BMJ Open

Living with Crohn's Disease: An exploratory cross-sectional qualitative study into expectations, experiences and decision-making in relation to Autologous Haematopoietic Stem Cell Treatment (The DECIDES study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015201
Article Type:	Research
Date Submitted by the Author:	20-Nov-2016
Complete List of Authors:	Cooper, Joanne; Nottingham University Hospitals NHS Trust, ; Blake, Iszara; Nottingham University Hospitals NHS Trust Lindsay, James Hawkey, Christopher; University of Nottingham, NDDC
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Gastroenterology and hepatology, Qualitative research
Keywords:	Crohn's disease, Autologous Haematopoietic Stem Cell Treatment, QUALITATIVE RESEARCH, Decision-making

Title page

Living with Crohn's Disease: Expectations, Experiences and Decision-Making in Relation to Autologous Stem Cell Treatment (The DECIDES study)

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Key words: Crohn's Disease; Autologous Haematopoietic Stem Cell Treatment; Qualitative research; Decision-making

Word count: 5901

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Abstract

Background/Objectives: Severe Crohn's disease impacts negatively on individual quality of life, with treatment options limited once conventional therapies have been exhausted. The aim of this study was to explore expectations, decision making and balancing of risk in relation to the Autologous Haematopoietic Stem Cell Treatment trial (ASTIC).

Methods: An international, cross-sectional qualitative study, involving semi-structured face to face interviews across five sites (4 UK and 1 Spain). 38 participants were interviewed (13 men, 25 women; age range 23-67 years; mean age 37 years). The mean age at diagnosis was 20 years. Interviews were audio recorded and transcribed verbatim and transcripts analysed using a framework approach.

Results: Five themes emerged from the analysis: (1) The hard fought battle of living with Crohn's disease; (2) 'making your mind up' - a determination to receive stem cell treatment despite risks; (3) a journey of hopeful uncertainty; (4) the challenges of study non-participation; (5) Recovery and reframing of expectations.

Conclusions: Decision-making, expectations and experiences of people with severe Crohn's disease in relation Autologous Haematopoietic Stem Cell treatment is a complex process. This involved the impact on balancing of risk due to individual histories of battling with their condition, a willingness to consider novel treatment options and a general raised level of expectation about the benefits of trial participation. Discussions with patients who are considering treatment should take into account potential 'therapeutic misestimation', thereby enhancing shared decision-making, informed consent, and the experiences of those deemed non-eligible.

Strengths and limitations of this study

- This paper provides new knowledge about the complex process of decision-making and experiences of people with receiving Autologous Haematopoietic Stem Cell Treatment for Crohn's disease.
- Decision-making processes often begin well in advance of formal clinical consultation and are influenced by physical, psychological, socioeconomic and relational aspects of a person's life with severe chronic illness. The concept of Therapeutic Misestimation emerged from the findings as a factor influencing decision-making in some participants.
- Findings from this international, qualitative study can inform future research that develops decision making and information support tools for future participants in 'radical' or 'frontier' clinical trials such as HSCT.
- Future research should harness the strengths of longitudinal and mixed methods enquiry to capture outcomes in relation to those receiving Haematopoietic Stem Cell Treatment, and for those for whom trial participation proved not to be an option.

Introduction

Providing effective health care services for people affected by chronic illness is an international priority [1]. In England alone, there are approximately 15.4 million people living with a long-term condition, affecting people of all ages, and accounting for 70% of the total health and social care budget. Individuals commonly face challenges relating to physical disability, reduced employment opportunities and an increased likelihood of experiencing depression and anxiety disorders[2].

Crohn's disease is a chronic relapsing inflammatory condition predominantly affecting the gastrointestinal (GI) tract and is commonly associated with abdominal pain, fever, clinical signs of bowel obstruction or diarrhoea with passage of blood and/or mucus [3]. The potential impact that living with Crohn's Disease can have on individuals is recognised in validated tools measuring quality of life [4], disease related concerns [5] and personal control [6]. Researchers have identified a negative association with quality of life and increased clinical disease activity[7]. Common concerns about living with Crohn's disease including managing uncertainty, the effects of medication, reduced energy levels and fatigue[8], having surgery and being a burden on others [5].

Hematopoietic stem cell transplantation

Immunosuppressive drugs are standard treatment for people living with Crohn's disease, however for those that do not respond, or lose response to this therapy, treatment solutions become more challenging to address[9]. The Autologous Stem Cell Transplantation International Crohn's Disease trial (ASTIC) commenced in 2008, building on previous non-randomised studies that investigated the impact of Autologous Haematopoietic Stem Cell Transplantation (HSCT) in Crohn 's disease [10, 11]. The benefit of Autologous HSCT has been examined at length in autoimmune conditions including Rheumatoid Arthritis and Lupus Erythematosus [12] and the ASTIC trial presented the first international parallel-group randomized clinical trial evaluating its effect in patients with refractory Crohn's disease, with the primary end point being assessed after 1 year[9].

Trial outcome measures included health related quality of life[13], clinical activity, mucosal healing [14], and medication use. However feedback from participants, or those who had considered taking part, suggested there were other factors that had influenced their expectations and experiences of the trial, including how they viewed the personal benefits gained from taking part. This has particular importance in relation to decision-making as, while the benefits of HSCT are acknowledged [15, 16], it has the potential to induce significant side effects in comparison to conventional therapies, including death [17, 18].

Decision Making

The evidence base for effective shared decision-making between patient and clinician, informed consent and appropriate feedback of results is well established in relation to clinical trial participation[19, 20]. Best practice is one where a sense of alliance is developed between patients and clinical staff, where information is presented using appropriate language, and one that accounts for the needs of the individual [17]. Previous research shows the importance of providing support for clinical decision-making in addition to utilising decision aids and tools[21]. However, less is known about key influences on patient decision-making in CD and the sources of information they use to assist them to understand personal benefits and risks in this process. It is essential to understand more fully the decision making process and how patients balance risk when considering participation in novel treatments with uncertain and potentially significant risks[22] .

Methods

Setting

This study was conducted at five ASTIC study sites in the UK (n=4) and mainland Spain (n=1). All were publically funded, acute hospitals.

Aims

This study aimed to explore, describe and understand experiences of living with severe Crohn's disease, with particular focus on peoples' expectations and decision-making in the context of Autologous HSCT, as part of the ASTIC trial.

This included the views of individuals from three distinct groups:

Group 1: Those who had taken part in the ASTIC trial

Group 2: Those who had considered taking part and chose not to participate

Group 3: Those who had considered taking part in the trial and were not able to so due to factors outside their personal control, i.e. halting of recruitment to the trial, inability to secure funding[1].

3.2 Objectives

The aim was explored within three key objectives:

1. To identify participants' expectations and concerns about novel, radical treatments for severe CD, including decision- making processes, balancing potential risks and benefits and attitudes towards risk.
2. To describe experiences of HSCT participation within the ASTIC trial and strategies participants employed to respond to the demands of treatment
3. To identify recommendations for future support and information giving.

Participants

1. [1] The study protocol also allowed recruitment of adults over 18 whose severity of Crohn's disease made them eligible for HSCT but who had not had any contact with the ASTIC trial. However this was not required as sufficient numbers were recruited from groups 1-3 in order to achieve data saturation.

Participants were recruited through sites involved in the ASTIC trial, where they usually received care. Participants were eligible if they were 18 and over, were diagnosed with severe CD by their specialist IBD consultant (who were also Principal Investigators in this study) and had taken part or had considered participation in the ASTIC trial. Fifty eight prospective participants were identified by the ASTIC clinical trial coordinator and Principle Investigators. Recruitment was conducted in a staged process, using blocks of 10 participants at a time. This was done so as to avoid having to withdraw invitation to any participant who indicated they were willing.

Invitation letters in both English and Spanish were addressed from Principal Investigators (CJH, JS, ST, JL, ER), were accompanied by a copy of the Participant Information Sheet and consent forms. Reminder letters were sent after 21 days if no response was received. Willing participants were asked to return the Consent Form using a freepost envelope, after which the Clinical Researcher (IB), Chief Investigator (JC) or Spanish researcher (AL) contacted them to arrange an interview. General Practitioners were informed by letter of the patient's participation in study.

Participant characteristics

Forty responses were received indicating agreement to participate, however two subsequently withdrew without specific explanation, therefore thirty eight participants took part in the study. The mean age was 37 years (range 23-67), 66% (n=25) were female and 58% (n=22) had participated in the ASTIC trial. Table 1 illustrates the basic demographics of the sample used in the study.

Table 1. *Basic demographic and study characteristics (n=38)*

Characteristics	n
Gender	
Male	13
Female	25
Mean age (yrs)	37
Range	23-67
Mean age at diagnosis (yrs)	20
Study groups	
Group 1 ASTIC participants	22
Group 2 NON ASTIC participants	6
Group 3 NON ASTIC participants	10
UK Centre study groups	
Group 1 ASTIC participants	16
Group 2 NON ASTIC participants (by personal choice)	6
Group 3 NON ASTIC participants (by external factors)	10
Spanish Centre study groups	
Group 1 ASTIC participants	6

Participants were categorised into 3 groups, distinguishing Group 1 ASTIC participants from 'NON ASTIC' participants. 'NON ASTIC' participants (Groups 2 and 3) were separated according to the reason for their non-participation to aid clarity and depth of analysis and discussion (table 2).

Table 2. Summary of Group Categories

Group 1	**Group 2**	**Group 3**
'ASTIC participants'	'Non-ASTIC' participants(by choice)	'Non-ASTIC participants (by external factors)'
Participated in ASTIC trial (including those unable to complete the whole trial)	Participants who did not take part in the trial because they made the decision not to participate themselves or there was another more suitable treatment option available to them	Participants who did not take part in the trial due external factors, for example, non-eligibility, lack of funding, trial halting recruitment.

Ethical considerations

Prior to commencement of the study, ethical approval for the UK was gained from the Nottingham 2 REC committee [Reference number 13/EM/0176]. During the study, ethical approval was gained participants from La Agencia Española de Medicamentos y Productos Sanitarios in Spain (Madrid) before interviewing Spanish participants. The study was conducted in accordance with the principles of Good Clinical Practice and the Research Governance Framework for English Health and Social Care [23]. A protocol was devised directing participants to relevant sources of support should they were to become distressed when talking about their experiences, however this did not become necessary to enact.

Data collection

Interviews were conducted by three female researchers (IB, JC, AL). All interviewers had experience of conducting qualitative research interviews. JC had conducted qualitative research previously with participants with IBD in her prior role as an IBD nurse specialist [24], however had no prior contact with participants in this study. Only IB and AL (clinical researchers) conducted the Spanish interviews. IB is bilingual in English and Spanish, AL a native Spanish researcher. Face to face interviews were conducted with participants in their usual IBD clinic, at their home or via Skype® between August 2013 and July 2014. Signed consent was obtained prior to starting the interviews, for the Skype® interviews, verbal consent was recorded before commencing. A provisional interview topic guide was devised and informed by a patient and public reference group. The topic guide included additional probes for in-depth explorations of perceived expectations of HSCT, decision making and living with severe Crohn's disease.

