future recommendations around supporting people undergoing this treatment in the future. I think that the data speaks to both of these purposes but perhaps could be more selective in parts (e.g. I'm not sure that reporting on theme 1 is entirely necessary to the argument?) and greater clarity is needed in the aims and objectives and in the discussion chapter to tie these together a bit more coherently as at present, for me, the discussion chapter sits a little separately from introduction and aims of the paper and the presentation of the results. The aim for example, reads 'with particular focus on peoples' expectations and decision

making in the context of autologous HSCT' which makes it sound like it's focussing on decision making relating to the treatment rather than decision making relating to participating in a 'clinical trial' per se.

On page 5, for example, the authors state that little is known about the sources of information that people with CD use to assist them in understanding the risks and benefits of participating in novel treatments and trials, however, the results do not appear to describe any instances where participants spoke of how their decision making was influenced by other sources of information and indeed the trial information and documentation itself. It appears that their participation in the trial, and thus HSCT, was largely driven by a lack of other treatment options as opposed to being part of a 'trial' per se.

Throughout the results sections in general, I felt that there needed to be a little more depth and perhaps some more examples added to more strongly illustrate the theme. I appreciate word count is a likely issue and I wonder whether the authors perhaps could make a decision on including the themes and findings that are only central to the main argument of the paper? Given that there were three different groups of participants, when using the word 'participants', I think more clarity is needed as to which group of participants the findings pertain to. I think that the subthemes would benefit from the inclusion of quotation examples from across the different groups, as it would be fair to say that the group 3 participants who were unable to undergo the treatment because of external factors, will still have participated in an initial decision making and deliberation process similar to those in Group 1 (however, there was no sense given of this in the paper). It would be good to include some examples from Group 2 participants to show how they perceived and deliberated about the treatment before coming to their decision not to participate. I would argue that some of the examples used to illustrate the themes do not demonstrate participants' own decision making processes but rather they are 'told' things or 'have things decided for them' e.g. in Hollie's case on page 21, it's not clear whether the decision to have the ileostomy was hers or taken by someone else - therefore is she strictly part of Group 2 if she didn't take part because a different treatment plan was chosen for her rather than by her?

There's inconsistency between the author's use of the term 'Crohn's Disease' and 'CD' throughout the paper. Spelling errors in places e.g. page 7 (Principal and Principle investigators spelt differently and 'trial' is misspelt on page 22.

Study limitations - these have not been acknowledged within the manuscript.

References - some of the references are missing a date.

Specific comments:

Page 5 - Introduction - I felt that the introduction could have benefited from a paragraph or two to describe the context of the ASTIC trial itself.

Page 8 - Table 1 - were the groups different in any of their characteristics - could this have been a factor involved in their decision making?

Page 10 - interviews - there's no detail on what was specifically asked in the interviews and what was asked of each group as presumably there were some slight differences in the questions for each group. For example were group 3 participants asked about their initial decision making processes and for those who wanted the treatment but were unable to take part in the trial, what was the impact of this for them in terms of managing their Crohn's and moving forward? The authors also commented that on two occasions family members were present for the interviews - how did this alter the dynamic of the interview? Did it add any more data that could have been reported on? If it didn't affect the interview in any

Page 9 - table 2 - repetition from the aims and objectives on page 6

Page 14 - I would argue whether reporting on theme 1 is central to the argument of the paper?

way then this needs to be clarified in the text.

Page 21 - 'remaining uncertainty or regret' subtheme - was there any data that suggested any of the participants in Group 1 who underwent the treatment experienced any negative impact of the treatment? I'm not sure what this subtheme specifically adds in relation to 'decision making' influences as such.

Page 22 - Discussion - the authors claim that the findings 'provide insight into the views of non-participants and for whom this outcome was not a result of personal choice and control' - I would argue however that the examples provided are heavily weighted towards how those in Group 1 (who had the treatment) made their decisions rather than the views of those in Groups 2 and 3 - I think if example quotes from participants in Groups 2 and 3 were included more within the body of the results section, then yes the paper could arguably address this claim but not how it currently reads.

Page 24 - Discussion - the authors state that 'while regular and written and verbal information about the benefits and risks were provided for some this was of lesser importance than an expectation that the treatment may provide direct personal benefit' - however, the findings presented do not allude to the information or other sources that participants drew on to make their decisions about participating in the trial. I think this sort of statement needs to be supported with direct evidence to make it clear that participants are valuing one over the other.

