**TRIAL PROTOCOL**

# Dietary therapy to improve nutrition and gut health in paediatric Crohn's disease; a feasibility study

**SHORT STUDY TITLE / ACRONYM:** "First milk" in paediatric Crohn's disease

This protocol has regard for the HRA guidance and order of content

**PROTOCOL VERSION NUMBER AND DATE: Version 0.7; Oct 15th 2018**

**SPONSOR:** Alder Hey Children's NHS Trust

**OTHER RESEARCH REFERENCE NUMBERS:**

| | |
|---|---|
| **IRAS Number:** | 246070 |
| **REC Reference:** | 18/NW/0637 |
| **International Standard Randomised Controlled Trials Number:** | tbc |
| **FUNDERS Number:** | NIHR Research for Patient Benefit: PB-PG-0816-20020 |

## SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor
I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

**For and on behalf of the Study Sponsor:**
Signature: Date:
..... ...../...../.....
Name (please print):
.....
Position:
.....

**Chief Investigator:**
Signature: Date:

Name: (please print): Stephen Allen
Position: Professor of Paediatrics
Date:

**Statistician:**
Signature:

.....
Name: (please print): Prof Duolao Wang
Position: Professor of Biostatistics

**KEY TRIAL CONTACTS**

| | |
|---|---|
| Chief Investigator | Stephen Allen, Department of Clinical Sciences, Liverpool School of Tropical Medicine; Honorary Consultant Paediatrician, Alder Hey NHS Foundation Trust. Tel: 0151 252 5467; Stephen.allen@lstmed.ac.uk |
| Study Co-ordinator | Alder Hey Research Nurse: to be appointed |
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| Joint-sponsor(s)/co-sponsor(s) | N/A |
| Funder(s) | NIHR Research for Patient Benefit |
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| Trials pharmacist | Not applicable |
| Committees | TMG: Stephen.allen@lstmed.ac.uk; Tel 0151 705 3752 |

**TRIAL SUMMARY**

| | | |
|---|---|---|
| Trial Title | Dietary therapy to improve nutrition and gut health in paediatric Crohn's disease; a feasibility study | |
| Internal ref. no. (or short title) | "First milk" in paediatric Crohn's disease | |
| Clinical Phase | Feasibility study | |
| Trial Design | Qualitative research and randomised, controlled feasibility trial | |
| Trial Participants | Children (age 8 to <18 years) with stable Crohn's disease in clinical remission or with mild/moderate disease severity managed at Alder Hey Children's hospital | |
| Planned Sample Size | 50 children for intervention study of whom 20 will be selected for qualitative research | |
| Treatment duration | 12 weeks | |
| Follow up duration | 12 weeks | |
| Planned Trial Period | April 1st 2018 to September 30th 2019 | |
| | **Objectives** | **Outcome Measures** |
| Primary | Assess whether a daily dietary supplement of first milk is acceptable to children/young people when administered over 3 months | Compliance with dietary supplement recorded in a daily diary |
| Secondary | Understand children's, young people's and parent's/carers' perceptions and views regarding dietary therapy and on participating in research on dietary therapy | Synthesis of findings from qualitative research |
| | Determine the recruitment rate, willingness to be randomised and retention rate in a double blind study of first milk versus matched placebo | Proportion of screened children who participate in and complete the study |
| | Determine the acceptability and feasibility of the dual sugar permeability test and collection of stool, urine and blood samples for research purposes | Proportion of participating children who provide required samples |
| | Generate preliminary data | |

| | | |
|---|---|---|
| | regarding the effect of first milk on nutrition, gut health and quality of life | Change in biomarkers of gut health and growth, clinical disease activity scores; paediatric inflammatory bowel disease disease-specific health-related quality of life instrument (IMPACT III questionnaire) |
| Investigational Medicinal Product(s) | Bovine colostrum (BC); Neovite: www.neovite.com | |
| Formulation, Dose, Route of Administration | Intervention: 20g/day BC (Neovite) powder made-up with about 150 mls semi-skimmed or full cream milk. Reduce dose to 10g/day if not well tolerated and body weight <40kg. Comparator: 20g/day of a mix of skimmed milk (70%) and milk protein concentrate (30%) powder. Reduce dose to 10g/day if not well tolerated and body weight <40kg. | |

**FUNDING AND SUPPORT IN KIND**

| **FUNDER(S)**<br>(Names and contact details of ALL organisations providing funding and/or support in kind for this trial) | **FINANCIAL AND NON FINANCIALSUPPORT GIVEN** |
|---|---|
| NIHR Research for Patient Benefit; Central Commissioning Facility<br>Grange House, 15 Church Street<br>Twickenham, TW1 3NL<br>Tel. 020 8843 8000 | Funding awarded: £222,514.00 |

**ROLE OF STUDY SPONSOR AND FUNDER**

The sponsor will be responsible for facilitating staff recruitment at Alder Hey, initiating and supporting the study, holding and disbursing the research funds, confirmation that ethical approval has been secured, prompt reporting of any suspected unexpected serious adverse events or reactions and ensuring that the study is conducted to an appropriate level of scientific quality.

The funder has assessed the scientific quality of the proposed research, confirmed its value for money and considered the suitability of the research environment and experience/expertise of the researchers. The funder will not have any role in the conduct of the study, the data analysis and interpretation, manuscript writing, and dissemination of results.

Neither the sponsor nor the funder will control the final decision regarding any of these aspects of the study.

**ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS**

**Trial Management Group**

We will establish a Trial Management Group (TMG) comprised of the CI, qualitative research lead, lead clinician (PI), dietician, Research Nurse, and PPI member. The TMG will be independent of the sponsor. The TMG will hold monthly teleconferences to oversee the overall conduct and progress of the study including recruitment to target, data management and data analysis.

We will appoint an external senior paediatric gastroenterologist experienced in research (volunteer) to join some TMG meetings to ensure that the study progresses according to GCP principles.

Data Monitoring and Trial Steering Committees are not required for this study given the minimal risk to participants and with no interim analysis planned.

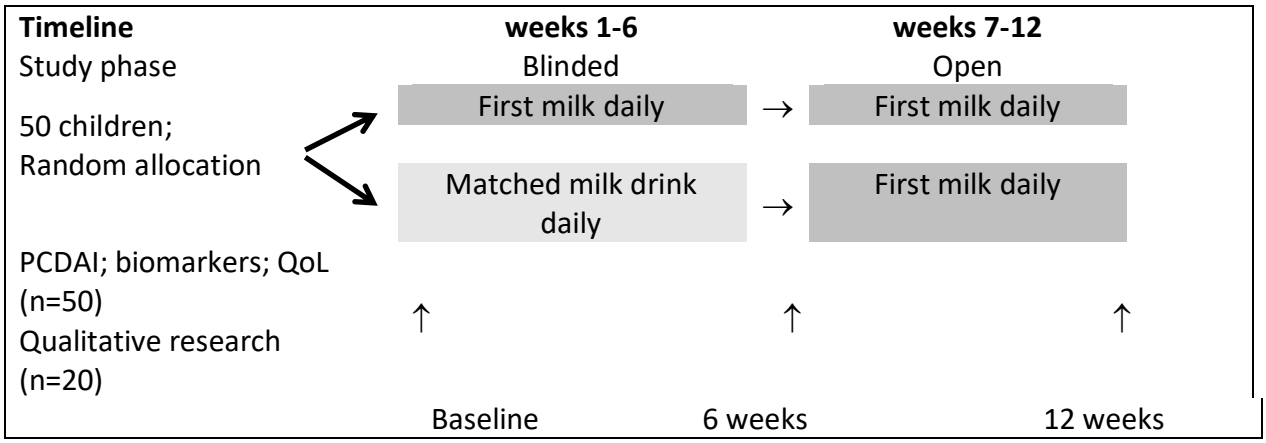
**KEY WORDS:** Children; Crohn's disease; bovine colostrum; intestinal inflammation; systemic inflammation; growth factors; quality of life

**LIST of CONTENTS**

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| BC | Bovine colostrum |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CD | Crohn's disease |
| DMC | Data Monitoring Committee |
| GCP | Good Clinical Practice |
| IBD | Inflammatory bowel disease |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. |
| IDMC | Independent Data Monitoring Committee |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trials Number |
| LSTM | Liverpool School of Tropical Medicine |
| N/a | Not applicable |
| NHS R&D | National Health Service Research & Development |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| QA | Quality Assurance |
| REC | Research Ethics Committee |
| SOP | Standard Operating Procedure |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| TMF | Trial Master File |