The interviews lasted between 29 minutes and 1 hour 52 minutes, with the majority of interviews lasting around 45 minutes. All interviews were audio recorded. Of the 38 interviews conducted, 15 took place in participants' homes, 16 at their usual clinic and seven via Skype®. On two occasions immediate family members accompanied participants during their interview at participant's request. Data was collected until no new themes emerged and therefore we assumed data saturation was reached (n=38) [25].

Data analysis

The study was informed by Pragmatic philosophy, acknowledging the importance of the research question in choosing the best research approach that interests and is of value to the researcher and studying it in the different ways thought to be most appropriate [26].

All UK interviews were transcribed verbatim by a professional transcriber. Spanish interviews were conducted in Castellano (Spanish) and transcribed into an English summary by IB. Transcripts were anonymised of identifiable information prior to analysis being undertaken, pseudonyms applied and then analysed using a framework approach [30]. The names allocated to participants in the results section of this paper are the pseudonyms chosen.

Framework analysis has five key stages:

1. ***Familiarisation.*** Immersion in the data began from the time of the first interview. Interviews were read and re-read until a broad framework of themes was identified, reflecting key issues of commonality or diversity emerging from the data. Transcripts were analysed either by single sentence or paragraph. A computerised qualitative data management package (QSR NVivo version 10) and Microsoft Excel® were used to assist data management.

2) ***Identifying a thematic framework.*** Key issues, concepts and themes were identified from in-depth examination of the data. The analytic framework was guided by (although not restricted to) the key themes identified in the published literature relating to living with chronic illness, experiencing HSCT and recommendations for effective shared decision-making. As themes emerged, subsequent interviews were adapted to explore specific areas of importance, for example, fertility and understanding around the concept of ASTIC treatment as a potential 'cure'.

3) ***Indexing.*** Indices were developed with terms that reflected the language used by participants. This thematic framework was then applied systematically to each transcript.

4) ***Charting.*** The data was sorted according to the appropriate part of the thematic framework to which it relates. Each theme was focused on in detail, returning to the context in which the participants' statements were made. Charting of the data was done by organising and arranging the data into categories using headings and subheadings.

To enhance rigour and validity, interview transcripts were analysed separately by IB and JC in order to ensure transparency, accuracy and concordance when developing themes[27]. Prior to further discussion and presentation of the analysis with other members of the research team, transcripts were anonymised to remove identifiable information.

Preliminary findings were presented to the study Advisory Group which included experts of qualitative research and two members of a patient and public involvement (PPI) group. This group acted as 'critical friends' to the on-going research process. An in-depth description of the research analysis process, in addition to a reflective diary, was maintained in order to promote transparency of the data collection and analysis and later transferability of the findings. Transcripts were actively analysed for 'deviant cases'[27], such as experiences and expectations that did not concur with the majority in order to promote dependability of the data.

Results

Five major themes, incorporating 14 subthemes emerged that collectively captured the experiences of living with severe Crohn's disease and factors influencing decision- making, treatment expectations and, experiences of HSCT (see table 4). Pseudonyms are used when reporting participants' direct quotations.

Table 4 Summary of Themes and Sub-themes

	Themes	Sub-themes
Living with Crohn's Disease: expectations, experiences and decision-making in relation to autologous stem cell treatment	**Theme 1: '**The hard fought battle' of living with severe Crohn's disease	Physical symptoms and side effects of treatment Impact on social life, education, employment and family Self-management strategies
	Theme 2: 'Making your mind up'- decision making and balancing risk	Mind made up and 'having to know' Opportunity of hope or cure Fulfilling family duty Making sense of risk
	Theme 3 'A journey of hopeful uncertainty' – the ASTIC experience.	Pre-test and randomisation Challenges of treatment and isolation Strategies for coping and support
	Theme 4: 'Non-participation'- your choice or mine?	Missed opportunity or lucky escape Communicating end of trial participation
	Theme 5: Recovery, reflection and reframing personal benefit	Remaining uncertainty or regret Reframing personal benefit

Theme 1: 'The hard fought battle' of living with severe Crohn's disease

The first theme that emerged from the data illuminated the challenges of living with severe Crohn's disease and how it affected participants physical and social functioning and independence.

Subtheme 1a- Physical symptoms and side effects of treatment

All participant groups described having experienced similar levels of severity of Crohn's disease, and had faced significant challenges and battles when managing their condition. Commonalities among the group included the uncertain nature of CD and lack of control over physical symptoms, rapid and significant weight loss, stomach pain and cramps, bloody diarrhoea and nausea. Less common symptoms included mouth and lip ulceration, bruising on legs and anaemia.

> *" I was fourteen, and I constantly, didn't know what was up with me, constantly in the toilet, being sick or having diarrhoea, really, really weak...bruises really sore to touch. And then I had ulcers and blisters all on my lips and my mouth, so I wasn't eating anything"* **(Jane, Group 1)**

Participants reported a range of treatment side effects due to long term use of medications for their CD, including corticosteroids. This had resulted in an array of secondary health conditions including damage to the central nervous system, osteopenia, liver scarring, vertigo, delayed recovery from surgery, wound dehiscence, short bowel syndrome, intestinal failure and a dysfunctional stoma.

Subtheme 1b- Impact on social life, education, employment and family

Living with severe CD was often described negatively in relation to its impact on education and employment. Participants reported constantly 'pre-planning' and described a lack of spontaneity and resulting social isolation. Prolonged absences from school or work due to fatigue and pain were

common, in addition to missing exams, leaving university or work or being medically retired. CD commonly impacted on their social lives causing them to withdraw from social activities, often maintaining a small network of close friends and readjusting their expectations for the future.

> *"Think what I miss more and more, as time's gone on, is the ability to be spontaneous, you know, I try to have to plan what I'm doing all the time…I'll be planning from the moment I get up, hoping that I can plan my day"* **(Keith, Group 1)**

Subtheme 1c- Self management strategies

Participants shared how over time they have learned to adapt to living with severe CD, a process that also involved 'psychological adaptation' as the gravity of living with such a debilitating physical disease was often described as having a profound impact on life. For all participants, living with severe CD was described as a continual battle for control over its physical, psychological and emotional impact, for some with anger, frustration and for many, with periods of limited success.

> *"You have to become so that you're on the ball with everything, you have to make sure you've got all your orders in….you can become kind of that organised in your head, of everything that you've got to do… and it becomes so that your mind never stops and that can become really, really tiring and you just think, I just want to get up... but you can't. Because it's always there"* **(Hollie, Group 2)**

Theme 2: 'Making your mind up'- decision making and balancing risk

A key objective of the study was to explore the expectations that participants had of treatment, factors influencing their decision making and how they understood potential risks associated with HSCT. This theme illustrates a common pre-determination to undertake treatment by a number of

participants due to the limited alternative options they perceived were available, in addition to maximising the potential benefits they may gain from trial participation.

Subtheme 2a- Mind made up and 'having to know'

All participants in Group 1 described having reached a point where they had either exhausted all treatment options, including medications or surgery, or that other potential options were much less preferable to HSCT. Participants commonly described having 'no other choice' and that this treatment was a 'last hope'. In relation to consenting to the trial, the majority stated that their minds were made up in advanced of discussing the treatment with the trial clinicians.

> *"I never, ever thought I didn't want to do it…. But, before I'd even started, I'd made up my mind that I'd wanted to do it….Obviously, I took every - I spoke to a lot of people and I took in their opinion but I, no matter what they said, I still was adamant I was going to do it"* **(Claire, Group 1)**

Subtheme 2b- Opportunity of hope or cure

Participants reflected on their expectations of the benefits of HSCT when making their decision to participate. Most participants saw trial participation as an opportunity for hope and improvement to their condition. Predominantly this reflected a 'need to know' and the need to extinguish future doubt or uncertainty about its potential impact on their condition. The majority of participants had previously participated in clinical trials and for some the ASTIC trial was viewed as an opportunity to radically change their life, and as even a potential cure.

> *"I was told, this is the one, this is going to make you well"* **(Sally, Group 1)**

Subtheme 2c- Fulfilling family duty

A small number of participants said that their decision to participate was viewed as a process to be discussed with family members yet based mainly on individual choice supported by expert advice. One participant deviated from this however, describing how his decision to participate was strongly influenced by a relative who was a healthcare professional. Despite being unsure about the prospect undergoing such 'radical' treatment, he described feeling obligated to go ahead with the trial due to the burden his condition had already placed on the family.

> *"I would have felt that I was letting her down, she did all that for me….I'd feel like I was being rude almost"* **(Amy, Group 1)**

Subtheme 2d- Making sense of risk

Participants described varied concerns about potential risks of the treatment. Hair loss, impact on fertility, severity of the treatment, the association of chemotherapy with cancer and even death were mentioned as potential reasons not to participate. Nevertheless, for most, these concerns were outweighed by the possibility of responding well to the treatment as 'something to hold onto'.

Risks to fertility were described as an important concern and commonly not an issue considered in-depth until the topic arose during their initial consultation. A number made recommendations that earlier discussions and greater time to prepare for harvesting of eggs/sperm would have been beneficial, particularly if randomized to the early intervention.

> *"Because I thought, Well, I've been given this opportunity; do I just say No, because I'm a little bit nervous about things like losing my hair, it going wrong, do I really want to put myself through that knowing I might not really get much out of it at the end?"* ***(Natalia, Group 1)***

"Right, yeah, I'll have the chemo, I'll lose my hair, I'll maybe not be able to have kids, have to have my eggs frozen, it's a crazy thing at twenty one to think about, it's not something that you want to decide between either or". ***(Scarlett, Group 2)***

Theme 3 'A journey of hopeful uncertainty' – the ASTIC experience

Twenty two participants were recipients of treatment as part of the ASTIC trial. This was reflected under a theme of hopeful uncertainty, where participants employed strategies to minimise the challenges of undergoing the significant demands of treatment, including technology and social media.

Subtheme 3a- Pre-test and randomisation

Participants underwent a range of blood tests, endoscopic and radiological investigations as part of the pre-test experience, describing this stage as, 'every horrible test going', 'grim', and 'exhausting'.

The challenges and uncertainty of the randomization process were discussed by the majority of participants; eight participants had been randomized to the 'early arm' of the study (4 weeks) and were unanimous that they were pleased about early randomization as early treatment was seen as 'the sooner the better'. Having to wait on 'the long arm' (59 weeks- late randomization) was viewed by them as bringing further doubt as it allowed time to dwell on uncertainties and was described as 'the worst thing to wait' and 'like life being on hold'.