## **VERSION 1 – AUTHOR RESPONSE**

	Review comments	Author responses
	Reviewer 1	
	INCVICWOI I	
4	In my opinion the number of patients should contain all or a greater number of participants of the ASTIC trial, not only 5 sites, and an additional group of	Great clarity has been given on page 5 regarding the total population of the ASTIC trial as a whole, including the total number of sites included (of which 5 comprised the study population of this study).

	patients who where not part or any involvement in the work of ASTIC, which leads to a lack of interpretation.  Reviewer 2	
5	There is no mention of limitations, which requires a few sentences.	Action as per point 1 above
	Reviewer 3	
6	The way authors have exposed the "aims" and the "objectives" is confusing. I would recommend clarifying which the main aim/objective is and then which the specific ones are	Completed and further clarified on page 6. As recommended by reviewer, main aim refined and now focused on decision-making, with other more general 'experiences' removed from the paper to promote clarity of purpose.
7	In the "Introduction" there is a lack of information and literature references that could justify why Spanish and British samples have been used in this study and which the cultural and social implications are for this study and according to other authors. For instance, any previous study regarding Crohn's Disease about Spanish Population? What about Social Support? Is it understood the same in both cultures?	Additional literature added in relation to the burden of Chronic disease and Crohn's disease across European groups, UK sites also included Scottish participants. Have attempted to clarify clearer why additional country was included, acknowledging the differences however major cultural differences and health service provision did not emerge as key factors in the analysis. This is not to say that a larger sample size with greater emphasis on socio-economic, and health service factors would not have emerged and is identified as a limitation and recommendations for future research.
8	Authors did not even mention the context description for each case, which is important when talking about "experiences" and "expectations" in Qualitative research. Moreover, the Crohn's Disease Organization and Management within the British and Spanish Health Systems are completely different and this situation	We have now included further reference to a more European (including Spanish) context. Furthermore, cultural differences did not emerge as a key influencing factor on experiences reported of living with severe CD, nor the decision to participate/not participate in ASTIC trial. The authors acknowledge however that this may be due to the limited sample size from the Spanish population and therefore identified as a limitation of the study findings and recommendation for future research.

	is crucial to understand about the "expectations", "lived experiences" and "decisions made along the process".	
9	The social and cultural approach of this study has not been exposed throughout the whole manuscript and not even in the "objectives" while this is one the manuscript's cores. The phenomenon studied seems to be the same or homogeneous in both cultures and this is an important flaw in Qualitative research	As point 8 above
10	About the identification of the theoretical framework, you said that they were based on other studies to start their own subjects, but they are no named or referred.	We are unsure what this statement means, but think this refers to theoretical input into use of Framework approach. Example supporting references are now provided in relation to informing concepts and theories for the analysis on page 10.
11	The schedule and structure that authors used in this manuscript seems to be the one usually implemented within quantitative research tradition. I would recommend authors to review especially the "Methods" section and the way the objectives have been exposed.	Based on framework utilised by previous qualitative studies reported in BMJ open. Now include 'methods' section to differentiate clearly between overarching qualitative methodology and the methods chosen – page 6
12	The Qualitative Method used in this study has not been explained and this is a key point for this sort of manuscript. Authors only say they used Qualitative Methodology and this is not enough.	This is now considered in more depth on page 6, paragraph 2
13	About the topics discussed, it is not clear that it	The themes have received substantial alteration, acknowledging the greater clarity required to ensure the

	includes all the subjects of the study in the same line. I think topics 1-2 are general, however 3, 4 and 5 are subtopics or even main themes for new lines of studies. It looks like topics 1-2 encompass all participants, while others only involve a part of the sample. I would recommend that you revisit the topics and sub-themes with the intention of clarify their priority.	findings are more tightly focused on the overall aim. We hope we have now made it much clearer that the paper focuses specifically on, 'decision-making and expectations' and that the inclusion of the 'hard fought battle' and 'ASTIC trial experience' while important were diluting the key message. The topics have now been reduced to 4 themes, with a contextual description of 'the hard fought battle'. Additional supporting excerpts are now provided which aims to ensure each theme is more adequately represented and described in the words of participants.
14	There is no talk about any piloting about the interviews.	Now clarified on page 9, paragraph 1.
15	Data collection its no clear. At the beginning there were three investigators in charge conducting interviews, but later he only two of them conducted the interviews. Clould you clarify this?.	We hope this is now clear, there were three investigators in charge of interviews (JC, IB and AL). We have included further references to how IB and AL managed the Spanish interviews and transcription.
16	I have serious doubts about ensuring the validity of the interview method. I think the three contexts (home, hospital and Skype) seem adequate, but not at the same study, because there are external influences not collected that are very important when a qualitative interview is conducted.	This is considered on page 9, paragraph 3. We acknowledge the variation that the inclusion of these options bring, however clarify that this was also a recommendation of the PPI group which provided an important role in the design of the study to reflect the needs of participants for whom access to toilet facilities and choice over how they were interviewed was paramount. We have included this is a limitation of the study as while health/social contexts did not emerge as a key finding of the study, this may have reflected the smaller sample size of Spanish participants and/or the method of data collection.
17	With regard to the sub- theme of the sense of risk, only seems to give importance to the subject of the fertility sou you should renamed the sub- theme.	Please see comment 13 above. We have also added additional example to more accurately reflect that making sense of risk was associated with other aspects rather than just fertility and parenthood.