**STUDY FLOW CHART: Intervention study**



**STUDY PROTOCOL: Dietary therapy to improve nutrition and gut health in paediatric Crohn's disease; a feasibility study**

## 1 BACKGROUND

*What is the problem being addressed?*
Crohn's disease (CD), an incurable, chronic inflammatory bowel disease, results in poor quality of life, adverse health outcomes and high treatment costs.[1,2] Common symptoms in children include abdominal pain, diarrhoea and poor growth. Globally, its frequency has increased markedly with the highest prevalence reported in Europe (322/100,000 population)[3] and with a marked increase in younger people[4] so that up to 25% of new diagnoses are now made in childhood or adolescence.[5]

CD results from a complex interplay between host genetic susceptibility, environmental factors and the intestinal microflora with abnormalities in the mucosal innate and adaptive immune responses and barrier function.[1] Initial treatment aims to achieve clinical remission but also mucosal healing as a critical factor in preventing disease flares and improving long-term outcomes.[6]

*Exclusive enteral nutrition* (EEN)
Although mechanisms of action are unclear, recommended first line treatment for active paediatric CD (pCD) is EEN using a Food for Special Medicinal Purpose (FSMP) as a sole source of nutrition.[7] Over 85% of children/adolescents with active disease achieve clinical remission or improve during 6-8 weeks of EEN and exclusion of normal diet.[8,9] Several different whole protein feeds, such as Modulen IBD (Nestlé Health Science; https://www.nestlehealthscience.co.uk/brands/modulen) or Alicalm (Nutricia Ltd; www.nutricia.co.uk), appear to be equally effective.[8] The remarkable effectiveness of EEN in the treatment of pCD is the basis for our research.

Following initial response to EEN, disease flares occur with re-introduction of usual diet. In 48 children in remission after EEN managed in Germany, 32 (67%) relapsed during 12-months follow-up.[10] Even with maintenance therapy (e.g. with immune modulators and biologicals), many children have persistent intestinal inflammation. In 82 children (median age 15.0 years) with CD in The Netherlands, 28 (34%) had active disease and 20/54 (37%) children in clinical remission had persistent intestinal inflammation.[11]

Continuing a FSMP alongside a normal diet (partial EN) appears to be effective in improving nutrition and maintaining gut health in both adults and children with CD.[12] Two retrospective studies have been reported in pCD. Overnight supplementary nasogastric feeding was associated with less frequent relapse within 12 months compared with young people who discontinued feeds (12/28, 42.9% vs. 15/19, 79.0% respectively; $p<0.02$).[13] Growth velocity was also greater with supplemental feeds. Similarly, the proportion of children in clinical remission at 12 months was greater in those who continued some feed (9/15; 60%) compared with those who did not (2/13; 15% $p=0.001$).[14] However, although partial EN is more acceptable to children than EEN,[15] adherence with continued feeds was low; only 15/48 (31%) children were able to continue feeds once normal diet was re-introduced.[14] The biggest single barriers to the success of feeds in children lies in their poor palatability[16,17] and reluctance to have a naso-gastric tube.[17] In some adult studies, the taste or smell of feeds was reported to cause intolerance.[12] We need a dietary supplement that is effective but also acceptable for longer term use.

Further research into diet in the management of mildly active or inactive inflammatory bowel disease was highlighted as a priority by patient and clinical representatives.[18] An intensive search of the literature revealed only one qualitative study of dietary therapy in adults[19] and one study focusing on perceptions of dietary therapy in pCD.[20] In a questionnaire survey of 29 children who had been managed with EEN and their parents/carers, the majority expressed a preference for alternative novel, solid food-based diets rather than further EEN. The majority of children (79%) and parents/carers (72%) expressed a willingness to participate in a clinical trial of nutritional therapy for the management of active CD.[20]

## 2 RATIONALE

A novel dietary intervention which may be acceptable for long-term use is bovine colostrum (BC). BC is the "first milk" produced by cows after parturition and contains high levels of naturally occurring antimicrobial, immunomodulatory, and growth-stimulating factors that reduce intestinal inflammation and improve mucosal integrity.[21] BC contains 100-fold more immunoglobulins than human milk and high concentrations of antimicrobial peptides (lactoferrin, lactoperoxidases, lysozyme and oligosaccharides). Immunoregulatory cytokines include transforming growth factor-α, important in maintaining epithelial function and integrity, and high concentrations of transforming growth factor-β which has anti-inflammatory effects, regulates cellular proliferation, differentiation and repair and is essential in the induction of regulatory T cells. Additional growth-promoting and mucosal repair factors include insulin-like growth factors 1 and 2, vascular endothelial factor, basic fibroblast growth factors and platelet-derived growth factor.[22-24] Most of these factors are resistant to dairy processing and bioactivity is preserved in colostrum preparations.[25,26]

*What is known of BC in improving gut health?*
In clinical trials, BC reduced intestinal damage induced by NSAIDs,[27] HIV-associated diarrhoea[28] and the increased intestinal permeability caused by heavy exercise.[29,30] BC given at 40mg/day for 3 months to 120 Iranian children aged 1-10 years with failure to thrive without an identified cause significantly improved weight gain.[31]

BC enemas in adults with distal colitis improved symptom and histological scores.[32] In a case series evaluating an exclusion diet with nutraceutical therapy that included BC, 6 children with moderate-to-severe CD all achieved clinical remission, a fall in systemic inflammatory markers and improved quality of life within 2 months. Clinical remission was sustained between 18 and 90 months and no significant adverse effects were reported.[33]

A recent systematic review of clinical trials of BC identified 51 studies of gastrointestinal diseases, other conditions (type II diabetes, upper respiratory tract infection, juvenile idiopathic arthritis) and exercise tolerance/athletic performance. BC was well tolerated and no serious side effects were reported in the 2,326 participants. Some people reported an unpleasant taste and mild adverse effects of nausea, flatulence, diarrhoea, skin rash, and unspecified abdominal discomfort. These studies were considered to be of variable quality and the authors emphasised the need for further trials including in patients with inflammatory bowel disease.[34]

We are aware of two on-going trials of BC both of which are assessing its potential to improve

nutrition and gut health in specific patient groups: BC administered to preterm/low birthweight infants to promote feeding and intestinal health (NCT02054091) and BC administered to children and adults with acute lymphoblastic leukaemia to limit gastrointestinal toxicity including chemotherapy induced inflammation (NCT01766804). We are not aware of any on-going trials in children or adults with Crohn's disease. There is insufficient research evidence at present to undertake a systematic review of the effectiveness of BC in CD.

Effects on quality of life are particularly important to consider with lifestyle interventions such as dietary therapy. The paediatric inflammatory bowel disease specific health-related quality of life (HRQOL) instrument, IMPACT III,[41] has been validated from age 8 years[42] and we have set the lower age limit for inclusion in the study accordingly.

Our hypotheses are that:

1 BC is acceptable to children and their parents/carers for long-term use (3 months) and free of significant adverse effects
2 Children/young people with CD and their parents/carers are interested in participating in research of dietary therapy as a possible safe, acceptable and long-term means of controlling intestinal disease
3 It is possible to perform additional sample collection and procedures alongside usual clinical care to enable assessment of novel dietary interventions
4 BC improves biomarkers of nutrition and gut health in pCD

### 2.1 Assessment and management of risk

Based on the commercial availability and widespread use of BC as a dietary supplement amongst athletes, its previous evaluation in inflammatory bowel disease[32] and the absence of serious adverse events reported during previous research including vulnerable children,[34] we consider that this qualitative research and feasibility study should be categorised as:

- Type A = No higher than the risk of standard medical care

## 3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The specific aims of this proposal are to:

1 Assess whether a daily dietary supplement of BC is acceptable to children/young people and their parents/carers when administered over 3 months
2 Understand better children's, young people's and parents'/carers' perceptions and views regarding dietary therapy and on participating in research on dietary therapy
3 Determine the recruitment rate, willingness to be randomised and retention rate in a double blind study of BC versus matched control
4 Determine the acceptability and feasibility of the dual sugar permeability test (DSPT) and collection of stool, urine and blood samples for research purposes
5 Generate preliminary data regarding the effect of BC on biomarkers of nutrition and gut health and quality of life as a basis for a subsequent clinical trial

## 3.1 Primary objectives

To assess whether a daily dietary supplement of BC is acceptable to children/young people and their parent/carers when administered over 3 months

## 3.2 Secondary objectives

1 To understand children's, young people's and parent's/carers' perceptions and views regarding dietary therapy and on participating in research on dietary therapy
2 To determine the recruitment rate, willingness to be randomised and retention rate in a double blind study of BC versus matched control
3 To determine the acceptability and feasibility of the DSPT and collection of stool, urine and blood samples for research purposes
4 To generate preliminary data regarding the effect of BC on disease activity, biomarkers of intestinal inflammation and integrity, systemic inflammation and growth factors and quality of life

## 3.3 Outcome measures/endpoints

Acceptability of the BC supplement over 6-12 weeks will be assessed through a daily diary and also qualitative research.

