

BMJ Open Protocol for a double-blind, randomised, placebo-controlled pilot study for assessing the feasibility and efficacy of faecal microbiota transplant in a paediatric Crohn's disease population: PediCRaFT Trial

Nikhil Pai ^{1,2}, Jelena Popov,¹ Lee Hill,¹ Emily Hartung¹

To cite: Pai N, Popov J, Hill L, *et al.* Protocol for a double-blind, randomised, placebo-controlled pilot study for assessing the feasibility and efficacy of faecal microbiota transplant in a paediatric Crohn's disease population: PediCRaFT Trial. *BMJ Open* 2019;9:e030120. doi:10.1136/bmjopen-2019-030120

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-030120>).

NP and JP are joint first authors.

Received 27 February 2019
Revised 09 October 2019
Accepted 23 October 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Pediatrics, Division of Pediatric Gastroenterology and Nutrition, McMaster University, Hamilton, Ontario, Canada

²Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada

Correspondence to

Dr Nikhil Pai; pain@mcmaster.ca

ABSTRACT

Introduction Crohn's disease (CD) is a chronic inflammatory condition with transmural involvement of the gastrointestinal tract. Extraintestinal manifestations are common, and the disease burden on patients and the healthcare system is significant. While treatment options have expanded in recent years, they have mainly focused on dampening the immune response, thus carrying notable risks associated with long-term immunosuppression. Faecal microbiota transplant (FMT) targets inflammatory bowel disease (IBD) by modifying intestinal dysbiosis. Limited adult and paediatric data have demonstrated a favourable response to FMT in IBD; however, no randomised controlled trial has yet been published in paediatrics. This double-blind, randomised, placebo-controlled pilot study will assess feasibility and efficacy outcomes of FMT in a paediatric CD population.

Methods and analysis Forty-five patients between the ages of 3 and 17 years, with established CD or IBD unclassified, will be enrolled 2:1 to undergo FMT intervention or placebo control. Participants will undergo a colonoscopic infusion to the terminal ileum at baseline, followed by oral capsules two times per week for 6 weeks. Outcomes will be measured throughout the intervention period and 18 weeks of subsequent follow-up. Primary outcomes will assess feasibility, including patient recruitment, sample collection and rates of adverse events. Secondary outcomes will address clinical efficacy, including change in clinical response, change in urine metabolome and change in microbiome.

Ethics and dissemination Ethics approval from the local hospital research ethics board was obtained at the primary site (McMaster Children's Hospital, Hamilton), with ethics pending at the secondary site (Centre Hospitalier Universitaire-Sainte-Justine, Montréal). RBX7455 and RBX2660 are human donor-sourced, microbiota-based therapeutic formulations. Both RBX7455 and RBX2660 are currently undergoing clinical trials to support potential US Food and Drug Administration approval. Approval to conduct this paediatric clinical trial was obtained from Health Canada's Biologics and Genetic Therapies Directorate. The results of this trial will be published

Strengths and limitations of this study

- This multicentre trial will be one of the first studies to assess feasibility and clinical efficacy of inducing remission in a paediatric Crohn's disease population using combination oral and colonic infusion faecal microbiota transplant (FMT).
- The randomised, double-blind design will provide the strongest evidence for clinical efficacy. Further, the intervention period is 6 weeks, including a 24-week follow-up period, making it one of the longest studies assessing efficacy and safety in FMTs.
- The anticipated sample size is a limitation (n=45).
- Results from this trial will provide information on the therapeutic efficacy of FMT and will inform future trials with larger sample sizes.

in peer-reviewed journals and will help inform a large, multicentre trial in the future.

Trial registration number NCT03378167; pre-results.