"I was on the straightaway, thank God….there's a bit of anxiety, because I was so ill, I didn't want to wait twelve months". **(Sally, Group 1).**

Subtheme 3b- Challenges of treatment and isolation

In describing their experience of undergoing HSCT, participants were almost unanimous in describing it as, 'tough', 'heavy' and even 'brutal', specifically both stages of chemotherapy. For some, significant psychological impacts were experienced due to the intensity of treatment. Participants described the side effects of chemotherapy including nausea, head and noise sensitivities, allergic reactions, feeling as though feet were broken and even 'smelling like sweetcorn'.

> *"Because I did, I had the long trial, I had like a year in the middle. That was pretty awful... It just felt like you were waiting, just your whole life was on hold, basically...So, yeah, that was very upsetting when I found out. [laughs] Because I just wanted it to carry on. I, I just wanted to do it all in six months rather than having a year in the middle dragging everything out"* **. (Claire, Group 1)**

Subtheme 3c- Strategies for coping and support

Participants commonly described the importance of social support as a coping strategy during treatment for the ASTIC trial. Support from friends and family was important in addition to support from participants who had previously experienced the trial treatment. Participants described the benefits of speaking to others who had experienced HSCT and the importance of peer social support. Furthermore, it was suggested that psychological support be made available whilst undergoing HSCT.

Technology including laptops, DVDs, media tablets, and mobile phones were referred to as effective coping tools when undergoing treatment. Other strategies included making a routine for the day, such as getting dressed, scheduling a shower or taking a walk. Communication to friends and family was also important to participants who described their appreciation for Skype® and FaceTime® in normalising the treatment process.

"But, I had Skype, which is fantastic, absolutely amazing, that was just brilliant...Because each day, I was making the effort to get up and have a shower and get dressed and, you know, at least, try and be as normal as possible". **(Hannah, Group 1)**

Theme 4: 'Non-participation'- your choice or mine?

Sixteen participants did not receive HSCT and were sub-divided into Groups 2 and 3. Group 2 represented those chose not to participate in the trial, whereas Group 3 comprised those who were unable to participate due to external factors such as the trial halting, non-eligibility or lack of funding. When reflecting on non-participation, participants most commonly described positive reflections on their decision. For those unable to influence this decision however this was more commonly reported as a missed opportunity and where effective communication of ineligibility was paramount.

Subtheme 4a- Missed opportunity or lucky escape

Participants in Group 3 (n=6) particularly reflected upon how they felt upon learning that they were no longer able to participate in the trial. The majority described accepting that the participation in the trial was probably not the best option for them, and while some had been initially disappointed, they described later feeling relieved.

"Erm. … I felt like, I felt, it was mixed feelings. It was like, mm, is it a missed opportunity or a lucky escape? **". (Saskia, Group 3)**

Subtheme 4b- Communicating end of trial participation

The majority of non-participants (n=10) had not received treatment due to factors outside their immediate control, for those for who viewed HSCT as a 'last chance', this was disappointing. The

way in which non-eligibility was communicated had particular relevance, illustrated by one participant who had placed great hope on receiving HSCT as a potential 'cure'.

> *"You tell your mum and you tell your daughters that you might be able to have the stem cell transplant and it means a cure, my eldest daughter was with me, when I went for that interview at the hospital… We got married earlier, we rushed to buy a house, we wanted to get settled, he [husband] got a new job, moved area, he took a less paid job because we were made to believe I was going to be having the treatment and it all fell through with just that letter [detailing her non-eligibility]".* ***(Rebecca, Group 3)***

Theme 5: Recovery, reflection and reframing personal benefit

The final theme captured the experiences of a small group of participants who described ongoing uncertainties about their condition following HSCT. This was particularly prominent when participants reported the onset of new physical symptoms or side effects due to prolonged medication prior to trial participation.

Subtheme 5a- Remaining uncertainty or regret

A minority described negative perceptions about the outcomes they have achieved. As exemplified in Hollie's statement below, undergoing such radical treatment without personal benefit led to ongoing disappointment. One participant, who decided to take another treatment option (ileostomy) rather than HSCT, described ongoing regret as having the ileostomy had made her experience of Crohn's disease substantially worse.

> *"I got offered the opportunity to do stem cell which went all the way through to the point of virtually going to do it, made the decision…[but] they thought the only thing left to do then was to give me the ileostomy bag….so, now, I had the ileostomy, regrettably for me now*

because I don't actually think it's done anything to help me…. It's made me worse. And, I, I regret the day I ever had it, I just wish that I'd had the stem cell done". **(Hollie, Group 2)**

Subtheme 5b- Reframing personal benefit

The majority of Group 1 participants reflected positively on the change that HSCT had made to their condition and quality of life. Most spoke of their gratitude at being given the chance to participate in the trial and spoke positively about being able to fulfil their 'need to know'. A number of participants described positive benefits in terms of eliminating previous symptoms or reducing the amount of medication they required. Participants also detailed how the treatment had enabled them to increase spontaneity, and to re-engage in activities due to a greater degree of energy and reduced fatigue.

"But I have managed to take myself off a couple of my medication. So I have, for me, as I look at it, I have got something out of it". **(Natalia, Group 1)**

Discussion

This study provides new knowledge about the experiences of people living with severe Crohn's disease, and in particular, factors affecting their decision-making and experiences of participation in Haematopoietic Stem Cell Treatment (HSCT) as part of the ASTIC study. Uniquely, it provides insight into the views of non-participants, and for whom this outcome was not a result of personal choice and control. Previous research has identified the importance of supporting patients with Crohn's disease to manage the often uncertain and unpredictable nature of their condition [24], this study further expands this to the context of clinical trial participation, both for recipients of trail treatment and those deemed ineligible.

Participants identified living with severe CD as a challenging and often complex balance of adaptation, self-management and acceptance of the restrictions to daily life. It involved prolonged periods of relapse or, for some, having never felt in remission since diagnosis. These findings are congruent with the broader literature on living with chronic illness [28-30], concerns about IBD and its impact on quality of life [31, 32], and findings from other IBD qualitative investigations [24, 33-36]. However for the first time, identifies how this 'hard fought battle' was a key driving factor when considering ASTIC trial participation and its associated risks and benefits.

Therapeutic Misconception and Misestimation and Decision-making

Although not considered specifically at the outset of this study, Therapeutic Misconception and in particular, Therapeutic Misestimation emerged as influencing factors in how a number of participants described their expectations and decision-making about ASTIC study participation.

Coined by Appelbaum and colleagues in 1982 [37, 38], Therapeutic Misconception refers to a phenomenon where individuals do not understand that the core objective of clinical trial research is to produce generalizable knowledge, rather than direct personal benefit, thereby conflating the aims of research with clinical care . Researchers have stressed the importance of allowing for Therapeutic Misconception to ensure effective decision-making and informed consent to trials[39, 40] .

Expanding on the concept of Therapeutic Misconception, Horng and Grady [41] outline a related concept, 'Therapeutic Misestimation' , where there is disconnect between the likelihood of personal benefit or risk from individual participation (summarised in Table 3).

Table 3 – Summary of Therapeutic Misconception and, Misestimation (adapted from Horng and Grady [24])

Concept	Definition	Ethical Significance
Therapeutic Misconception	The research participant conflates research with clinical care	*Rarely* tolerable because understanding the nature of research is necessary for an autonomous decision to participate in research
Therapeutic Misestimation	The research participant underestimates risk, overestimates benefit, or both	*Sometimes* tolerable because understanding the exact probability of harm and benefit may not be necessary for an autonomous decision to participate in research

Decision-making in relation to trial participation was commonly predetermined and 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 this treatment may provide direct personal benefit. This suggests an element of Therapeutic Misconception in some cases. Daugherty et al [42] suggest that research participants may experience difficulty in distinguishing the differences between the therapeutic and research components of a trial, highlighting the vulnerability of trial participants when faced with limited treatment options.

Participants in Group 1 (who took part in ASTIC) were unanimous that they had reached a point where other treatment options were either unavailable or less preferable than HSCT. Shannon-Dorcy and Drevdahl [43] identified a similar decision making strategy in their qualitative study of HSCT in cancer, exploring the views of patients (n=25) and caregivers (n=20). Key influencing factors were having no other option, seeking a cure and trusting the recommendations of home oncologists. Similarly Snowden et al's [44] survey of patients with Rheumatoid Arthritis, described a willingness to take mortality-related risks from HSCT in order to return to normality off all medication, particularly those with significant disability. While participants in the current study were not facing a cancer diagnosis (and potential end of life outcomes), they had experienced significant disability and impact

on life from CD. It is noteworthy therefore that decisions about risk and likelihood of individual success in novel treatments for severe CD may be influenced by Therapeutic Misestimation.

Although expectations about personal benefits and outcomes varied across the three groups, the ASTIC trial was viewed by many an opportunity to improve symptom control or treatment tolerance and by some as a potential cure. Similar to findings in the current study, Lidz *et al*. [45] identified that 24% of participants reported no risks or disadvantages to participation, even though they had been informed about such risks. This may go some way to explain why a number of participants focused predominantly on the positive likelihood of benefit from trial participation and interpreted positive outcomes of other participants as indicators that they too would experience the same.

Where participants were able to proceed with treatment, reflections on individual benefits were positively reframed or reprioritised [46]. Having extinguished the 'need to know', participants were often able to make greater sense of the future, despite health-related uncertainties and limited quantitative benefits in some cases.

Coolbrandt and Grypondck's [47] mixed model qualitative study, specifically identified the courage and continued hope for a positive outcome in HSCT treatment. The recurring theme of 'being out of options' again provided a driving force for persistence and coping strategies that participants employed to minimise the challenges of cancer treatment, including coping with isolation, treatment side effects, and maintaining beliefs in a happy ending. The current study provides new insights into the coping strategies and support needs of people with severe CD undergoing HSCT, including the use of technology and social support to overcome isolation and the challenges of late versus early randomisation which brought repeated hair loss and concerns for ongoing trial eligibility.

Agrawal and Emanuel [48] stated that there is no gold standard or a specific criterion that determines the reliability or validity of trial information comprehension by potential participants- and that it is to be judged on face validity. Studies have examined the use of language in consent forms and identified numerous inclusions of broad statements such as "you may or may not benefit" with

statements such as "the hope is that we can improve your symptoms and prolong your life with this treatment", and used terms such as "research" and "treatment" interchangeably [49]. These studies suggest that researchers can and should guard against encouraging the Therapeutic Misconception, both in informed consent forms and in publications. Findings from this current study also identify the importance of minimizing potential Therapeutic Misconception and Misestimation resulting from all communication interventions, including public meetings, face-to-face consultations and during the eligibility stages of clinical trial participation. Agreement about the communication of trial results, including the outcome of tests for eligibility is a key factor in this experience, and identifies the benefit that individualised communication plans could offer [50].