*Clinical outcomes* will be assessed using the weighted Paediatric Crohn's Disease Activity Index (wPCDAI)[35]

*Quality of life* will be assessed using the paediatric inflammatory bowel disease specific health-related quality of life (HRQOL) instrument: the IMPACT III questionnaire[41] validated from age 8 years[42] (see Appendix 1)

*Biomarkers*: Faecal calprotectin is recommended as a non-invasive biomarker of intestinal inflammation and as a secondary outcome in clinical trials in pCD.[40] To provide insights regarding potential mechanisms of action of BC in improving gut health and nutrition in pCD and to correlate with clinical outcomes, we will also assess a range of biomarkers of intestinal inflammation, mucosal integrity and growth:[43,44]

- Intestinal inflammation: stool calprotectin, stool α1 -antitrypsin
- Intestinal permeability: serum endotoxin antibodies, iFABP; DSPT
- Systemic inflammation: serum CRP, ESR, platelets, α-1 acid glycoprotein; serum cytokine assay (multiplex method)
- Growth factors: serum IGF-1, IGFBP3

## 3.4 Primary endpoint/outcome

1 Compliance with dietary supplement recorded in a daily diary

## 3.5 Secondary endpoints/outcomes

1 Synthesis of findings from qualitative research
2 Proportion of screened children who participate in and complete the study

3 Proportion of participating children who provide required samples
4 Change in clinical disease activity scores, biomarkers, paediatric inflammatory bowel disease disease-specific health-related quality of life instrument: IMPACT III questionnaire

### 3.6 Exploratory endpoints/outcomes

N/a

## 4 TRIAL DESIGN

A prospective, qualitative and randomized, controlled interventional study in children with stable CD of mild/moderate severity.

## 5 STUDY SETTING

Recruitment of children will be undertaken in the paediatric gastroenterology department, Alder Hey Children's Hospital, Liverpool, UK.

Laboratory analyses for biomarkers will be done at Alder Hey Children's Hospital and the Liverpool School of Tropical Medicine.

Dual sugar permeability tests will be done at the Blizzard Institute, Queen Mary University of London.

Management and analysis of clinical data will take place at the Liverpool School of Tropical Medicine.

Management and analysis of qualitative data will take place at Edge Hill University, Ormskirk, UK.

## 6 ELIGIBILITY CRITERIA

### 6.1 Inclusion criteria

1 Age 8 years and above
2 CD in clinical remission or mild/moderate disease severity (weighted pCD Activity Index [wPCDAI] ≤57.5)[35]
3 Stable clinical condition defined as either receiving no treatment or maintenance therapy* that has been unchanged for at least the last 2 months with no intention to change therapy at the time of recruitment
4 Willing for clinical information to be used for the purposes of the trial
5 Willing to partake in the study procedures
6 Able to complete the daily diary in English

*Maintenance therapy includes drugs recommended for the management of CD such as aminosalicylates, thiopurines, steroids and biologicals.

### 6.2 Exclusion criteria

1 Severe CD (wPCDAI >57.5)[35]
2 Intolerance of dairy products
3 Receiving dietary therapy for the management of Crohn's disease (e.g. Modulen IBD)

4 Already taking BC regularly
5 Established diagnosis of a significant gut disorder other than CD (e.g. short bowel syndrome)
6 Failure to obtain informed consent from the patient and/or parent/guardian

## 7 TRIAL PROCEDURES

### 7.1 Recruitment

#### 7.1.1 Patient identification

Potential participants will be identified by the clinical team by reviewing the clinical database of children with CD under our care.

#### 7.1.2 Screening and recruitment

The clinical team will review patients' clinical details to assess eligibility to participate.

Children who participate in the activities-based PPI workshop (see section 13.3) will be eligible for screening for inclusion in the intervention study but will not be eligible for the qualitative component. Following ethical approval, we will invite children (age 8 to <18 years) who are under our care for CD these being approx. 200; we will ask approximately 50 of these patients to participate in the intervention study and the qualitative research.

The recruitment process will be informed by PPI as described in section 13.3. Provisionally, we will notify families about the study by post including the age appropriate Patient Information Forms (likely 8-10 years, 11-15 years, 16-17 years and for parents/guardians) in advance of a routine hospital visit and/or follow-up phone call as part of their usual clinical care. In this feasibility study, patient Information Sheets will be provided in English only as children/families will require sufficient English to complete the daily diary. They will receive a follow-up phone call from the research nurse within one week of receiving information. Children and their parents/carers can express an interest in participating during this follow-up call, by phoning the research nurse or during their next hospital attendance. We will avoid any coercion to join the study and reassure them not to worry if are not interested.

Where possible, research visits will coincide with visits for routine clinical care (e.g. out-patient appointments; infliximab infusions).

Recruitment will likely be limited to a maximum of 3 children/week for logistical purposes and continue until we have reached the required sample size. Should additional hospital visits be required to participate in the study, payment of appropriate travel expenses will be made.

### 7.2 Consent

If the young person or the parents/guardians of young children express an interest to join the study, the Research Nurse will confirm their understanding of what the study involves and ensure that they have had the opportunity to ask any questions. Informed consent/assent for both the intervention and qualitative studies will be secured by the study clinicians or trained research nurses either at a

routine hospital visit or a visit arranged specifically for the purposes of joining the study. Should the child or his/her parents/carers require more time to consider their participation, consent will be deferred. There is no time limit regarding the period for considering their participation in the study. However, if consent is delayed, screening would be repeated to confirm eligibility. Young people will have the option to participate in the intervention study but not the qualitative research if they wish.

No information will be collected or sample processing done before consent has been obtained. Signed, informed consent will be secured from young people themselves (age 16-17 years) or from the parents/guardians of children <16 years. We will invite children aged <16 years to provide signed assent.

Young people and parents/guardians will be free to withdraw at any time from the intervention study. If they withdraw from the intervention study, they would also be required to withdraw from the qualitative research. They would also have the option to continue in the intervention study but withdraw information they have provided for the qualitative research within 7 days of having given information.

Information and samples collected up to the point of withdrawal would be maintained in the study. We would also ask for final exit stool and blood samples and undertake the sugar permeability test on withdrawal but participants would be free to decline to provide these.

They can withdraw without giving reasons and without prejudicing their clinical management in any way.

To assess generalizability, the clinician/specialist nurse/research nurse will record date reviewed, age, gender, ethnicity and reason for declining to participate if provided (but no personal identifiers) of all children invited to participate in the study.

### 7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Young people or parents/guardians will be asked if the data and samples collected for this study can be used for future ancillary studies regarding IBD or other gastrointestinal diseases in children and young people. Consent for any ancillary studies will be separate to that for the current study. Young people or parents/guardians are free to opt-out of any ancillary studies and this will not affect their participation in the current study. Young people or parents/guardians will be free to withdraw their consent for use of their data and stool sample in ancillary studies at any time and without giving a reason.

Young people or children's parents/guardians will be also asked if they wish to gift their anonymised data and left-over samples for future research in IBD and other gastrointestinal disorders in young people.

### 7.3 The randomisation scheme:

Children will be randomised 1:1 to either a daily dietary supplement of BC or a comparator placebo milk for 6 weeks (weeks 1-6) using a computer-generated random allocation sequence with blocks of varied size. The random allocation sequence will be generated and held by the CTU at LSTM.

### 7.3.1 Method of implementing the allocation sequence:

The Research Nurse will allocate children at baseline to the next unique research number in the allocation sequence. Plain bags of the appropriate milk powder, identified only by the unique research number, will be prepared in advance according to the random sequence. The Research Nurse will provide the child/family with the appropriate milk powder and also flavourings.

## 7.4 Blinding

Children, parents/carers and research staff will be blinded to treatment allocation for the first 6 weeks of the intervention trial.

After 6 weeks, all children will be offered the daily BC supplement for 6 weeks in an open study (weeks 7-12). Children will remain under the care of their usual clinicians and, other than the dietary supplements, no other changes to treatment or routine clinical care will be made.