INTRODUCTION

Crohn's disease (CD) is a systemic disease characterised by chronic, idiopathic inflammation of the gastrointestinal tract.¹⁻⁴ Quality of life may be impaired by flares of abdominal pain, haematochezia, potentially toxic treatments and limited surgical options.^{5,6} Nearly 150 000 Canadians suffer from this condition, and notably, one of the highest incidences worldwide is in children aged <10 years and living in Ontario, Canada.^{3,4} Childhood-onset CD classically presents as a severe phenotype,⁷ with a potentially significant impairment on child and adolescent linear growths as a complication of undertreated inflammation.^{8,9} Children may experience poor nutrition and weight loss, frequent school absences and unpredictable flares involving

bloody diarrhoea, severe abdominal pain and fatigue.^{5 6 10} This overlap of a chronic autoimmune condition occurring during critical periods of growth, bone accretion and psychosocial development makes inflammatory bowel disease (IBD) exacerbations disproportionately affect the growing child. This heightened morbidity increases the clinical urgency to identify alternative treatments for paediatric IBD.

While the exact aetiology remains unknown, IBD is typically attributed to a breakdown in immune tolerance to commensal intestinal microbiota.⁴ The intestinal tract is an immunologically rich organ, containing the largest number and diversity of immune cells in the entire body.^{11 12} A vast number of predominantly CD4⁺ T cells and plasma cells reside in gastrointestinal-associated lymphoid tissues (GALTs) within the lamina propria.¹³ GALTs are highly specialised regions composed of Peyer's patches and isolated lymphoid follicles, responsible for sampling luminal contents and mediating tolerance to commensals via IgA secretions and regulatory T-cell activity.^{13 14} Disruptions to this complex intestinal–microbial–immune interaction may result in aberrant lymphocyte activation, formation of tertiary lymphoid organs and establishment of ectopic high endothelial venules, which serve as conduits for migration of effector memory T cells and extravasation to the intestinal mucosa, where they initiate an adaptive immune response.^{15 16}

The traditional approach to managing CD has involved immunosuppression to dampen the overactive immune system.¹⁷ This has been shown to result in higher lifetime rates of infection,¹⁸ medication side effects^{10 17} and potential malignancies.¹⁹ Surgical options involving colectomy or bowel resection are also performed; however, prophylactic removal of the colon during childhood and adolescence may have long-term impacts on fertility,^{20 21} nutritional status²² and psychosocial function.²³ As a result of the significant drawbacks to traditionally available treatment options, alternative strategies are now targeting IBD by way of manipulating the intestinal microbiome.

As reported in detail elsewhere,²⁴ the role of the microbiome in mediating intestinal homeostasis is supported by evidence of specific alterations in the gut microbiota of patients with ulcerative colitis (UC) and CD compared with healthy controls.^{25 26} These microbial signatures of IBD have led to several hypotheses about the protective and pathological roles of different resident intestinal bacterial species, including downregulating inflammation and decreasing production of short-chain fatty acids and other metabolites with immune regulatory properties.^{27–29} Faecal microbiota transplant (FMT) does not provide targeted, species-specific inoculations, but whole stool transplant could introduce a broad range of bacteria, including those that are theoretically 'favourable' to the host.

Rationale

FMT has been used for the treatment of recurrent *Clostridoides difficile* colitis with notable success. According to

a recent review, over 90% of patients treated with FMT for *C. difficile* infection were cured.³⁰ Strong evidence supports the role of FMT in the treatment of adult UC, a related class of IBD. To date, only a handful of randomised controlled trials (RCTs) have been published, with pooled clinical and endoscopic remission rates of 42.1% and 26.4%, respectively.^{31–36}

In contrast, FMT literature in paediatric IBD remains limited, with only four small case series and one unpublished trial (personal communication) demonstrating success.^{37–40} Protocols, routes of administration and outcomes varied across all series, but promising results were found in the FMT treatment groups, and patients with paediatric CD showed favourable response with upper gastrointestinal tract FMT delivery. Major drawbacks to the currently available paediatric FMT data include small sample sizes, invasive interventions and/or open-label study designs.