Conclusions and implications

Decision-making, expectations and experiences of people with severe CD in relation to HSCT is a complex process, involving a history of battling with the condition, a willingness to consider novel treatment options and a general raised level of expectation about the benefits of trial participation. Decision-making processes often begin well in advance of formal clinical consultation and are influenced by physical, psychological, socioeconomic and relational aspects of a person's life. Benefits described by participants receiving the treatment may be more subtle than those captured on standard quality of life questionnaires, where 'improved quality' may be related to having extinguished the doubt of knowing whether the treatment would have direct personal benefit.

Author contributions:

1. Dr Joanne Cooper – study chief investigator. Main author of the paper, leading each section from grant capture, study design, data collection, analysis and each section of this paper.
2. Miss Iszara Blake – clinical researcher. Second author of the paper, involved in data collection, analysis, interpretation and drafting each section of this paper.
3. Dr James O Lindsay – study principal investigator at Barts Health NHS Trust. Contributed to participant recruitment, and overall review of the paper.
4. Prof CJ Hawkey – study principal investigator at Nottingham University Hospitals NHS Trust. Senior advisor to the study (also chief investigator of the ASTIC trial). Contributed to grant capture for this study, participant recruitment, data interpretation and overall review of the paper.

Conflicts of interest

Each author has confirmed the following:

1. Dr Joanne Cooper – no conflicts of interest to declare
2. Miss Iszara Blake – no conflicts of interest to declare
3. Dr James O Lindsay - no conflicts of interest to declare
4. Professor CJ Hawkey - no conflicts of interest to declare

Funding

This work was funded by Crohn's and Colitis UK Living with IBD Award

Data sharing statement

A podcast is under development using additional participant statements which will be available free of charge once completed and via request to the study CI. Otherwise no additional data is available due to the consent taking at the time of participant recruitment.

Acknowledgements

We are indebted to the individuals who freely gave their time to participate in this research. Sincere thanks also to Dr Jack Satsangi, Dr Eleanor Ricart and Dr Alicia Lopez who provided support in recruiting participants to this study.

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Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the interview or focus group?	9 - Methods
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Author information
3. Occupation	What was their occupation at the time of the study?	6 - Methods and author information
4. Gender	Was the researcher male or female?	9 - Methods
5. Experience and training	What experience or training did the researcher have?	Methods
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	9
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	N/A
8. Interviewer characteristics	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	9 - Methods
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	9 & 10 Methods
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Methods
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	6 - Methods
12. Sample size	How many participants were in the study?	6 - Methods
13. Non-participation	How many people refused to participate or dropped out? Reasons?	6 - Methods
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	9 - Methods
15. Presence of non-	Was anyone else present besides the	9Methods

participants	participants and researchers?	
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	7 - methods
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	9 – N/A
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	N/A
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	9 - Methods
20. Field notes	Were field notes made during and/or after the inter view or focus group?	11 Methods
21. Duration	What was the duration of the inter views or focus group?	9 - Methods
22. Data saturation	Was data saturation discussed?	9 - Methods
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	N/A
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	10 -11 Methods
25. Description of the coding tree	Did authors provide a description of the coding tree?	N/A
26. Derivation of themes	Were themes identified in advance or derived from the data?	10 Methods
27. Software	What software, if applicable, was used to manage the data?	10 - NVivo
28. Participant checking	Did participants provide feedback on the findings?	11 - Methods
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	13-21 - Results
30. Data and findings consistent	Was there consistency between the data presented and the findings?	13-21 Relationship to existing knowledge
31. Clarity of major themes	Were major themes clearly presented in the findings?	12 - Results
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	13 – 25 - Discussion

BMJ Open

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)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015201.R1
Article Type:	Research
Date Submitted by the Author:	20-Apr-2017
Complete List of Authors:	Cooper, Joanne; Nottingham University Hospitals NHS Trust, ; Blake, Iszara; Nottingham University Hospitals NHS Trust Lindsay, James Hawkey, Christopher; University of Nottingham, NDDC
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Gastroenterology and hepatology, Qualitative research
Keywords:	Crohn's disease, QUALITATIVE RESEARCH, Decision-making, Autologous Haematopoietic Stem Cell

Title page

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)

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Key words: Crohn's Disease; Autologous Haematopoietic Stem Cell Treatment; Qualitative research; Decision-making

Word count: 7877

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Abstract

Background/Objectives: Severe Crohn's disease impacts negatively on individual quality of life, with treatment options limited once conventional therapies have been exhausted. The aim of this study was to explore factors influencing decision making and expectations of people considering or participating in the Autologous Haematopoietic Stem Cell Treatment trial (ASTIC).

Methods: An international, cross-sectional qualitative study, involving semi-structured face to face interviews across five sites (4 UK and 1 Spain). 38 participants were interviewed (13 men, 25 women; age range 23-67 years; mean age 37 years). The mean age at diagnosis was 20 years. Interviews were audio recorded and transcribed verbatim and transcripts were analysed using a Framework approach.

Results: Four themes emerged from the analysis: (1) 'Making your mind up' - a determination to receive stem cell treatment despite potential risks; (2) Communicating and understanding risks and benefits; (3) Non-participation – your choice or mine?; (4) Recovery and reframing of personal expectations.

Conclusions: Decision making and expectations of people with severe Crohn's disease in relation Autologous Haematopoietic Stem Cell treatment is a complex process influenced by participants' histories of battling with their condition, a frequent willingness to consider novel treatment options despite potential risks and a, in some cases, a raised level of expectation about the benefits of trial participation. Discussions with patients who are considering novel treatments should take into account potential 'therapeutic misestimation', thereby enhancing shared decision-making, informed consent, and the communication with those deemed non-eligible.

Strengths and limitations of this study

- This paper provide new knowledge about the factors that may influence decision-making and expectations of people considering and receiving Autologous Haematopoietic Stem Cell Treatment for Crohn's disease.
- We focused on the factors influencing decision-making and expectations of individuals with severe CD, an important yet often excluded group of participants in studies due to the severity of their disease. We also examined decision-making by participants and non-participants in a trial, the latter being often excluded from study results or the impact that non-participation may have on their experiences.
- Findings from this international, qualitative study can inform future research that develops decision making and information support tools for future participants in 'radical' or 'frontier' clinical trials such as HSCT.
- Face-to-face semi-structured Interviews were conducted at only one time-point and did not explore in-depth the cultural and specific health care service factors that may have influenced participants' decision-making and trial experiences across study sites. Future research should harness the strengths of longitudinal study designs taking greater account of the impact of individual, socio-economic, cultural and health service factors to capture outcomes in relation to those receiving Haematopoietic Stem Cell Treatment, and for those for whom trial participation proved not to be an option.
- In response to stakeholder recommendations, interview settings involved a choice between undertaking an interview at home, in a hospital interview room or via Skype®. Although this had strengths in allowing participation for those who lived in rural settings, or for who travel was not desired, we cannot exclude the impact that different settings may have had on the impact of the quality of data collected and the impact of the researcher when using such diverse methods.

INTRODUCTION

Providing effective health care services for people affected by chronic illness is an established global priority[1] . European data on the most frequently recorded chronic illnesses identifies that, while an ageing population is a key factor in the increasing incidence of single and multiple conditions, chronic illness increasingly affects younger populations and experiences of care may be impacted by national and regional variations in care provision[2].

In England for example, there are approximately 15.4 million people living with a long-term condition, affecting people of all ages, and accounting for 70% of the total health and social care budget. Individuals commonly face challenges relating to physical disability, reduced employment opportunities and an increased likelihood of experiencing depression and anxiety disorders[3].

This paper reports on a qualitative exploration of decision-making and expectations of people living with Crohn's disease (CD) in the context of Autologous Hematopoietic Stem Cell Transplantation (HSCT). CD is a life-long, chronic relapsing inflammatory condition predominantly affecting the gastrointestinal tract and is commonly associated with abdominal pain, fever, clinical signs of bowel obstruction or diarrhoea with passage of blood and/or mucus [4, 5].

The potential impact of living with CD can have on individuals is recognised in validated tools measuring quality of life [6], disease related concerns [7] and personal control [8]. Researchers have identified a negative association with quality of life and increased clinical disease activity[9]. Common concerns about living with CD including managing uncertainty, the effects of medication, reduced energy levels and fatigue[10], having surgery and being a burden on others [11].

Incidence of CD is increasing almost worldwide with increasing trends in industrialized developing countries [12, 13]. An estimated 1.6 million people in Europe are living with CD with the highest prevalence rates in northern countries [14]. There is growing evidence of European wide approaches to treatment interventions and management strategies [15], however variation exists in the delivery

of health care systems, for example, regional variation of provision in Spain [16] which may have relevance to the current study's generalisability.

Hematopoietic stem cell transplantation

Immunosuppressive drugs are standard treatment for people living with CD, however for those that do not respond, or lose response to this therapy, treatment solutions become more challenging to address[17]. The Autologous Stem Cell Transplantation International CD trial (ASTIC) commenced in 2008, building on previous non-randomized studies that investigated the impact of Autologous HSCT in CD [18, 19]. The ASTIC trial was conducted in 11 European transplant units from July 2007 to September 2011, with follow-up through March 2013. Patients were aged 18 to 50 years with impaired quality of life from refractory Crohn disease not amenable to surgery despite treatment with 3 or more immunosuppressive or biologic agents and corticosteroids [17]. The benefit of Autologous HSCT has been examined at length in autoimmune conditions including Rheumatoid Arthritis and Lupus Erythematosus [20] and the ASTIC trial presented the first international parallel-group randomized clinical trial evaluating its effect in patients with refractory CD, with the primary end point being assessed after 1 year[17].

Trial outcome measures included health related quality of life[21], clinical activity, mucosal healing [22], and medication use. However, anecdotal feedback from those who had undertaken HSCT, and those who had considered taking part, suggested there were other factors that had influenced their expectations and decision-making about the trial, including how they viewed the personal benefits gained from taking part. This has particular importance in relation to decision-making as, while the benefits of HSCT are acknowledged [23-25], it has the potential to induce significant side effects in comparison to conventional therapies, including death [26-28].

Decision Making

The evidence base for effective shared decision-making between patients and clinicians, informed consent and appropriate feedback of results is well established in relation to clinical trial participation[29, 30]. Best practice is one where a sense of alliance is developed between patients and clinical staff, where information is presented using appropriate language, and one that accounts for the needs of the individual[31]. Previous research shows the importance of providing support for patient decision-making in addition to utilising decision aids and tools[32]. However, little was known about key influences on patient decision-making in CD and the sources of information they use to assist them to understand personal benefits and risks, with no previous studies investigating this in relation to HSCT. It is essential to understand more fully the decision-making process and how patients balance risk when considering participation in novel treatments with uncertain and potentially significant risks[33] .