## 7.5 Unblinding

Treatment allocation during weeks 1-6 can be unmasked as required such as in the event of a serious adverse event and participant withdrawal and request from the patient/parents/carers. This can be done by contacting the CTU at LSTM. In addition, a copy of the random allocation sequence will be held securely in the gastroenterology office at Alder Hey to be opened by a clinician independent of the study in the event that unblinding is needed for a participant out of office hours.

## 7.6 Baseline data

To describe the patients and assess comparability between the intervention arms, demographic, clinical and laboratory information will be collected onto standard forms:

- Demographic information will include age, gender, ethnicity
- Clinical information will include anthropometry, current diet (e.g. vegan), current medication, disease distribution and associated manifestations (e.g. presence of fistulas) classified according the Paris classification,[36] disease severity according to the wPCDAI.
- Routine laboratory information will include the most recent measurement of haemoglobin, white cell count, inflammatory markers (platelets, C-reactive protein, ESR), albumin, liver function tests, urea, creatinine
- Quality of life using the IMPACT III questionnaire[41]

## 7.7 Trial assessments

All children across the cohort (supported by their parents/carers, as appropriate) will also be asked to keep a diary over the course of the intervention. The format and content of the diary will be informed by the activities-based PPI workshop. Provisionally, the diary will generate information on symptoms, adherence and responses to/experiences of tests/procedures. We will use a mix of closed, scaling questions (e.g., 0-10, non-smiley-smiley faces) and some open questions to elicit key data. There will be four weeks requiring daily diary entries, the remaining weeks will only require a single entry per

week. Daily diary entries over 7 days will be requested at 4 time points in the study: week -1 (before starting the intervention); week 1 (at start of intervention); and weeks 6 and 12 (last weeks of each intervention period). At each of these time points the diary will prompt the collection of symptoms data and at weeks 1, 6 and 12 we will also collect adherence data (e.g. through questions such as: Have you had your drink today? Did someone have to encourage you to have your drink today?).

Disease activity will be assessed at baseline and weeks 6 and 12 by a research clinician using the wPCDAI[35] which is recommended as an alternative primary outcome for clinical trials in pCD.[39,40]

Quality of life will be assessed at at baseline and weeks 6 and 12 using the paediatric inflammatory bowel disease disease specific health-related quality of life (HRQOL) instrument (the IMPACT III questionnaire)[41] which has been validated from age 8 years.[42] The questionnaire assesses HRQOL during the preceding two weeks according to 35 items combined into six domains (bowel symptoms, systematic symptoms, emotional functioning, social functioning, body image and treatments/interventions). Each item is scored using a Likert scale ranging from 1 to 5 for all answers. The outcome score ranges from 35 to 175; higher scores suggest better quality of life. Patients can also write any additional comments they may have at the end of the questionnaire. Children/young people will complete the questionnaire themselves with help from their parents/carers as appropriate. It takes about 10-15 minutes to complete.[42]

Biomarkers of nutrition and gut health will be collected at baseline and weeks 6 and 12:

- Faecal calprotectin as a non-invasive marker of intestinal inflammation and as a secondary outcome in clinical trials in pCD.[40]
- Intestinal inflammation: stool calprotectin, stool $\alpha_1$–antitrypsin
- Intestinal permeability: serum endotoxin antibodies, iFABP; DSPT
- Systemic inflammation: serum CRP, ESR, platelets, α-1 acid glycoprotein; serum cytokine assay (multiplex method)
- Growth factors: serum IGF-1, IGFBP3

At baseline and weeks 6 and 12, 5 mls of venous blood will be drawn. In the DSPT, a solution of lactulose and rhamnose will be administered orally on going to bed at night and all urine collected over the next 8 hours including the first sample passed the following morning. In an aliquot of urine stored frozen, the sugars will be separated by HPLC and quantitated by use of a pulsed amphometric detector.[27,29,30] Samples will be processed and stored for batch testing as the study progresses.

Children and their families will have direct access to the research team to facilitate reporting of adverse events throughout the study.

**7.8 Long term follow-up assessments:** Participants will not be followed-up after the end of the intervention phase.

**7.9 Qualitative assessments – Nested studies:**

*Qualitative interviews:* We will purposively sample 20 children from those participating in the intervention study and their parents/carers. Selection of the children will be supported by the TCU at LSTM that holds the randomisation sequence to ensure that 10 children from each arm of the study

are selected without unblinding during the first 6 weeks of the study. The CTU will be informed which children have contributed to the initial PPI activities workshop so that they would not be eligible for selection for the qualitative study.

We will undertake 3 interviews (end of first week, end of week 6 and after completion of the intervention by week 13-14) with the children and a single interview with the parents/carers at the end of the intervention (by week 13-14). When interviewing the child, their parent/carer can be present if the child/and or parent feels this is appropriate. Preferentially interviews will be face-to-face with the option of home visits by research staff. We will also offer secure remote video contact and telephone interviews as alternatives. The midpoint interview will be a light touch (remote) interview to maintain contact and elicit any specific issues or concerns.

We anticipate that each of the three interviews with the children will last between 15-30 minutes, (depending on the age of the child and their interest) and that the single interview with the parents should last between 20-60 minutes.

All interviews, with the permission of the children and parents will be audio-recorded.

Across the interviews we will focus on two key issues of interest to the feasibility trial:

- factors relating to adherence to the dietary supplement, collection of samples and data collection (e.g., what were children's experiences of having to drink the milkshake, what were the barriers, what helped, what could improve adherence in a future trial; satisfaction with research materials)
- factors relating to outcomes of dietary supplement (e.g., what outcomes are important to the young person and parent/carer; are these being adequately addressed within the current framework; how could these be measured/assessed).

See Appendix 2: Interview guides

### 7.10 Withdrawal criteria

Children can withdraw from the study at any time and without giving a reason. In addition, children can be withdrawn should there be any concerns that their participation in the trial may be adversely affecting their disease or general well-being.

### 7.11 Storage and analysis of samples

Samples collected during the study will be separated and stored at -20$^{o}$C pending analysis. Analyses of stool and blood samples will be undertaken for the variables described above using ELISA kits according to manufacturers' instructions.

For the SPT, in an aliquot of urine stored frozen shipped to the Blizzard Institute, lactulose, rhamnose and mannitol will be separated by HPLC and quantitated by use of a pulsed amphometric detector.[27,29,30]

Samples will be stored frozen for up to 5 years for possible use in ancillary studies. Samples gifted for future research would be kept indefinitely. Samples will be transported, stored, accessed and

processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

### 7.12 End of trial:

The end of trial will be the date of the last visit/data item of the last patient undergoing the trial. The sponsor will notify the MHRA of the end of a clinical trial within 90 days of its completion.

## 8 DIETARY SUPPLEMENT:

### 8.1 Name and description:

BC: 20g/day made-up with about 150 mls semi-skimmed or full cream milk. BC is available as a powder (https://www.neovite.com/) and is tasteless. We will provide a range of flavourings that can be added according to personal preference to make a palatable milkshake.

BC is used by elite athletes as a performance enhancer including those in national teams.[37,38] We expect that its use by athletes, the small volume required daily and ability to add flavourings will make it acceptable to children for long-term use even in those who do not usually drink milk. If children find the volume too great, then the daily dose can be reduced to 10g.

Comparator: 20g/day of a mix of skimmed milk powder (70%) and milk protein concentrate (30%) to make a matched comparator with equivalent protein and lactose content that is made-up and flavoured in the same way. This will be provided by the same supplier (Neovite). As above, the dose could be reduced to 10g/day if a larger volume is not tolerated.

### 8.2 Legal status of the dietary supplement:

BC is commercially available (https://www.neovite.com/)

**8.3 Storage and supply of dietary supplement**: Intervention and placebo products will be provided by the manufacturer: Colostrum UK Limited, 25 Giles Coppice, London SE19 1XF. The products will be sent to Alder Hey by courier at ambient temperature. Both milk powders will be stored at room temperature and provided to the participants double-bagged and in aliquots suitable for use at home.

Participants will be instructed to dispose of any remaining milk powders at the end of the study in the usual household waste. The Department of Nutrition and Dietetics will also dispose of any remaining product at the end of the study.

**8.4 Preparation and labelling of milk powders**: Both milk powders will be provided in plain packaging labelled "Milkshake for First Milk study", "Store at room temperature", the expiry date and the unique number from the random allocation sequence.

**8.5 Administration schedules**: 20g daily (4 rounded dessert spoons) made-up with about 150 mls semi-skimmed or full cream milk. Should be stirred or blended to a smooth paste with a little fluid before slowly diluting to full volume. If available, an electric blender will give a very smooth drink. Flavourings (e.g. vanilla, chocolate), honey or sugar can be added according to individual patient preference.