Three unpublished trials assessing the role of FMT in paediatric CD are currently registered on ClinicalTrials.gov (table 1). With no published protocols available, study designs vary considerably. Five prospective open-label studies and two placebo-controlled RCTs are registered. One ongoing trial has published results including paediatric patients but was limited in its unblinded study design, subjective assessment of FMT efficacy using the Harvey Bradshaw Index without objective laboratory or endoscopic markers reported, and absence of stratification to parse paediatric and adult response rates.^{41 42} This sparsity of research highlights the need for a rigorous study design with a robust sample size to determine the efficacy of FMT in clinically meaningful outcomes for patients with paediatric CD.

Need for a pilot study

There are several justifications for performing this pilot study. FMT for the treatment of paediatric CD is a new procedure. No defined protocols exist in the literature, and the use of combination oral and colonoscopic FMT infusions has not been previously tested. Oral FMT preparations are being increasingly used in clinical trials^{43–46} and offered through industry.^{47 48} These preparations may be easier to administer than rectal enema or endoscopic infusion and may be particularly amenable to serial administration. Nevertheless, dosing and frequency of administration are inconsistent across studies; our protocol may help to standardise methods across future trials to support robust systematic reviews and meta-analyses. Our study is targeted at a paediatric population. The potential challenges of performing clinical trials in children are both significant and often unexpected; parent and child acceptance of interventions vary widely, and the tolerance of healthcare providers to recommend paediatric patients into trials is not predictable. The success of our recruitment will help inform whether FMT for paediatric CD is truly wanted or is simply an intriguing concept that is ultimately rejected by families and children. Finally, this pilot is also necessary to establish power

Table 1 Active and completed paediatric Crohn's disease FMT trials registered on ClinicalTrials.gov

Location	Registration number	Status	Age (years)	FMT donor	Route	Randomisation	Sample size
Seattle, USA	NCT01757964 ^{38 69}	Completed	12–21	Parent	Nasogastric tube	Open label	13
Pittsburgh, USA	NCT02108821 ^{38 70}	Completed	2–22	Parent, sibling	Jejunum, terminal ileum via endoscopy	Open label	21
Boston, USA	NCT02330211 ⁷¹	Completed	5–30	OpenBiome (anonymous) ⁴⁸	Retention enema+oral capsules	Placebo-controlled randomised trial	4
Jiangsu, China ⁴²	NCT01793831 ⁴²	Recruiting, some results published	6–80	Family, friends, China FMT Bank (anonymous) ⁷²	Midgut via gastroscopy	Open label	200
Los Angeles, USA	NCT03194529 ⁷³	Recruiting	7–21	Anonymous donors	Jejunum via endoscopy	Open label	10*
Hamilton, Canada	NCT03582969 ⁶⁷	Recruiting	3–17	Rebiotix (anonymous) ⁵⁰	Terminal ileum via endoscopy +oral capsules	Placebo-controlled randomised trial	45*

*Estimated enrolment.
FMT, faecal microbiota transplant.

calculations for a full-scale study. A multicentre, larger programme of research is necessary to fully assess the role of FMT in paediatric CD treatment. This will include establishing noninferiority against alternative treatment options. Canada is well poised to adopt national studies in this population, as care of Canadian patients with paediatric IBD is largely centralised between 12 major paediatric hospitals across the country.⁴⁹ Nevertheless, launching an expensive, resource-intensive programme across this network must demonstrate regional feasibility first. Financial, technical, logistical and administrative barriers must be discerned.

Significance

Factors that contribute to the success of FMT in the treatment of IBD remain unclear. No RCT for FMT in CD has been published, to date, in children or adults. Furthermore, the currently available literature has not measured response in paediatric CD after FMT inoculation from an anonymous donor, an important distinction given that cohabiting family members may share colitogenic faecal microbiota with one another. The use of a combination colonoscopic+oral microbiota therapy protocol is particularly unique and may provide a useful method of targeting small intestinal and colonic disease, both hallmarks of CD. This study may provide important preliminary data to support alternative therapeutic treatments for this lifelong disease, with potential ramifications on pharmaceutical costs, medication side effects and disease burden for patients with paediatric CD and the health-care system.