METHODS

The study was informed by Pragmatic philosophy, acknowledging the importance of the research question in choosing the best research approach that interests and is of value to the researcher and studying it in the different ways thought to be most appropriate [34]. The study employed the strengths of qualitative research methodology to fill an important gap in the understanding of decision-making and expectations in CD. We acknowledge that qualitative research embodies diverse, even conflicting theoretical positions [35]. However, it was the broad principles of qualitative inquiry that were adopted within this study, namely the ability to uncover social processes, opinions and experiences of the decision-making process and how this reflected initial expectations of participants [36].

Study design and context

The overall aim of this study was to explore, describe and understand peoples' decision-making and expectations in relation to Autologous HSCT for severe CD. In addition to interviews with ASTIC trial participants, this study also aimed to explore decision-making and expectations of those for whom initial trial assessment resulted in ineligibility, or those who declined participation by personal choice.

Sampling and recruitment

This study was conducted at five ASTIC study sites, four sites in the UK and one Spanish regional site. UK and Spanish hospitals were publically funded, acute, inner city university teaching hospitals, providing specialist gastrointestinal and haematological services across a healthcare region. It was acknowledged that variations between health care provision models and cultures between UK and Spanish sites was a potential influencing factor, however the number of Spanish participants recruited to the study made effective exploration of cultural contexts a limiting factor to this study.

Participants were eligible if they were 18 and over, were identified as having severe CD by their specialist IBD consultant (who were also Principal Investigators in this study) and had taken part, or had considered participation, in the ASTIC trial. Fifty eight prospective participants were identified by the ASTIC clinical trial coordinator and Principal Investigators. Recruitment was conducted in a staged process, using blocks of 10 participants at a time. This was done so as to avoid having to withdraw invitation to any participant who indicated they were willing to do so.

Invitation letters in both English and Spanish were addressed from Principal Investigators (CJH, JS, ST JL, ER), were accompanied by a copy of the Participant Information Sheet and consent forms. Reminder letters were sent after 21 days if no response was received. Willing participants were asked to return the Consent Form using a freepost envelope, after which the Clinical Researcher (IB),

Chief Investigator (JC) or Spanish researcher (AL) contacted them to arrange an interview. General Practitioners were informed by letter of the patient's participation in study.

Participants were categorised into 3 groups, distinguishing Group 1 'ASTIC participants', or those who had received HSCT, from 'NON ASTIC' participants. 'NON ASTIC' participants (Groups 2 and 3) were separated according to the reason for their non-participation to aid clarity and depth of analysis and discussion (table 2).

Table 2. Summary of Group Categories

Group 1	**Group 2**	**Group 3**
'ASTIC participants'	'Non-ASTIC' participants(by choice)	'Non-ASTIC participants (by external factors)'
Participated in ASTIC trial (including those unable to complete the whole trial)	Participants who did not take part in the trial because they made the decision not to participate themselves or there was another more suitable treatment option available to them	Participants who did not take part in the trial due external factors, for example, non-eligibility, lack of funding, trial halting recruitment.

Ethical considerations

Prior to commencement of the study, ethical approval for the UK was gained from the Nottingham 2 REC committee [Reference number 13/EM/0176]. During the study, ethical approval was gained participants from La Agencia Española de Medicamentos y Productos Sanitarios in Spain (Madrid) before interviewing Spanish participants. The study was conducted in accordance with the principles of Good Clinical Practice and the Research Governance Framework for English Health and Social Care [37]. A protocol was devised directing participants to relevant sources of support should

they were to become distressed when talking about their experiences, however this did not become necessary to enact.

Data collection

Interviews were conducted by three female researchers (IB, JC, AL). All interviewers had experience of conducting qualitative research interviews. JC had conducted qualitative research previously with participants with IBD in her prior role as an IBD nurse specialist [38], however had no prior contact with participants in this study. Only IB and AL (clinical researchers) conducted the Spanish interviews. IB is bilingual in English and Spanish, AL a native Spanish researcher.

A provisional interview topic guide (see online supplementary material Appendix 1) was devised with topic themes informed by a patient and public involvement group with expertise in gastrointestinal conditions. The topic guide included additional probes for in-depth explorations of perceived expectations of HSCT, decision making and living with severe CD. It was piloted with two UK participants including ongoing revision of the schedule as interviews progressed and concurrent data analysis undertaken.

Face to face interviews were conducted with participants according to their preferred method; in their usual IBD clinic, at their home, or via Skype® where participants were at home and the researchers interviewing from the hospital. While this introduced varied social contexts in which the interviews were conducted, they reflected recommendations of the study patient and public advisory group and allowed participation of participants who identified this as a preference, including participants who lived large distances from their hospital and for whom ongoing physical symptoms of CD limited their willingness for home visits or travel. Iacono et al [39] acknowledge the challenges such forms of communication can bring on the ability to interpret non-verbal cues

language and rapport, they also work well as a viable alternative or complimentary data collection tool for qualitative researchers.

Interviews were conducted between August 2013 and July 2014. Signed consent was obtained prior to starting all interviews except for those by Skype® where verbal consent was confirmed and recorded before commencing.

The interviews lasted between 29 minutes and 1 hour 52 minutes, with the majority of interviews lasting around 45 minutes. All interviews were audio recorded. Of the 38 interviews conducted, 15 took place in participants' homes, 16 at their usual clinic and seven via Skype®. On two occasions immediate family members accompanied participants during their interview at participant's request however they did not contribute to the discussion. Data was collected until no new themes emerged and therefore we assumed data saturation was reached (n=38) [40].

Data analysis

All UK interviews were transcribed verbatim by a professional transcriber. Spanish interviews were conducted in Castellano (Spanish)(by AL and IB) and transcribed into an English summary by IB. Transcripts were anonymised of identifiable information prior to analysis being undertaken, pseudonyms applied and then analysed using a framework approach [41].

Framework analysis has five key stages:

1. Familiarisation. Immersion in the data began from the time of the first interview. Interviews were read and re-read until a broad framework of themes was identified, reflecting key issues of commonality or diversity emerging from the data. Transcripts were analysed either by single sentence or paragraph. A computerised qualitative data management package (QSR NVivo version 10) and Microsoft Excel® were used to assist data management.

2) Identifying a thematic framework. Key issues, concepts and themes were identified from in-depth examination of the data. The analytic framework was guided by (although not restricted to) the key themes identified in the published literature relating to living with chronic illness [42], experiencing HSCT[43] and recommendations for effective decision-making [44]. As themes emerged, subsequent interviews were adapted to explore specific areas of importance, for example, fertility and early menopause, understanding around the concept of ASTIC treatment as a potential 'cure' [45] and therapeutic misestimation[46, 47].

3) Indexing. Indices were developed with terms that reflected the language used by participants. This thematic framework was then applied systematically to each transcript.

4) Charting. The data was sorted according to the appropriate part of the thematic framework to which it relates. Each theme was focused on in detail, returning to the context in which the participants' statements were made. Charting of the data was done by organising and arranging the data into categories using headings and subheadings.

(5) *Mapping and interpretation*. The charts were then used to illustrate and define the concepts, map the range and nature of expectations and decision-making that participants described.

Rigour

To enhance rigour, interview transcripts were analysed separately by IB and JC in order to maximise transparency, accuracy and concordance when developing themes[48]. Prior to further discussion and presentation of the analysis with other members of the research team, transcripts were anonymised to remove identifiable information.

Preliminary findings were presented to the study Advisory Group which included experts of qualitative research and two members of the patient and public involvement (PPI) group. This group acted as 'critical friends' to the on-going research process. An in-depth description of the research

analysis process, in addition to a reflective diary, was maintained in order to promote transparency of the data collection and analysis and later transferability of the findings. Transcripts were actively analysed for 'deviant cases'[48], such as experiences and expectations that did not concur with the majority in order to promote dependability of the data.

RESULTS

Forty initial responses were received indicating agreement to participate, however two subsequently withdrew without specific explanation, and therefore thirty eight participants were interviewed in the study. The mean age was 37 years (range 23-67), 66% (n=25) were female and 58% (n=22) had participated in the ASTIC trial. Table 1 illustrates the basic demographics of the sample used in the study.

Table 1. *Basic demographic and study characteristics (n=38)*

Characteristics	**n**
Gender	
Male	13
Female	25
Mean age (yrs)	37
Range	23-67
Mean age at diagnosis (yrs)	20
Study groups	
Group 1 ASTIC participants	22
Group 2 NON ASTIC participants (by personal choice)	6
Group 3 NON ASTIC participants (by external factors)	10
UK Centre study groups	
Group 1 ASTIC participants	16

Group 2 NON ASTIC participants (by personal choice)	6
Group 3 NON ASTIC participants (by external factors)	10
Spanish Centre study group	
Group 1 ASTIC participants	6

Four major themes collectively captured the factors influencing participants' decision-making, and expectations in relation to HSCT (see Figure 1). Irrespective of UK or Spanish context, these were described within contextual background of the 'hard fought battle of living with Crohn's disease' which summarized a unanimous description of the challenges and battles participants had experienced preceding their consideration of trial participation, and what was an ongoing experience for many at the time of their interview. Commonalities among the group included the uncertain nature of CD and lack of control over physical symptoms, rapid and significant weight loss, stomach pain and cramps, bloody diarrhoea and nausea. Less common symptoms included mouth and lip ulceration, bruising on legs and anaemia.

Participants reported a range of treatment side effects due to long term use of medications for their CD, including corticosteroids. This had resulted in secondary health conditions including damage to the central nervous system, osteopenia, liver scarring, vertigo, delayed recovery from surgery, wound dehiscence, short bowel syndrome, intestinal failure and a dysfunctional stoma.

Living with severe CD was described negatively in relation to its impact on education and employment. Participants reported constantly 'pre-planning' and described a lack of spontaneity and resulting social isolation. Prolonged absences from school or work due to fatigue and pain were common, in addition to missing exams, leaving university or work or being medically retired. CD commonly impacted on their social lives causing them to withdraw from social activities, often maintaining a small network of close friends and readjusting their expectations for the future.

Participants shared how over time they have learned to adapt to living with severe CD, as the gravity of living with such a debilitating physical disease was often described as having a profound impact on life. For all participants, living with severe CD was described as a continual battle for control over its physical, psychological and emotional impact, for some with anger, frustration and for many, with periods of limited success.

Figure 1 Summary of factors influencing decision-making and expectations of HSCT in CD.

[Insert Figure 1 here]

The following four themes therefore describe aspects of decision-making and expectations that emerged from the data within the background of this hard fought battle, and are supported by excerpts from the transcripts. Participants are identified by patient ID and study group number. Theme three 'Non-participation – your choice or mine?', presents analysis of data from interviews of all study groups 2 and 3, i.e. those that did not receive HSCT as part of the ASTIC trial. All other themes present analysis of data from all three study groups.