Can be taken at any time of day 2 hours after or 30 mins before eating. The daily supplement can be taken in one go or split into two. Once made-up, the milkshake can be stored in the refrigerator for up to 3 days.

**8.6 Modifications to administration**: Reduced to 10g once daily if a larger volume is not tolerated

**8.7 Concomitant medication:** Children will continue on their usual treatment for CD and other conditions. There are no other restrictions regarding medications.

**8.8 Trial restrictions:** There are no study restrictions.

**8.9 Assessment of compliance:** This will be by use of a daily diary (see above)

## 9 SAFETY MONITORING: Pharmacovigilance definitions

| Term | Definition |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| **Serious Adverse Event (SAE)** | A serious adverse event is any untoward medical occurrence that:<br>• results in death<br>• is life-threatening<br>• requires inpatient hospitalisation or prolongation of existing hospitalisation<br>• results in persistent or significant disability/incapacity<br>• consists of a congenital anomaly or birth defect<br><br>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.<br>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. |

### 9.2 Operational definitions for (S)AEs

Non-serious AEs, such as mild gastrointestinal symptoms, will be recorded in the CRF but not reported to the sponsor.

It is not expected that any SAEs, SARs or SUSARS, as defined above, will be ascribed by the child's clinicians to the study dietary supplements. However, should this occur, the SAE would be reported to the Sponsor.

Should any adverse events be reported during the course of undertaking interviews for the qualitative research, these will be reported to the Research Nurse for recording in CRF.

### 9.3 Recording and reporting of SAEs

All SAEs, occurring from the time of start of trial treatment until 7 days post cessation of trial treatment will be recorded on the BC in pCD SAE Form (appendix 9) and faxed to the Sponsor within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAE**,** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered anticipated.

Any change of condition or other follow-up information will be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached."

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The sponsor will inform the MHRA, the REC and Marketing Authorisation Holder (if not the sponsor) of SUSARs within the required expedited reporting timescales.

### 9.4 Overdose

Taking too much of the first milk by mistake is unlikely to result in any adverse effects. We will ask participants to report any inadvertent overdose (defined as taking more than the advised daily amount) to the research nurses. Should any adverse event(s) occur, these will be reported as described above.

# 10 STATISTICS AND DATA ANALYSIS

## 10.1 Sample size calculation

We will recruit 50 children for the intervention study and consider this number is sufficient to generate the information required to design a subsequent larger trial. The likely feasibility of a subsequent clinical trial can be assessed from data regarding faecal calprotectin (FC) levels, as a biomarker of intestinal inflammation, in an observational study of 82 children (median age 15.0 years) with CD in The Netherlands. These children had a spectrum of disease severity from clinical remission (aPCDAI <10) to moderate (aPCDAI 26-39). FC was <50 ug/g in 16 (19.5%), <250 ug/g in 41 (50.0%), <1000 ug/g in 58 (70.7%) and >1000 ug/g in 24 (29.3%).[11] Assuming a similar profile of disease activity in our patients, with 80% power and at the 5% significance level, 116 patients would be required to detect 50% more children with FC <250 ug/g receiving a dietary intervention compared with placebo (i.e. from 50.0% to 25.0%). This number of cases would likely be able to be recruited from perhaps 2-3 tertiary paediatric gastroenterology units depending on the acceptability of the intervention and study procedures required.

## 10.2 Planned recruitment rate

We will recruit an average 5-6 children/month over 9 months) from the approximately 200 with CD under our care. We consider that this will be feasible given the high level of interest in nutritional therapy and participating in research based on the findings from our questionnaire surveys (see PPI section).

## 10.3 Statistical analysis plan

### 10.3.1 Summary of baseline data and flow of patients

We will summarise the demographic, clinical and laboratory data using simple descriptive statistics. Continuous variables will be summarised according to number of subjects with non-missing data as mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised according to the absolute frequency and percentage of subjects in each category level. The denominator for the percentages is the number of subjects with data available unless noted otherwise.

### 10.3.2 Primary outcome analysis

Clinical, biomarker and quality of life outcomes will be anonymised, identified only by the patient's unique study number, held securely and available only to the research team. Data will analysed using standard statistical approaches for parametric and non-parametric data as appropriate. The decision on whether or not to proceed to a clinical trial of BC will depend on the findings regarding feasibility and also of the likelihood of clinical benefit based on the trend in change clinical disease activity, biomarkers of nutrition and gut health and quality of life attributable to BC.

### 10.3.3 Secondary outcome analysis

The qualitative data will be analysed systematically using Framework Analysis[45,46] as this will support the production of a structured approach to address the issues of importance in this feasibility study. Analysis will be undertaken using a staged approach: transcription; familiarisation with the interview; coding; developing a working analytical framework; applying the analytical framework; charting the

data into the framework matrix and interpreting the data. Throughout the process, codes and categories will be developed and indexed, analytic memos will be generated resulting in the development of key themes (interpretive concepts) generated through comparison between and within cases (young people/families). The analysis will be undertaken by a minimum of two experienced qualitative researchers. Any areas of difference in interpretation will be explored and subjected to critical dialogue and reflexive consideration until consensus is reached. We will liaise with members of the PPI/Advisory Group(s) to explore our preliminary findings and to ensure that these are grounded in the reality of the lives of children and their parents. We will incorporate any modifications or refinements to our interpretation before producing a final and robust set of findings.[45,46]

**10.4 Subgroup analyses** – N/a
**10.5 Adjusted analysis** – N/a
**10.6 Interim analysis and criteria for the premature termination of the trial -** N/a

**10.7 Subject population**
Children (age <18 years) with stable Crohn's disease in clinical remission or with mild/moderate disease severity managed at Alder Hey Children's hospital.

**10.8 Procedure(s) to account for missing or spurious data**
Maximum efforts will be made to avoid missing values in the database. However, where this does occur, missing covariates will be imputed using simple imputation methods in the covariate adjusted analysis based on the covariate distributions. For a continuous variable, missing values will be imputed from random values from a normal distribution with mean and SD calculated from the sample. For a categorical variable, missing values will be imputed from random values from a uniform distribution with probabilities P1 , P2 , …, and Pk from the sample. For count data, missing values will be imputed from random values from a Poisson distribution with λ from the sample. Seed for the imputation is set as 128. Monitoring of data quality will be done by the Clinical Trials Unit at the Liverpool School of Tropical Medicine.

**10.9 Other statistical considerations:** N/a

**10.11 Economic evaluation:** N/a

## 11 DATA HANDLING

### 11.1 Data collection tools and source document identification

Routine clinical and laboratory information required for the study will be extracted from patient medical records. All study data will be recorded onto standardized paper case report forms. Participants will be followed-up by telephone call if any data is incomplete.

Case report forms for all participating patients and signed informed consent forms will be stored securely at the hospital sites.

All qualitative interviews will be audio-recorded, with permission from the child/parent and subsequently transcribed. All audio recordings will be retained in a secure environment until transcripts have been finalised.

### 11.2 Data handling and record keeping

Participants in the study will be allocated a unique study number. Personal identifiers will be recorded only on the participant log and linked to the case report forms by the participant's initials and study number.
Baseline and outcome information will be collected by the research nurse and checked with the child's clinician or specialist nurse.
Data collection will use paper forms. Data from the CRFs will be entered by the research nurse into an electronic database. Data transfer to LSTM will be by established and secure LSTM procedures. The Data Manager will monitor data quality and ensure adequate data back-up. Data analysis will be undertaken by the study statistician.

All audio recordings will be retained in a secure environment until transcripts have been finalised.

No data will be transferred outside of the European Economic Area.

### 11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

### 11.4 Archiving

CRFs will be archived for a minimum of 5 years after completion of study. A central index held at the Research Business Unit, Alder Hey, will be prepared to identify the archived contents and their location. Access to the archives will be controlled and limited to authorized personnel only. Destruction of CRFs will require authorisation from the Sponsor.

## 12 MONITORING, AUDIT & INSPECTION

Study Monitoring will be undertaken by the Sponsor and will include participant enrolment, consent, eligibility, provision of samples and completeness of data collection.

## 13 ETHICAL AND REGULATORY CONSIDERATIONS

### 13.1 Research Ethics Committee (REC) review & reports

Ethical approval will be secured before the start of recruitment from the National Research Ethics Service and Regional Committee for the study protocol, informed consent forms and study information sheets. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. The Chief Investigator will produce the annual reports and notify the REC of the end of the study. Within one year after the end

of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

### 13.2 Peer review

The study proposal has undergone independent, expert peer review organised by the funder.