18	The sub-theme Self-management strategies and Strategies for coping and supoort are very similar so they could be merged although I know that could be impossible with different groups.  Because oh that I still think you should rephrase the topics	Please see comment 13 above.
19	There is not any specification about the way both cultural samples' data have been analysed. There is not any specification about the theoretical and/or conceptual approach of this qualitative manuscript.	Framework analysis section (page 10 paragraph 4) now identifies more clearly examples of theoretical concepts used to guide the analysis, including perceptions of control, self-management, decision-making. As also detailed, the emerging concept of therapeutic misestimation was also systematically applied to the transcript framework as the interviews developed and analysis conducted concurrently.
20	Topic 5 states that it was on the part of a small group, what does this mean? It was two, three	Unclear what this statement refers to, we hope that the work taken to add clarity to all themes now addresses this?
21	Discussion stated that the factors affecting decision-making are shown, but this is not clear in the results. Also, at the discussion section, it is exposed that there are studies where the influence of being clear the objective of the treatment when deciding is studied, but I could find that at the results in no moment or referred to if this was taken into account when the analysis of the relats.	As per comment 13 above. The re-focusing of the themes and excerpts on decision-making now includes examples of references to the use of language/terms such as 'good candidate', expectations of a cure and communication regarding eligibility.
22	Some bibliographical references are obsolete. Number 4 and 5 have more than twenty years. I would suggest reviewing literature again to update and collect more recent studies of the same subject and objective.	4 and 5 were seminal pieces of work relating to the development of these measures however now replaced by more recent applications. Updated references also provided for reference 1 and 2.

23	You also alludes at the	Please see con	nment 21 above.	
25	discussion how important	. 10030 366 0011	mion 21 above.	
	language is when			
	communicating a			
	treatment, but in your study			
	the language used to			
	communicate it to the			
	interviewees is not shown			
	at any moment, reason			
	why this affirmation can not			
	be valued.			
24	Although more factors	We have this is	addressed with changes referred to in	
24	appear in their results, it	comment 13 an	_	
	assures in the discussion	Comment 13 and 21.		
	that the only factor to			
	choose the participation in			
	the study was that they had			
	no other option of			
	treatment therefore that			
	would be the only factor of			
	decision making. Does not			
	match results			
	materresults			
25	In my opinion you should	Undertaken, tha	ank you for this invaluable advice.	
	redo the text and focus			
	much and better on the			
	goal, and ensure			
	consistency between			
	results and discussion.			
	Reviewer 4			
36	I feel a little confused as to w	hether the	Please see comment 13 above regarding re-	
	main message in the manuscript was		focusing of all themes on the core aim	
	around the factors that influenced an		regarding decision-making and expectations	
	individuals' decision to participate in the trial		in relation to HSCT.	
	and subsequently, the need t			
	participants' and researchers			
	(and intentions) in relation to			
	participation and to offer future			
	recommendations around 'go	•		
	involving people in trials who			
	potentially vulnerable cross-roads in their lives. Or whether the main message was how participants decided upon, and			
	experienced, undergoing HS			
	future recommendations arou			
	people undergoing this treatment in the			
	future. I think that the data s			
	of these purposes but perhap	os coula be		

	more selective in parts (e.g. I'm not sure that reporting on theme 1 is entirely necessary to the argument?) and greater clarity is needed in the aims and objectives and in the discussion chapter to tie these together a bit more coherently as at present, for me, the discussion chapter sits a little separately from introduction and aims of the paper and the presentation of the results. The aim for example, reads 'with particular focus on peoples' expectations and decision making in the context of autologous HSCT' which makes it sound like it's focussing on decision making relating to the treatment rather than decision making relating to participating in a 'clinical trial' per se.	
27	On page 5, for example, the authors state that little is known about the sources of information that people with CD use to assist them in understanding the risks and benefits of participating in novel treatments and trials, however, the results do not appear to describe any instances where participants spoke of how their decision making was influenced by other sources of information and indeed the trial information and documentation itself. It appears that their participation in the trial, and thus HSCT, was largely driven by a lack of other treatment options as opposed to being part of a 'trial' per se.	Please see comments 13 and 21 above, we acknowledged the need to revise the focus of the article and anticipate that the removal of two themes has aided this (keeping hard fought battle as a contextual factor).
28	Throughout the results sections in general, I felt that there needed to be a little more depth and perhaps some more examples added to more strongly illustrate the theme. I appreciate word count is a likely issue and I wonder whether the authors perhaps could make a decision on including the themes and findings that are only central to the main argument of the paper?	As above in comment 27.
29	Given that there were three different groups of participants, when using the word 'participants', I think more clarity is needed as to which group of participants the findings pertain to. I think that the subthemes would benefit from the inclusion of quotation examples from across the different groups, as it would be fair to say	Great breadth of examples in the results section have now been included which we anticipate articulates more clearly the findings and relevance to the study aim and discussion section.