Theme 1: 'Making your mind up'

The term 'making your mind up' illustrates a common pre-determination to undertake treatment by the majority of participants, often due to the limited alternative options described as being available to them, but also an opportunity to maximise the potential benefits they may gain from trial participation.

Mind made up and 'having to know'

All participants described having reached a point where they had either exhausted all treatment options, including medications or surgery, or that other potential options were less preferable to

HSCT, for example having a stoma formed. Participants described having, 'no other choice', for many that this treatment was a 'last hope'.

> *"I never, ever thought I didn't want to do it…. But, before I'd even started, I'd made up my mind that I'd wanted to do it….Obviously, I took every - I spoke to a lot of people and I took in their opinion but I, no matter what they said, I still was adamant I was going to do it"* (Patient 30, Group 1).

> *"I was at a desperate stage, a real dead end and needed a drastic option. I was facing other health threats and looked like I might need a stoma"* (Patient 8, Group 3).

Opportunity of hope or cure

Participants reflected on their expectations of the benefits of HSCT when making their decision to participate. Most participants saw trial participation as an opportunity for hope and a substantial improvement to their condition. Expectations about personal benefits of the trial were viewed as an opportunity to improve their condition and responsiveness to conventional treatment.

> *"I think that was one of the main things, I kind of felt like, if I don't go for this, you know, in a couple of years' time, if my Crohn's is exactly the same and my doctor's saying, Oh, there's nothing new we can give you or anything, am I going to be thinking, I wish I'd done it?* (Patient 6, Group 3).

For others, expectations were greater, and the trial was described as offering a potential cure.

> *"Definitely, yeah. I mean, when I first heard about it, I thought it was going to be this like, cure...I wouldn't say it was the radical cure I was hoping for but, I mean, it's certainly helped a lot"* (Patient 26, Group 1).

" It's just all a bit, I got excited that I might go on the stem cell one because it looked like it, you know, from what they'd said that I was hoping that it was going to be my miracle cure, so I was gutted when I couldn't go on that" (Patient 12, Group 2).

Theme 2 – Communicating and understanding risks and benefits

Participants from all groups described using a variety of sources of information and guidance that informed their decisions about trial participation. Key factors included support from, and duty to family members, trust and communication with specialist clinicians and perceived personal benefits despite the risks involved.

Communication of study information

Participants described having received information about the ASTIC trial study from a variety of sources, including internet searches and online CD forums.

" I went on Crohn's forums and things and, and looked at, you know, the experiences of people, other people who'd done it. Although there wasn't too many of them around, but there was a few people who were talking about it and considering it and I think, eventually, I said, Okay, you know, I'll go ahead with it, it's worth a try" (Patient 6, Group 3).

"I read the literature, that, you know, that gets supplied when you're thinking of a new drug, talk it over with my husband, and we always say, Well, anything's worth a go" (Patient 14, Group 3).

In contrast, four participants were clear that they had actively avoided thinking about the risks to a great extent and that that to fully understand them is difficult, as exemplified in the quote below:

"Obviously, I was, but I just don't think you can take them on, again, you can't take them on board because if you do, it's too scary to take them on board, isn't it? .... My father,

certainly, I think, found that aspect of it quite hard, the amount of risks that came with it" (Patient 24, Group 1).

However, the predominant form of communication and guide for decision-making was based on communications with their specialist CD medical consultant. Trust in the expertise of the specialist CD consultant emerged as key influencing factor in decision-making to consider participation in the trial. This was a therapeutic relationship that had been developed over the course of their condition and their view on the potential risks or benefits were frequently described as influencing decision-making, and most predominantly in Group 1 participants.

"I know it's weird to say but he takes so much time with a patient, it's kind of like, well, you obviously know what you're talking about. I mean, I wouldn't trust any other doctor. I've got a kind of close bond with him but, if he says something, he says that, you know, it probably will work, I probably will trust him anyway, you know, because he is that nice" (Patient 25, Group 1).

"And I think that if, if he thought it wasn't going to do me any good, he would never offer that to me...You know what I mean? So, I think if that anything that's offered from him, I would recommend as well, to anybody else, if he's recommending it". (Patient 29, Group 1)

Balancing the risks and benefits

Participants described varied concerns and perceptions about potential risks of the treatment. Physical risks such as potential hair loss, impact on fertility, the severity of the treatment, the association of chemotherapy with cancer and even death were described. Fertility and risks to future parenthood emerged as a key issue and is examined in more depth below, however overall risks relating to treatment for participants were outweighed by the possibility of responding well to the treatment within the context of a hard fought battle and trust in the expertise of specialist clinical staff.

> *"There was nothing there that stopped me in my tracks… I know there was risks but, there's risks in everything, isn't there? ...I mean, I, I suppose, I was aware there were some risks but I generally…I trust the people that are looking after me, and, you know, that, sometimes, things don't work out".* (Patient 19, Group 1)

> *"In the past, it was …… I was more, shall I say, I was more critical of treatments and I'd weigh it up. Now, I just think I've got nothing to lose so the process is pretty easy, you know, it's, let's give it a go, let's give it a go and I'll put up with the side effects". (*Patient 18, Group 3)

For five participants, one of whom was male, the issue of fertility and parenthood formed a key element of their discussion about the ASTIC trial and understanding of risk to future parenthood. Risks to fertility were described as an important concern and commonly not an issue that they had considered in-depth until the topic arose during their initial consultations, and for some who stated that earlier discussions and preparation would have been beneficial.

Decisions about fertility and future parenthood reflected a varying degree of understanding about the impact that the treatment could have. For some this presented significant anxiety as illustrated below:

> *"And then you start thinking, like, you always think of the pros and the cons, and obviously, I don't know, it's just crazy, when I've been told that, like, you possibly couldn't have kids, that's probably the thing that's the scariest thing you could be told, because you just want to be, again, you, you're coming back to this, I want to be normal".* (Patient 7, Group 3)

Concerns about potential risks to fertility were also evident in the tension faced by some due to a strong desire to participate and undertake treatment as part of the early randomisation arm of the study. This was in addition to having sufficient time to make choices about freezing eggs or future impacts on parenthood rather than just getting 'on with the trial' treatment:

> *"Yeah, I did freeze my eggs. They didn't actually give that much advice on sort of that. Because I think, from the doctor's point of view, he wanted me to just like, get on with kind of the trial… obviously fertility was quite important so that I actually delayed starting because I wanted to do the fertility treatment first but it was very much me, really, that pushed for that, rather than them offering to do it.* (Patient 30, Group 1).

Three participants described experiencing early onset menopause following trial participation however qualified this decision further by stating that they had not desired to have a family:

> *"Lucky for me, I don't want children but if I suddenly woke up tomorrow thinking, Actually, I want a child, I now can't".* (Patient 9, Group 1)

Theme 3: 'Non-participation'- your choice or mine?

This theme considers the data of Groups 2 and 3 only, representing the sixteen participants who did not receive HSCT. Group 2 represented those chose not to participate in the trial (n=6), whereas Group 3 (n=10) comprised those who were unable to participate due to external factors such as the trial halting, non-eligibility or lack of funding.

When detailing their decision-making not to participate, participants in Group 2 most commonly described positive reflections on their decision. For those in Group 3 who had been unable to influence this decision however this was frequently reported as a missed opportunity, and where effective communication of trial eligibility was paramount in ensuring effective decision-making and expectations in relation to HSCT.

<u>Missed opportunity or lucky escape</u>

Participants in Group 3 (n=10) particularly reflected upon how they felt upon learning that they were no longer able to participate in the trial. The majority described accepting that the participation in

the trial was probably not the best option for them, and while some had been initially disappointed, they described later feeling more accepting.

> *"Erm. … I felt like, it was mixed feelings. It was like, is it a missed opportunity or a lucky escape?* " (Patient 7, Group 3).

> *"So yeah, I was a bit devastated when they told me that the trial was stopped...It was like, Yeah, I'll do it. So yeah, a bit sort of deflated when I got that, because there was all the fighting for the funding and, you know, all the rest of it, and I thought, maybe, maybe that would work"* (Patient 18, Group 3).

> *"I felt disappointed, but also relieved because what I wouldn't want is for them to put me through something that wasn't going to help, because I'd already been there with other things"* (Patient 5, Group 3).

Decision-making not to participate for the six participants in Group 2 was commonly influenced by the potential isolation that undergoing HSCT would entail, in addition to being treated a long distance from family and home. These are illustrated in the excerpts below and represents data from UK participants only (all Spanish participants were Group 1 participants) :

> *"Being up there by myself, with nobody, you know, and, I came back and I went to see my consultant gastroenterologist, and that. I just, I was frightened. If I could have had it done in [local hospital] I would have done it in a heartbeat"* (Patient 12, Group 3).

> *"Yeah. But also, of the quarantine as well, where I'd have to spend a lot of time down there on my own, away from the kids, away from my husband. And, there wasn't any guarantee that it could work and also...It wasn't actually, you know, because of infection, if you got infection and pneumonia and again, that sort of put me off".* (Patient 17, Group 2)

For another participant, their age and the additional risks they perceived this to bring also influenced their decision:

> "So it was total isolation. You know, it's not like it used to be where you're in that bubble, and, nobody can come in and, it's not like that anymore. From what I've seen on, on the news, you know, as long as you're sort of clean and…You know, so, that was obviously age factor again played a big massive part in it (Patient 12, Group 2).

Communicating eligibility

Of particular pertinence to participants in Group 2, the way in which potential eligibility was communicated throughout their assessment stage was important. For those for who viewed HSCT as a 'last chance' to improve their hard fought battle, later ineligibility proved highly disappointing. Participants from all groups had described terms being used such as, 'you're a likely candidate', 'you'll be a good candidate', or 'you're severe enough', during initial trial discussions. This had relevance for how some participants interpreted their likely eligibility and the personal benefits that the treatment could bring due to the significant demands of the trial itself.

While some participants were aware of an earlier death related to the trial, this did not reduce their willingness to participate or expectations of personal eligibility by the language used:

> *"Well, considering the person before died from it…..yeah, I'd have still done it, I'd have done it, if they'd have said, Look, you know, there is a risk but you can go ahead"* (Patient 23, Group 3).

For one participant who had placed great hope on receiving HSCT as a potential 'cure' the way in which their ineligibility was communicated had a strong impact on her reflections on the trial and experience of considering participation.

"So, there was messages there already that somebody had died on it, but I was still willing to go, I mean, a main doctor, tells me that I'm a good candidate for it, that gave me too much hope I'd get it…..You tell your mum and you tell your daughters that you might be able to have the stem cell transplant and it means a cure, my eldest daughter was with me, when I went for that interview at the hospital… We got married earlier, we rushed to buy a house, we wanted to get settled, he [husband] got a new job, moved area, he took a less paid job because we were made to believe I was going to be having the treatment and it all fell through with just that letter [detailing her non-eligibility]" (Patient 16, Group 3).