### 13.3 Public and Patient Involvement

Input to the research questions posed by our study, the plain English summary and the patient information sheets was provided by a member of the research team who is the PPI representative on the Joint British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) / NIHR Children Gastroenterology, Hepatology and Nutrition Research Working Group. Ms. Moule has extensive personal experience of engaging with the health service on behalf of relatives including as parents of young people with inflammatory bowel disease. She helped to clarify the role that a novel dietary intervention may play in long-term disease management.

Ms. Moule will be a member of the TMG and advise on the pragmatic aspects of undertaking the project especially regarding engaging participants in the study.

We also discussed the research in dietary interventions with parents and younger people who attended the CICRA North West England IBD Family Information Day, Manchester, June 25th, 2016.

Prior to ethics approval we will undertake PPI work and actively engage with children and young people with CD under our care and their parents/carers. We will invite young people (n=10) and their parents/carers (n=10) to participate in an activities-based workshop to explore the key issues underpinning the research and enable us to:

1 Refine our explanations of key study-related concepts (e.g. dietary supplements; nutraceuticals)
2 Further examine patients' interest/lack of interest in and their perceptions of BC dietary therapy, their likelihood of participating in a study and how to facilitate such a study; and seek feedback on the proposed range, number and type of samples collected and procedures to be undertaken (blood, stool and urine samples; dual sugar permeability test)
3 Seek feedback on design and content of consent/assent forms and information sheets for children and young people (likely age groups: ≤7yrs; 7-≤14yrs; 14-18yrs) and parents/carers, to best explain the study and how to convey possible benefits and risks
4 Seek feedback on design of a daily adherence and symptom diary and explore the best tool to elicit child/parent-reported data (e.g., paper diary; SMS text questions; suitable App that rewards completion)
5 Identify potential child, young person and/or parent-centred STOP and GO markers based on above insights.

We will also liaise with the GenerationR Young Persons' Advisory Group based at Alder Hey to identify a young person with Crohn's disease to engage in the research project. We will explore with the

young person how best they can contribute; this may be as a member of the TMG or advising on specific issues raised during trial set-up or as the trial progresses.

### 13.4 Regulatory Compliance

The protocol and study conduct will comply with Good Clinical Practice.
Before enrolment of patients into the study, the Chief Investigator or designee will apply for NHS permission from the Alder Hey Research & Development (R&D) department. For any amendment that will potentially affect NHS permission, the Chief Investigator or designee will confirm with the Alder Hey R&D department that NHS permission is ongoing.

### 13.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the study protocol. Accidental protocol deviations will be adequately documented on relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur will require immediate action and could potentially be classified as a serious breach.

### 13.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The sponsor will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with the study; or the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that breach.

### 13.7 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Personal information will be collected by members of the research team. Participants in the study will be allocated a unique, site-specific study number. Personal identifiers will be recorded only on the participant log and linked to the case report forms by the participant's initials and study number. Paper forms will be kept in a locked cabinet in an office with restricted access. Digital data will be kept on password protected computers and storage media and transmitted through secure means between sites. Data will be stored for a minimum of 5 years after the publication of results. The Sponsors are the custodians of the data.

Any identifiable data collected during the course of the qualitative component will be managed according to appropriate data protection and research governance measures.

### 13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The chief investigator and other applicants do not have any financial and other competing interests.

### 13.9 Indemnity

All investigators are covered by the NHS indemnity scheme

### 13.10 Amendments

A valid notice of amendment will be submitted to the REC for consideration for any amendments to the REC application or the supporting documents. Approved amendments will be notified to NHS R&D departments of the participating sites.

**13.11 Post trial care:** All participants will continue their usual clinical care at the end of the trial.

**13.12 Access to the final trial dataset:** The investigators will have access to the final dataset.

## 14 DISSEMINATION POLICY

### 14.1 Dissemination policy

The data arising from the study will be owned by the Sponsor.

On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared.

Results of the research analyses will not be available to individual patients but participants will be able to access a summary of the study findings written in lay language.

Our findings will be of interest to clinicians, allied health professionals and researchers working in IBD. We will publish the study protocol and share our findings at specialist society meetings and key scientific conferences.

The study database of the quantitative data will be publicly accessible through a central data management system at the Liverpool School of Tropical Medicine or available on request. Dissemination of results to clinicians, allied health professionals and academics will be facilitated by membership of the investigators on specialist society groups and charity boards. We will use these channels to encourage further research in dietary management of paediatric CD.

### 14.2 Authorship eligibility guidelines and any intended use of professional writers

All of the investigators will be eligible to author the final study report. There is no intention to use professional medical writers.

## 15 REFERENCES

1. Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. Lancet 2016; Published Online November 30, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31711-1.

2. Day AS, Ledder O, Leach ST, Lemberg DA. Crohn's and colitis in children and adolescents. World J Gastroenterol 2012; 18:5862-9.

3. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46–54.

4. Malmborg P, Hildebrand H. The emerging global epidemic of paediatric inflammatory bowel disease - causes and consequences. J Intern Med 2016;279:241-58.

5. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011; 17:423-39.

6. Ruemmele FM. Mucosal Healing for Paediatric Crohn's Disease: Is It Really Worth the Effort or Just Much Ado About Nothing? J Crohns Colitis 2016;10:1-2.

7. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, Amil Dias J, Barabino A, Braegger CP, Bronsky J, Buderus S, Martín-de-Carpi J, De Ridder L, Fagerberg UL, Hugot JP, Kierkus J, Kolacek S, Koletzko S, Lionetti P, Miele E, Navas López VM, Paerregaard A, Russell RK, Serban DE, Shaoul R, Van Rheenen P, Veereman G, Weiss B, Wilson D, Dignass A, Eliakim A, Winter H, Turner D; European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis 2014;8:1179-207.

8. Day AS, Whitten KE, Sidler M, Lemberg DA. Systematic review: nutritional therapy in paediatric Crohn's disease. Aliment Pharmacol Ther 2008;27:293-307.

9. Cameron FL, Gerasimidis K, Papangelou A, Missiou D, Garrick V, Cardigan T, Buchanan E, Barclay AR, McGrogan P, Russell RK. Clinical progress in the two years following a course of exclusive enteral nutrition in 109 paediatric patients with Crohn's disease. Aliment Pharmacol Ther 2013;37:622-9.

10. Frivolt K, Schwerd T, Werkstetter KJ, Schwarzer A, Schatz SB, Bufler P, Koletzko S. Repeated exclusive enteral nutrition in the treatment of paediatric Crohn's disease: predictors of efficacy and outcome. Aliment Pharmacol Ther 2014;39:1398-407.

11. Hoekman DR, Diederen K, Koot BG, Tabbers MM, Kindermann A, Benninga MA. Relationship of clinical symptoms with biomarkers of inflammation in pediatric inflammatory bowel disease. Eur J Pediatr 2016;175:1335-42.

12. El-Matary W, Otley A, Critch J, Abou-Setta AM. Enteral Feeding Therapy for Maintaining Remission

in Crohn's Disease: A Systematic Review. JPEN J Parenter Enteral Nutr 2015 Dec 8. pii: 0148607115621051.

13. Wilschanski M, Sherman P, Pencharz P, Davis L, Corey M, Griffiths A. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. Gut 1996;38:543-8.

14. Duncan H, Buchanan E, Cardigan T, Garrick V, Curtis L, McGrogan P, Barclay A, Russell RK. A retrospective study showing maintenance treatment options for paediatric CD in the first year following diagnosis after induction of remission with EEN: supplemental enteral nutrition is better than nothing! BMC Gastroenterol 2014;14:50.

15. Johnson T, Macdonald S, Hill SM, Thomas A, Murphy MS. Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: a randomised controlled trial. Gut 2006, 55:356–361.

16. Kansal S, Wagner J, Kirkwood CD, Catto-Smith AG. Enteral Nutrition in Crohn's Disease: An Underused Therapy. Gastroenterol Res Pract 2013;2013:482108.

17. Aloi M, Nuti F, Stronati L, Cucchiara S. Advances in the medical management of paediatric IBD. Nat Rev Gastroenterol Hepatol 2014:11;99-108.

18. James Lind Alliance 2013: http://www.jla.nihr.ac.uk/priority-settingpartnerships/inflammatory-bowel-disease/downloads/IBD-PSP-Top-10-withdetail.pdf

19. Halmos EP, Gibson PR. Dietary management of IBD - insights and advice. Nat Rev Gastroenterol Hepatol 2015;12:133-46.

20. Svolos V, Gerasimidis K, Buchanan E, Curtis L, Garrick V, Hay J, Laird S, Munro J, Gaya DR, Russell RK, Hansen R. Dietary treatment of Crohn's disease: perceptions of families with children treated by exclusive enteral nutrition, a questionnaire survey. BMC Gastroenterol 2017;17:14.