Study objectives

Our clinical objective was to determine whether FMT can improve clinical, biological and mucosal disease status in paediatric CD using a double-blind, placebo-controlled study design. This trial will test the hypothesis that combination endoscopic FMT at induction, followed by oral microbiota capsules (OMCs) two times per week for 6 weeks using live faecal material from anonymous unrelated donors, can improve the disease activity of patients with paediatric CD. Our primary objective was to assess the feasibility of our study protocol. Our secondary objective was to assess the clinical efficacy of FMT in paediatric CD. We will evaluate the following measures:

1. Participant recruitment (sample size).
2. Participant retention (sample size).
3. Participant eligibility criteria (sample size).
4. Acceptance of patients to participate (process).
5. Effect of intervention on primary and secondary disease outcomes (clinical).
6. Effect of intervention on faecal bacterial community structure (clinical).
7. Rate of adverse events in patients undergoing FMT (clinical).

METHODS AND ANALYSIS

Study design

The Paediatric Crohn's Disease Faecal Transplant Trial will be a double-blind, randomised, placebo-controlled multicentre trial. Following our previous methodology, the study will use a parallel-arm approach composed of an intervention FMT group and a placebo group.²⁴ An unblinded, open-label arm will be offered to patients

initially randomised to the control arm on completing the study. The primary site involved in this multicentre trial is McMaster Children's Hospital, Hamilton, Ontario, and the secondary site is Centre Hospitalier Universitaire Sainte-Justine (CHU-SJ), Montréal, Quebec. Patient enrolment will begin in March 2019 at McMaster Children's Hospital and is tentatively planned for September 2019 at CHU-SJ.

Patients will be seen on-site for all scheduled visits in accordance with the protocol (figure 1). All colonoscopic infusions and oral capsules are screened, prepared and tested by Rebiotix,⁵⁰ and sent to the sites for patient

administration. The protocol design will involve baseline colonoscopic infusion to the terminal ileum, followed by oral capsule therapy two times per week for 6 weeks.

Inclusion/exclusion criteria

Subjects will be included if they are paediatric patients (3–17 years old) diagnosed with CD or IBD unclassified, strongly favouring CD (as deemed by the patient's primary paediatric gastroenterologist). Eligible patients must demonstrate signs of disease activity, as determined by measures of elevated inflammatory markers (faecal calprotectin and C reactive protein (CRP)) or increased