Theme 4: Recovery and reframing personal expectations

The final theme represents participants' reflections on their decision-making and how they viewed this in light of their current experience of living with CD. Participants representing all groups detailed ongoing uncertainties about their condition even if they were content with their current experience of CD.

Remaining uncertainty or regret

Participation in HSCT had not achieved disease remission for the majority of Group 1 participants, who detailed continued uncertainties or regret, including reflections on the value of their decision-making and the expectations they had held in relation to personal benefit as exemplified in the following quotations:

*"the Crohn's has returned, and that's, that's just, I suppose, incredibly frustrating, disappointing, you know, just totally gutted that you feel you've been through so much, you think, you know, is this the one that's going to get my life back on track?" (*Patient 19, Group 1).

> "It's, my Crohn's is still bad, it's still severe, it's still, well, there in two places, the same places it was before and then again also in my colon" (Patient 2, Group 1).

For Group 2 and 3 participants, ongoing uncertainty also remained, but only with significant regret for four participants. Patient 10, for example, who after much deliberation in decision-making had personally chosen another treatment option (ileostomy) rather than HSCT, described ongoing regret as having the ileostomy had made her experience of CD substantially worse:

> *"I got offered the opportunity to do stem cell which went all the way through to the point of virtually going to do it, made the decision…[but] they thought the only thing left to do then was to give me the ileostomy bag….so, now, I had the ileostomy, regrettably for me now because I don't actually think it's done anything to help me…. It's made me worse. And, I, I regret the day I ever had it, I just wish that I'd had the stem cell done"* (Patient 10, Group 2).

Reframing personal benefit

The majority of participants across groups reflected positively on the decisions they had taken, although described doing so after adjusting their expected personal benefits at the outset to the experiences at the time of interview.

Particularly for Group 1 participants, reflections on the benefits participation in HSCT had brought involved a sense of gratitude at being given the opportunity to participate in the trial and being able to fulfil their 'need to know'. All spoke about their life after HSTC. Five participants were very positive about their condition, including substantial remission of symptoms and ability to, 'get on with life as normal'. Furthermore the majority identified positive benefits such as being able to reduce the amount of medication they required and/or allowing them to receive conventional treatments to which they had previously become intolerant:

"But the biggest change has got to be from the stem cell trial where after all of that heavy medication I've had, I was pretty much free of ninety percent of disease" (Patient 4, Group 1).

"But I have managed to take myself off a couple of my medication. So I have, for me, as I look at it, I have got something out of it" (Patient 2, Group 1).

Participants also detailed how the treatment had enabled them to increase spontaneity, and to re-engage in activities due to a greater degree of energy and reduced fatigue:

"It's like actually being able to make plans and I start, started to do my courses and everything like that which was incredible, to actually be able to start to study and to be able to exercise was incredible...I can still work and earn money and pay rent and everything like that……You know, I'm studying and I can actually go and do an exercise class before I study, which you could never, never do before, so it was quite good... even now, like, I, I'm teaching seven (spin) classes a week now" (Patient 24, Group 1).

"I got back to relatively normal life straightaway, and it was like again, do what you feel you need to do. I had the transplant in October and then I returned to work, sort of, a phased return, in January. I was back doing full time work six weeks after the treatment" (Patient 32, Group 1).

DISCUSSION

This study provides new knowledge about the factors affecting decision-making for people living with severe CD in relation to HSCT as part of the ASTIC study. Uniquely, it provides insight into the views of non-participants, and for whom this outcome was not a result of personal choice and control. Previous research has identified the importance of supporting patients with CD to manage the often uncertain and unpredictable nature of their condition [38], this study further expands this to the context of clinical trial participation, both for recipients of trail treatment, those deemed ineligible and those who declined participation.

Participants identified living with severe CD as a 'hard fought battle' involving a complex balance of adaptation, self-management and acceptance of the restrictions to daily life. It involved prolonged periods of relapse or, for some, having never felt in remission since diagnosis. These findings are congruent with the broader literature on living with chronic illness [49-51], concerns about IBD and its impact on quality of life [52, 53], and findings from other IBD qualitative investigations [38, 54-57]. However for the first time, identifies how this 'hard fought battle' was a key driving factor when considering ASTIC trial participation and its associated risks and benefits.

Decision-making and clinical trial participation

Decision making in relation to clinical trials is guided by organisational, professional and clinical trial ethics and legislation, including regulation provided by the European Union [58]. While best practice in research recommends that informed consent includes an understanding of the treatment involved, its risks, benefits, treatment alternatives and the opportunity to withdraw, many participants in this study described a prior determination to undertake the ASTIC trial. This was often taken before meeting with trial clinicians, based on a limited understanding of information about the nature of HSCT, yet guided dominantly by trust in specialist clinicians with whom they had

developed a relationship over a number of years. While written and verbal information about the benefits and risks were sought and provided, for many this was of lesser importance than an expectation that this treatment may provide direct personal benefit, and that they were a 'likely' or 'good candidate' for eligibility as communicated to them. This decision also reflected their 'hard fought battle with CD' including limited options for future treatment, or that alterative options such as surgery were less desirable.

Shannon-Dorcy and Drevdahl [59] identified a similar decision making strategy in their qualitative study of HSCT in cancer, exploring the views of both patients (n=25) and caregivers (n=20). Key influencing factors were having no other option, seeking a cure and trusting the recommendations of home oncologists. Similarly Snowden et al's [60]survey of patients with Rheumatoid Arthritis, described a willingness to take mortality-related risks from HSCT in order to return to normality off all drugs, particularly those with significant disability. While participants in the current study were not facing a cancer diagnosis (and potential end of life outcomes), they had experienced significant disability and impact due to CD and it is noteworthy that decisions about risk and likelihood of individual success may not be considered sufficiently in some cases.

The balancing of risks associated with the treatment process and future outcomes was strongly evident in relation to decisions about fertility, and 'freezing of eggs' or sperm. Concerns about pregnancy and fertility were consistent with those identified by Kane [61] and Alstead and Nelson-Piercy [62], however the challenges were heightened for participants in this study due to the tensions between sufficient information and time to fully consider impacts on fertility and future parenthood and their desire to go ahead with treatment as fast as possible due to potential personal benefits .

The concept of therapeutic misconception has much to inform this study in relation to decision making and perceptions of risk in HSCT and CD.

Therapeutic Misconception and Misestimation

Although not considered specifically at the outset of this study, Therapeutic Misconception and in particular, Therapeutic Misestimation emerged as an influencing factor on how a number of participants described their decision-making and expected personal outcomes in relation to HSCT and ASTIC study participation.

Coined by Appelbaum and colleagues in 1982 [63, 64], Therapeutic Misconception refers to a phenomenon where individuals do not understand that the core objective of clinical trial research is to produce generalizable knowledge, rather than direct personal benefit, thereby conflating the aims of research with clinical care . Researchers have stressed the importance of allowing for Therapeutic Misconception to ensure effective decision-making and informed consent to trials[65, 66] .

Expanding on the concept of Therapeutic Misconception, Horng and Grady [47] outline a related concept, 'Therapeutic Misestimation' , where there is disconnect between the likelihood of personal benefit or risk from individual participation (summarised in Table 3).

Table 3 – Summary of Therapeutic Misconception and, Misestimation (adapted from Horng and Grady [47])

Concept	**Definition**	**Ethical Significance**
Therapeutic Misconception	The research participant conflates research with clinical care	*Rarely* tolerable because understanding the nature of research is necessary for an autonomous decision to participate in research
Therapeutic Misestimation	The research participant underestimates risk, overestimates benefit, or both	*Sometimes* tolerable because understanding the exact probability of harm and benefit may not be necessary for an autonomous decision to participate in research

Daugherty et al [67] suggest that research participants may experience difficulty in distinguishing the differences between the therapeutic and research components of a trial, highlighting the vulnerability of trial participants when faced with limited treatment options. Similarly Snowden et al's [60] survey of patients with Rheumatoid Arthritis, described a willingness to take mortality-related risks from HSCT in order to return to normality off all medication, particularly those with significant disability. While participants in the current study were not facing a cancer diagnosis (and potential end of life outcomes), they had experienced significant disability and impact on life from CD. It is noteworthy therefore that decisions about risk and likelihood of individual success in novel treatments for severe CD may be influenced by Therapeutic Misestimation.

Although expectations about personal benefits and outcomes varied across the three groups, the ASTIC trial was viewed by the majority as an opportunity to improve symptom control or treatment tolerance and by some as a potential cure. As Cho and Magnus [66] identify, the extent of therapeutic misconception in clinical trials is extensive and particularly pertinent to stem cell research which may be perceived as frontier research. Appelbaum *et al*.[68] found that 31% of research participants had inaccurate beliefs about the nature of their treatment (e.g., presuming that they would definitely receive the active treatment rather than the placebo), and 51% had unrealistic beliefs about the nature or likelihood of benefit to themselves of participating in the study. Similar to findings in the current study, Lidz *et al*. [69] identified that 24% of participants reported no risks or disadvantages to participation, even though they had been informed about such risks. This may go some way to explain why a number of participants focused predominantly on the positive likelihood of benefit from trial participation.

For Group 1 participants in particular reflections on individual benefits were positively reframed or reprioritised [70]. Having extinguished their 'need to know', participants were often able to make greater sense of the future, despite ongoing health-related uncertainties and limited quantitative benefits in some cases.

Coolbrandt and Grypondck's [71] mixed model qualitative study, specifically identified the courage and continued hope for a positive outcome in HSCT treatment. The recurring theme of 'being out of options' as part of the hard fought battel again provided a driving force for decisions to participate in treatment that required the challenges of cancer treatment, including coping with isolation, treatment side effects, and maintaining beliefs in a happy ending. Nevertheless the majority of those not participating in ASTIC, also reflected positively on not undergoing treatment as in hindsight the treatment risks (including awareness of one death) and the demands of isolation during the treatment regimen were deemed excessive.

Supporting decision-making

Agrawal and Emanuel [72] stated that there is no gold standard or a specific criterion that determines the reliability or validity of trial information comprehension by potential participants- and that it is to be judged on face validity. Studies have examined the use of language in consent forms and identified numerous inclusions of broad statements such as "you may or may not benefit" with statements such as "the hope is that we can improve your symptoms and prolong your life with this treatment", and used terms such as "research" and "treatment" interchangeably [73]. These studies suggest that researchers can and should guard against encouraging the Therapeutic Misconception, both in informed consent forms and in publications. Findings from this current study also identify the importance of minimizing potential Therapeutic Misconception and Misestimation resulting from all communication interventions, including face-to-face consultations and during the eligibility stages of clinical trial participation. Agreement about the communication of trial results, including the outcome of tests for eligibility is a key factor in this experience, and identifies the benefit that individualised communication plans and tailored decision-making aids could offer [74].Siegel ref here!