21. Hill DR, Newburg DS Clinical applications of bioactive milk components. Nutr Rev 2015;73:463-76.

22. Hurley WL, Theil PK. Perspectives on immunoglobulins in colostrum and milk. Nutrients 2011;3:442–474.

23. Pakkanen R, Aalto J. Growth factors and antimicrobial factors of bovine colostrum. Int Dairy J 1997;7:285–297.

24. Playford RJ, MacDonald CE, Johnson WS. Colostrum and milk-derived peptide growth factors for the treatment of gastrointestinal disorders. Am J Clin Nutr 2000;72:5–14.

25. Sacerdote P, Mussano F, Franchi S, et al. Biological components in a standardized derivative of bovine colostrum. J Dairy Sci 2013;96:1745–1754.

26. Elfstrand L, Lindmark-Månsson H, Paulsson M, et al. Immunoglobulins, growth factors and growth hormone in bovine colostrum and the effects of processing. Int Dairy J 2002;12:879–887.

27. Playford RJ, MacDonald CE, Calnan DP, Floyd DN, Podas T, Johnson W, Wicks AC, Bashir O, Marchbank T. Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. Clin Sci (Lond) 2001;100:627-33.

28. Florén CH, Chinenye S, Elfstrand L, Hagman C, Ihse I. ColoPlus, a new product based on bovine colostrum, alleviates HIV-associated diarrhoea. Scand J Gastroenterol 2006;41:682-6.

29. Marchbank T, Davison G, Oakes JR, Ghatei MA, Patterson M, Moyer MP, Playford RJ. The nutriceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes. Am J Physiol Gastrointest Liver Physiol 2011;300:G477-84.

30. March DS, Marchbank T, Playford RJ, Jones AW, Thatcher R, Davison G. Intestinal fatty acid-binding protein and gut permeability responses to exercise. Eur J Appl Physiol 2017 Mar 13. doi: 10.1007/s00421-017-3582-4. [Epub ahead of print]

31. Panahi Y, Falahi G, Falahpour M, Moharamzad Y, Khorasgani MR, Beiraghdar F, Naghizadeh MM. Bovine colostrum in the management of nonorganic failure to thrive: a randomized clinical trial. J Pediatr Gastroenterol Nutr 2010;50:551-4.

32. Khan Z, Macdonald C, Wicks AC, Holt MP, Floyd D, Ghosh S, Wright NA, Playford RJ. Use of the 'nutriceutical', bovine colostrum, for the treatment of distal colitis: results from an initial study. Aliment Pharmacol Ther 2002;16:1917-22.

33. Slonim AE, Grovit M, Bulone L. Effect of exclusion diet with nutraceutical therapy in juvenile Crohn's disease. J Am Coll Nutr 2009;28:277-85.

34. Rathe M, Müller K, Sangild PT, Husby S. Clinical applications of bovine colostrum therapy: a systematic review. Nutr Rev 2014;72:237-54.

35. Turner D, Griffiths AM, Walters TD, Seah T, Markowitz J, Pfefferkorn M, Keljo D, Waxman J, Otley A, LeLeiko NS, Mack D, Hyams J, Levine A . Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. Inflamm Bowel Dis 2012;18:55-62.

36. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, Fell J, Ruemmele FM, Walters T, Sherlock M, Dubinsky M, Hyams JS. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17:1314–21.

37. Shing CM, Jenkins DG, Stevenson L, et al. The influence of bovine colostrum supplementation on exercise performance in highly trained cyclists. Br J Sports Med 2006;40:797–801.

38. Hofman Z, Smeets R, Veriaan G, et al. The effect of bovine colostrum supplementation on exercise

performance in elite field hockey players. Int J Sport Nutr Exerc Metab 2002;12:461–9.

39. Turner D, Levine A, Walters TD, Focht G, Otley A, López VN, Koletzko S, Baldassano R, Mack D, Hyams J, Griffiths AM. Which PCDAI Version Best Reflects Intestinal Inflammation in Pediatric Crohn's Disease? J Pediatr Gastroenterol Nutr 2016 Apr 4.
[Epub ahead of print]

40. Ruemmele FM, Hyams JS, Otley A, Griffiths A, Kolho KL, Dias JA, Levine A, Escher JC, Taminiau J, Veres G, Colombel JF, Vermeire S, Wilson DC, Turner D. Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee. Gut 2015;64:438-46.

41. Otley A. Measurement of quality of life in pediatric inflammatory bowel disease. In: Baldassano RN, Mamula P, Markowitz J, eds. Pediatric inflammatory bowel disease. Springer, 2008:565–80.

42. Uggla C, Lindh V, Lind T, Lindkvist M. IMPACT-III is a valid and reliable questionnaire for assessing health-related quality of life in Swedish children with inflammatory bowel disease. Acta Paediatr 2017 Oct 15. doi: 10.1111/apa.14119. [Epub ahead of print]

43. Sands BE. Biomarkers of Inflammation in Inflammatory Bowel Disease. Gastroenterology 2015;149:1275-1285.e2.

44. Zubin G, Peter L. Predicting Endoscopic Crohn's Disease Activity Before and After Induction Therapy in Children: A Comprehensive Assessment of PCDAI, CRP, and Fecal Calprotectin. Inflamm Bowel Dis 2015;21:1386-91.

45. Ritchie J, Spencer L 1994. "Qualitative data analysis for applied policy research" in A. Bryman and R. G. Burgess [eds.] "Analyzing qualitative data", 1994, pp.173-194. London: Routledge.

46. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Medical Research Methodology 2013;13:117.

**16.**

**16.1 Risk**

Risks associated with trial interventions
☒ LOW ≡ Comparable to the risk of standard medical care
☐ MODERATE ≡ Somewhat higher than the risk of standard medical care
☐ HIGH ≡ Markedly higher than the risk of standard medical care

Justification: Based on the commercial availability and widespread use of BC as a dietary supplement amongst athletes, its previous evaluation in inflammatory bowel disease[32] and the absence of serious adverse events reported during previous research including in vulnerable children,[34] we consider that this qualitative research and feasibility study should be categorised as: Type A = No higher than the risk of standard medical care.

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)
An external senior paediatric gastroenterologist experienced in research will be appointed to review any serious adverse events arising from the study and join TMG meetings to ensure that the study progresses according to GCP principles.

**16.2 Study management / responsibilities**

**16.2.1 Patient registration/randomisation procedure:**
Dedicated Research Nurses will be responsible for patient identifier details and unique study numbers held on a participant log at Alder Hey and random allocation to the two arms of the study.

**16.2.2 Data management**
Research nurses will check data with clinicians. The study Data Manager will be responsible for CRF checking, data queries and clarifications.

**16.2.3 Preparation and submission of amendments**
The CI will be responsible for amendments.

**16.2.4 Preparation and submission of Annual Safety Report/Annual**
The CI will be responsible for preparing and submitting progress reports.

**16.2.5 Data protection/confidentiality**
All investigators and study site staff will comply with the requirements of the Data Protection Act 1998.

**16.2.6 Trial documentation and archiving**
The study Data Manager will be responsible for study documentation and archiving

**16.3 Authorisation of participating sites**

**16.3.1 Required documentation**
CVs and evidence of completion of GCP training will be required for each member of the research team.

**16.3.2 Procedure for initiating/opening a new site –** N/a

### 16.3.3 Principal Investigator responsibilities

Responsibilities of the PI include attendance at the initiation and subsequent TMGs, training of new members of the study team in the protocol and its procedures, ensuring that the ISF is accurately maintained, dissemination of important study related information to all stakeholders, supporting recruitment to target, ensuring that all study procedures are compliant with GCP, contributing to interpretation of findings and final report writing.

### 16.4 Schedule of Procedures

| **Procedures** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** |
|---|---|---|---|---|
| | **Screening** | **Week 1** | **Week 6** | **Week 12** |
| Informed consent (including qualitative study) | x | | | |
| Demographics | x | | | |
| Medical history | x | | | |
| Physical examination | x | | | |
| Concomitant medications | x | | | |
| Eligibility assessment | x | | | |
| Keep diary for 1 week prior to starting interventions | x | | | |
| Start first milk or placebo milkshake daily weeks 1-6 | | x | | |
| First milk milkshake daily weeks 7-12 | | | x | |
| Disease activity; HRQoL; Sample collection (5 mls venous blood, sugar absorption test, stool) | | x | x | x |
| Qualitative research; 20 children | | x | x | x |

### 16.5 Safety Reporting Flow Chart: N/a

### 16.6 Amendment History

| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
|---|---|---|---|---|
| | | | | |

## Appendix 1: Impact – III questionnaire (UK)

### Instructions

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohn's disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. *Please put a cross in the box above the answer that best fits your answer.*

First, an example.