	that the group 3 participants who were unable to undergo the treatment because of external factors, will still have participated in an initial decision making and deliberation process similar to those in Group 1 (however, there was no sense given of this in the paper).	
30	It would be good to include some examples from Group 2 participants to show how they perceived and deliberated about the treatment before coming to their decision not to participate. I would argue that some of the examples used to illustrate the themes do not demonstrate participants' own decision making processes but rather they are 'told' things or 'have things decided for them' e.g. in Hollie's case on page 21, it's not clear whether the decision to have the ileostomy was hers or taken by someone else - therefore is she strictly part of Group 2 if she didn't take part because a different treatment plan was chosen for her rather than by her?	Now included within all sections of the results, and in particular to this theme on Pages 20-21 where deliberations about non-participation are outlined in more detail.
31	There's inconsistency between the author's use of the term 'Crohn's Disease' and 'CD' throughout the paper. Spelling errors in places e.g. page 7 (Principal and Principle investigators spelt differently and 'trial' is misspelt on page 22.	Now corrected
32	Study limitations - these have not been acknowledged within the manuscript.	Now updated and also included on page 30
33	References - some of the references are missing a date.	Now corrected.
34	Page 5 - Introduction - I felt that the introduction could have benefited from a paragraph or two to describe the context of the ASTIC trial itself.	This now includes additional details about the ASTIC trial including total number of sites.
35	Page 8 - Table 1 - were the groups different in any of their characteristics - could this have been a factor involved in their decision making?	We do not wish to go in greater depth about characteristics due to the unique populations and risk to anonymity as agreed at ethical approval.
36	Page 9 - table 2 - repetition from the aims and objectives on page 6	Removed

37	Page 10 - interviews - there's no detail on what was specifically asked in the interviews and what was asked of each group as presumably there were some slight differences in the questions for each group. For example were group 3 participants asked about their initial decision making processes and for those who wanted the treatment but were unable to take part in the trial, what was the impact of this for them in terms of managing their Crohn's and moving forward?	Supplementary material 1 now included which provides an example of the provisional interview schedule used in all interviews.
38	The authors also commented that on two occasions family members were present for the interviews - how did this alter the dynamic of the interview? Did it add any more data that could have been reported on? If it didn't affect the interview in any way then this needs to be clarified in the text.	This is now clarified on page 9, paragraph 2.
39	Page 14 - I would argue whether reporting on theme 1 is central to the argument of the paper?	Now included as a contextual factor (and surrounding arrows to Figure 1) as recommended by the reviewer
	Page 21 - 'remaining uncertainty or regret' subtheme - was there any data that suggested any of the participants in Group 1 who underwent the treatment experienced any negative impact of the treatment? I'm not sure what this subtheme specifically adds in relation to 'decision making' influences as such.	Please see comments 13 and 21.
40	Page 22 - Discussion - the authors claim that the findings 'provide insight into the views of non-participants and for whom this outcome was not a result of personal choice and control' - I would argue however that the examples provided are heavily weighted towards how those in Group 1 (who had the treatment) made their decisions rather than the views of those in Groups 2 and 3 - I think if example quotes from participants in Groups 2 and 3 were included more within the body of the results section, then yes the paper could arguably address this claim but not how it currently reads.	Please see comments 13 and 21.
41	Page 24 - Discussion - the authors state	Please see comments 13 and 21.

that 'while regular and written and verbal information about the benefits and risks were provided for some this was of lesser importance than an expectation that the treatment may provide direct personal benefit' - however, the findings presented do not allude to the information or other sources that participants drew on to make their decisions about participating in the trial. I think this sort of statement needs to be supported with direct evidence to make it clear that participants are valuing one over the other.

## **VERSION 2 – REVIEW**

REVIEWER	Dr Karen Kemp
	Manchester Royal Infirmary, Manchester.
	University of Manchester, Manchester.
REVIEW RETURNED	28-Apr-2017
GENERAL COMMENTS	The authors have addressed each comment by the reviewers
REVIEWER	Lisa Kidd
	Robert Gordon University, Aberdeen, UK
REVIEW RETURNED	02-May-2017
GENERAL COMMENTS	Many thanks for your revisions on this manuscript. I am happy that
	the main areas that I identified have been addressed within the text
	and wish you the best of luck with future work in this field.