STRENGTHS AND LIMITATIONS

This study has several strengths and limitations. We focused on the factors influencing decision-making and expectations of individuals with severe CD, an important yet often excluded group of participants in studies due to the severity of their disease. We also examined decision-making by participants and non-participants in a trial, the latter being often excluded from study results or the impact that non-participation may have on their experiences. Findings from this international, qualitative study can inform future research that develops decision making and information support tools for future participants in 'radical' or 'frontier' clinical trials such as HSCT. The study is limited however as we conducted face-to-face semi-structured Interviews at only one time-point and did not explore in-depth the cultural and specific health care service factors that may have influenced participants' decision-making and trial experiences across study sites. Future research should harness the strengths of longitudinal study designs taking greater account of the impact of individual, socio-economic, cultural and health service factors to capture outcomes in relation to those receiving Haematopoietic Stem Cell Treatment, and for those for whom trial participation proved not to be an option. In response to stakeholder recommendations, interview settings involved a choice between an interview at home, hospital interview room or via Skype®. Although this had strengths in allowing participation for those this was a preferred option and enhanced recruitment of those living in rural settings, we cannot exclude the impact that different settings may have had on the impact of the quality of data collected, including non-verbal cues, and the impact of the researcher when using such diverse methods.

CONCLUSIONS AND IMPLICATIONS

Decision-making and expectations of people with severe CD in relation to HSCT is a complex process, involving a history of battling with the condition, a willingness to consider novel treatment options and a raised level of expectation about the benefits of trial participation by many participants in this study. Decision-making processes often begin well in advance of formal clinical consultation and are influenced by physical, psychological, socioeconomic and relational aspects of a person's life as captured in the 'hard fought battle of living with CD'. Benefits described by participants receiving the treatment may be more subtle than those captured on standard quality of life questionnaires, where 'improved quality' may be related to having extinguished the doubt of knowing whether the treatment would have direct personal benefit. The development of decision-making and information support tools for future participants in clinical trials such as HSCT are recommended, subject to further research that takes greater account of individual and socio-cultural influencing factors on decision-making over time.

Author contributions:

1. Dr Joanne Cooper – study chief investigator. Main author of the paper, leading each section from grant capture, study design, data collection, analysis and each section of this paper.
2. Miss Iszara Blake – clinical researcher. Second author of the paper, involved in data collection, analysis, interpretation and drafting each section of this paper.
3. Dr James O Lindsay – study principal investigator at Barts Health NHS Trust. Contributed to participant recruitment, and overall review of the paper.
4. Prof CJ Hawkey – study principal investigator at Nottingham University Hospitals NHS Trust. Senior advisor to the study (also chief investigator of the ASTIC trial). Contributed to grant capture for this study, participant recruitment, data interpretation and overall review of the paper.

Conflicts of interest

Each author has confirmed the following:

1. Dr Joanne Cooper – no conflicts of interest to declare
2. Miss Iszara Blake – no conflicts of interest to declare
3. Dr James O Lindsay - no conflicts of interest to declare

4. Professor CJ Hawkey - no conflicts of interest to declare

Funding

This work was funded by Crohn's and Colitis UK Living with IBD Award

Data sharing statement

A podcast is under development using additional participant statements which will be available free of charge once completed and via request to the study CI. Otherwise no additional data is available due to the consent taking at the time of participant recruitment.

Acknowledgements

We are indebted to the individuals who freely gave their time to participate in this research. Sincere thanks also to Dr Jack Satsangi (JS); Dr Simon Travis (ST); Dr Eleanor Ricart (ER); Dr Alicia Lopez (AL) who provided support in recruiting participants to this study. Also thanks to Dr Alicia Lopez (AL) for assistance in data collection of the Spanish participant study group.

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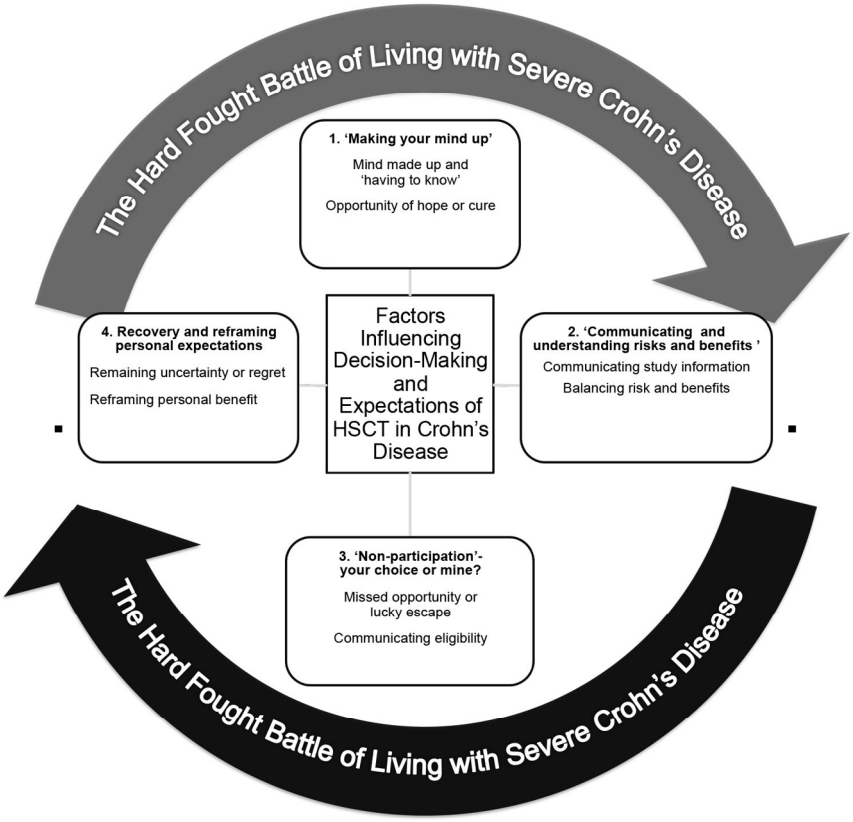
Figures



Summary of factors influencing decision-making and expectations of HSCT in CD

148x123mm (300 x 300 DPI)

PROVISIONAL INTERVIEW SCHEDULE

(Version 1.0 20/03/2013)

Study title: Living with Crohn's Disease: Expectations, Experiences and Decision-Making in Relation to Autologous Stem Cell Treatment

Introduction and thanks

Confirm participant agrees with the use of the digital recorder. Confirm consent to take part; assure that they are free to withdraw at anytime.

Themes and prompts*:

1. ***Patient journey***:

(prompts) To get us started I wonder if you would mind telling me about the story of your condition?
How did you come to be diagnosed with Crohn's disease?
What made you think there was something wrong and go to your doctor?
How did you feel when you found out there was something wrong?
What was a normal day like for you before your condition started?

2. **Perceived impact of CD**:

(prompts) How would you describe what life is like living with Crohn's disease?
What is life like for you? During times of flare or remission of symptoms?
What does it mean to you to be a person with your condition?
What role does your condition play in your life?
What picture do you have of yourself now?
What do you know about your condition?
What information have you had about it?

3. ***Treatments received for CD (for those who have taken part in ASTIC, focusing predominantly on HSCT)***:

(prompts) Please describe your thoughts about the treatments you have received for your Crohn's disease?
What treatments have you had so far for your CD?
For example, what are your experiences of - drug treatments (including stem cell treatment for relevant participants), nutritional therapy treatments, surgical treatments?
How did you come to find out you needed the treatment?
What was your understanding about the treatment?
What was your understanding about clinical trials?

4. ***Expectations of treatment***:

(prompts) Please take me through what you remember about your expectations about the treatment before having it?
What information did you receive about the treatment before having it?
How was this provided?
How did you feel about this part of your care?

5. Decision-making & risk:

(prompts) How would you describe your part in the decision-making process about the treatments you have had for your CD?
How would you describe your feelings about the potential benefits of the treatments?
How would you describe your feelings about the potential risks of the treatments?

6. Experiences:

(prompts) Could you tell me about your experience of your treatment?
Were there any things that you did that you found helped you most during your treatment?
How did the treatment meet with your expectations?
Since having the treatment, how do you feel about it now?
If you were talking about the treatment to another person with CD, what would you say to them?
How would you describe your views on taking part in clinical trials that test treatments for people with CD?
If relevant, please describe your experiences of taking part in clinical trials relating to your CD?

7. Recommendations:

(prompts) What recommendations would you have for ensuring other people with CD like yours have the best possible experience?
What is the best way to provide information about treatments and clinical trials for CD?
What is the best way of supporting people during the treatment itself?
How best can we support people before the treatment?
How best can we support people during the treatment?
How best can we support people after the treatment is finished?

Is there anything else you would like to say about your experience of living with CD?

8. Finally, Would you like me to send you a copy of the research findings?

General probes:

Could you tell me a bit more about that?
What do you mean by….
What could have been done differently?
How did you find that experience?
How did that make you feel?

*please note – not all prompts will be asked, they provide a guide to the interviewer as to the potential topic areas should this be required during the interview.

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the interview or focus group?	9 - Methods
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Author information
3. Occupation	What was their occupation at the time of the study?	6 - Methods and author information
4. Gender	Was the researcher male or female?	9 - Methods
5. Experience and training	What experience or training did the researcher have?	Methods
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	9
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	N/A
8. Interviewer characteristics	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	9 - Methods
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	9 & 10 Methods
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Methods
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	6 - Methods
12. Sample size	How many participants were in the study?	6 - Methods
13. Non-participation	How many people refused to participate or dropped out? Reasons?	6 - Methods
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	9 - Methods
15. Presence of non-	Was anyone else present besides the	9Methods

participants	participants and researchers?	
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	7 - methods
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	9 – N/A
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	N/A
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	9 - Methods
20. Field notes	Were field notes made during and/or after the inter view or focus group?	11 Methods
21. Duration	What was the duration of the inter views or focus group?	9 - Methods
22. Data saturation	Was data saturation discussed?	9 - Methods
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	N/A
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	10 -11 Methods
25. Description of the coding tree	Did authors provide a description of the coding tree?	N/A
26. Derivation of themes	Were themes identified in advance or derived from the data?	10 Methods
27. Software	What software, if applicable, was used to manage the data?	10 - NVivo
28. Participant checking	Did participants provide feedback on the findings?	11 - Methods
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	13-21 - Results
30. Data and findings consistent	Was there consistency between the data presented and the findings?	13-21 Relationship to existing knowledge
31. Clarity of major themes	Were major themes clearly presented in the findings?	12 - Results
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	13 – 25 - Discussion