The question is: How afraid are you of tigers?

| ☐ | ☐ | ☐ | ☒ | ☐ |
|---|---|---|---|---|
| Not at all afraid | A little afraid | Quite afraid | Afraid | Very much Afraid |

So, this person is afraid of tigers.

| ☐ | ☒ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all afraid | A little afraid | Quite afraid | Afraid | Very much Afraid |

This person is a little afraid of tigers.

Please answer all of the questions! If you do not understand a question, ask someone for help.
Good luck with filling in the questionnaire and… many thanks in advance for your efforts!

**Question 1.**
**How much has your stomach been hurting you in the past two weeks?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 2.**
**Taking medicines or tablets bothers you.**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 3.**
**Has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 4.**
**How much have you been worrying about having a flare-up (increase of symptoms) in the past two weeks?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 5.**
**How much does it bother you that you have an illness that does not just go away?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 6.**
**How much energy did you have during the past two weeks?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Very much energy | Much energy | Quite a bit of energy | A little energy | No energy at all |

**Question 7.**
**How do you feel about your weight?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| I feel great about my weight | I feel good about my weight | I don't feel good or bad about my weight | I feel bad about my weight | I feel awful about my weight |

**Question 8.**
**How has your inflammatory bowel disease affected your family?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| The effect has been great | The effect has been good | It has not affected our family | The effect has been bad | The effect has been awful |

**Question 9.**
**How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two years?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 10.**
**How often have you been bothered by diarrhoea (loose or frequent bowel movements) in the past two weeks?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 11.**
**How much do you worry about health problems you might have in the future?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 12.**
**How often do you think it is unfair that you have inflammatory bowel disease?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 13.**
**During the past two weeks, were you ever angry that you have inflammatory bowel disease?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 14.**
**Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 15.**
**How do you feel about the way you look?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| I think I look great | I think I look good | I don't think I look good or bad | I think I look bad | I think I look awful |

**Question 16.**
**Are you embarrassed because of your bowel condition?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 17.**
**Did you have fun during the past two weeks?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 18.**
**Is it harder to make friends because of your inflammatory bowel disease?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 19.**
**How often do you worry about your stool (bowel movement) containing blood?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 20.**
**Are you worried you cannot have a boyfriend or girlfriend because of your inflammatory bowel disease?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Not at all | A little | Quite a bit | Much | Very much |

**Question 21.**
**How often did you feel sick in the past two weeks?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 22.**
**How do you feel about the tests you have to go through?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| I do not mind them at all | I mind them a tiny bit | I mind them a little | I mind them a lot | I hate them |

**Question 23.**
**Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 24.**
**How often do you worry about having an operation?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 25.**
**How often are you afraid you might have an accident (not get to the toilet in time)?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Never | Rarely | Sometimes | Often | Very often |

**Question 26.**
**Do you try to hide your inflammatory bowel disease?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| | | I try a little | I try hard | |

| | | | | |
|---|---|---|---|---|
| No, I do not try at all | I don't try much | | | Yes, I try very hard |

**Question 27.**
**Does your inflammatory bowel disease make it difficult to travel or go on holiday?**

| | | | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |
| No, not difficult | Slightly difficult | Quite difficult | Very difficult | Yes, extremely difficult |

**Question 28.**
**How did you feel during the past two weeks?**

| | | | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |
| Great | Good | Not good or bad | Bad | Awful |

**Question 29.**
**Are you happy with your life?**

| | | | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |
| Yes, very happy | Happy | Not happy or unhappy | Unhappy | Very unhappy |

**Question 30.**
**Do you feel there is someone you can talk to about your inflammatory bowel disease?**

| | | | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |
| Always | Often | Sometimes | Rarely | Never |

**Question 31.**
**How often did you have to pass wind in the past two weeks?**

| | | | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |
| Never | Rarely | Sometimes | Often | Very often |

**Question 32.**
**How tired have you felt in the past two weeks?**

| | | | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |
| Not at all tired | A little tired | Quite tired | Tired | Very tired |

**Question 33.**
**How do you feel about your height?**

| | | | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel great about my height | I feel good about my height | I don't feel good or bad about my height | I feel bad about my height | I feel awful about my height |

**Question 34.**
**Despite your inflammatory bowel disease, can you take part in as much sport as you would like?**

| | | | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |
| Yes, as much as I would like | Almost as much as I would like | About half as much as I would like | Less than half as much as I would like | Much less than I would like |

**Question 35.**
**How often are you able to go to school?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Always | Often | Sometimes | Rarely | Never |

- **END OF QUESTIONNAIRE –**

This completes the questionnaire. If you have anything else to add which you feel is important about having inflammatory bowel disease, please write it below.

**Appendix 2:** Interview guides - tbc

## Appendix 3: SAE reporting form

### BC in pCD - SERIOUS ADVERSE EVENT REPORT FORM

v1.0 31st Dec 2017

Report date: ___ ___ ___ (Day Month Year) SAE# _____ (insert SAE# only if 2 SAEs occur on the same day) Report Type: ☐ Initial ☐ Follow up ☐ Final

**INVESTIGATOR AND SUBJECT DETAILS**

Investigator name _____

Subject ID number _____ Subject's initials _____ ☐ Male ☐ Female

Date of Birth ___ ___ ___ (Day Month Year) Weight (kg): _____ Height (cm): _____

**SERIOUS ADVERSE EVENT INFORMATION**

Event details (diagnosis): _____
Note: death is not a diagnosis, please give condition causing death

Date investigator informed of SAE ___ ___ ___ (Day Month Year)

Expected : Yes ☐ No ☐

Event start date: ___ ___ ___ (Day Month Year)

Event end date: ___ ___ ___ (Day Month Year)

SAE Onset date: ___ ___ ___ (Day Month Year) time: ___ : ___ (24 hours)
Date SAE criteria were met

If hospitalized, date of admission
Date: ___ ___ ___ (Day Month Year)

If hospitalized, date of discharge
Date: ___ ___ ___ (Day Month Year) ☐N/A

**SAE Criteria:**

- Death ☐
- Life-threatening ☐
- In-patient hospitalization required ☐
- Existing hospitalization prolonged ☐
- Persistent/significant disability/incapacity ☐
- Congenital anomaly/birth defect ☐
- Other important medical event ☐

**Severity/Intensity:**

- Mild (Grade 1) ☐
- Moderate (Grade 2) ☐
- Severe (Grade 3) ☐
- Life threatening (Grade 4) ☐
- Fatal (Grade 5) ☐

**Relationship to Study Drug:**

- Unrelated ☐
- Unlikely related ☐
- Possibly related ☐
- Probably related ☐
- Definitely related ☐

Other possible causes of the event: _____

**OUTCOME:**

- ☐ Resolved/recovered — Date resolved: ___ ___ ___ (Day Month Year)
- ☐ Resolved/recovered with sequelae
- ☐ Condition improving
- ☐ Condition still present & unchanged
- ☐ Condition deteriorating
- ☐ Death — Date of death: ___ ___ ___ (Day Month Year) Autopsy performed? YES ☐ NO ☐ If Yes, attach a copy of the autopsy report

**STUDY TREATMENT DETAILS**

Start date of study drug: ___ ___ ___ (Day Month Year) Enroll ID_____

Date of most recent study drug administration prior to onset of the event:
___ ___ ___ (Day Month Year)

Lot Number _____

Stop date of study treatment: ___ ___ ___ (Day Month Year) ☐ N/A

**Action taken with study drug in response of the event:**

- ☐ None
- ☐ Drug reduced
- ☐ Drug interrupted
- ☐ Drug permanently stopped

| | | | |
|---|---|---|---|
| Did the event improve after reducing/interrupting/stopping study drug? | ☐ YES | ☐ NO | ☐ N/A |
| Did the event re-occur after study drug was restarted? | ☐ YES | ☐ NO | ☐ N/A |
| Does the subject want to discontinued study drug in response to the AE? | ☐ YES | ☐ NO | |

Appendix 4: Material Safety Data Sheet
Appendix 5: Full Powder Analysis
Appendix 6: Pasteurised Sample
Appendix 7: Raw Product samples