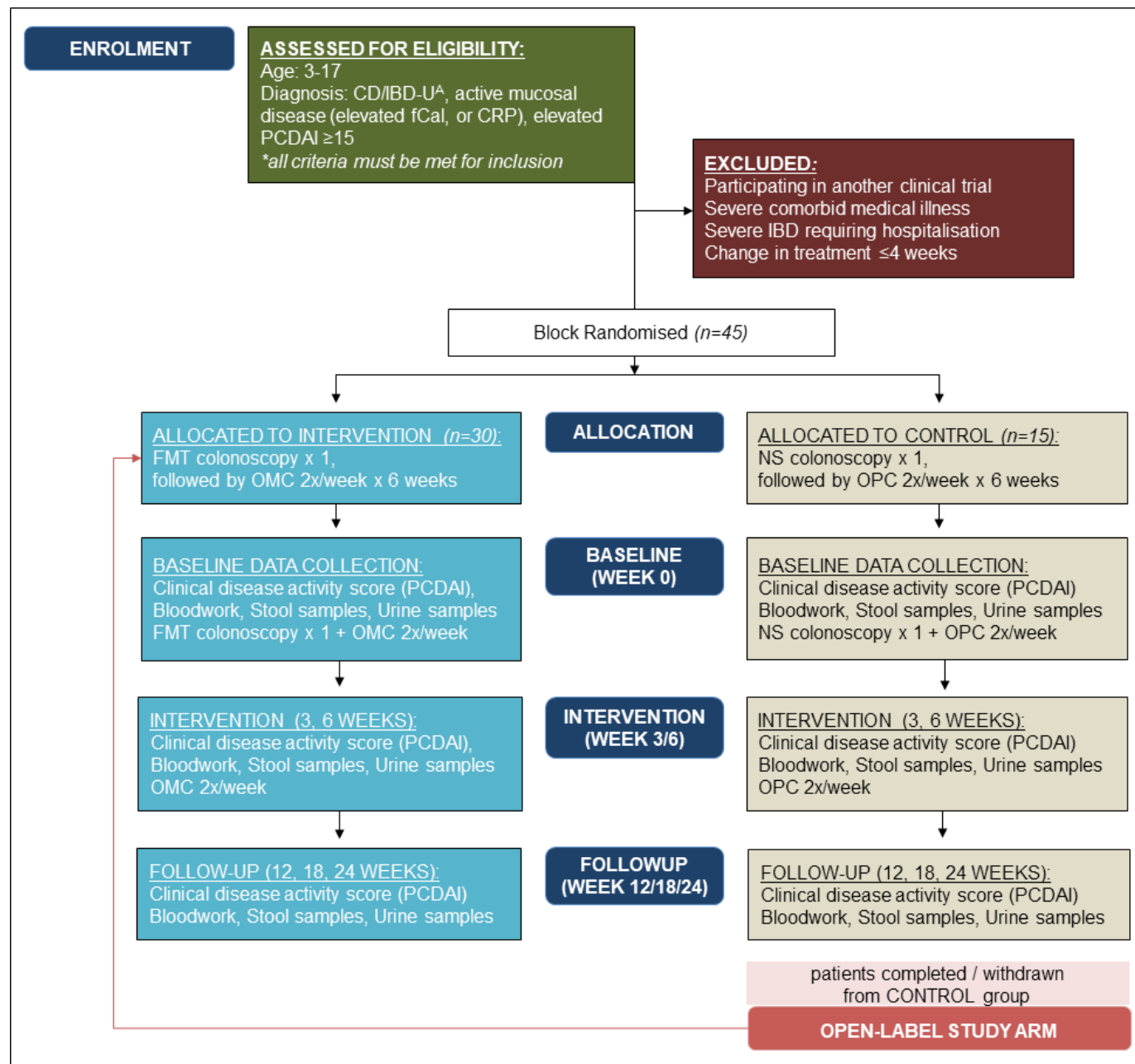


Figure 1 Protocol flowchart indicating intervention, control and open-label arms. ^AStrongly favouring CD as deemed by patient's primary gastroenterologist; CD, Crohn's disease; CRP, C reactive protein; fCal, faecal calprotectin; FMT, faecal microbiota transplant; IBD, inflammatory bowel disease; NS, normal saline; OMC, oral microbiota capsule; OPC, oral placebo capsule; PCDAI, Paediatric Crohn's Disease Activity Index .

disease activity supported by endoscopic findings and a Paediatric Crohn's Disease Activity Index (PCDAI) score of ≥ 15 .⁵¹⁻⁵³

Subjects will be excluded if they are currently enrolled in another clinical trial, unable to give informed consent or assent, have severe comorbid medical illnesses, have concomitant *C. difficile* infection, have active fistulae or exhibit severe CD flares requiring hospitalisation.²⁴ Eligible patients must remain on stable doses of all pre-existing medications, that is, azathioprine, 6-mercaptopurine, methotrexate or biological therapy. Patients will be excluded if they have commenced new or temporary medical therapies (eg, corticosteroids and antibiotics) within 4 weeks prior to commencing the trial. At the discretion of local principal investigators (LPIs), patients will not be excluded if they are completing weaning doses of corticosteroid therapy (ie, typically less than 0.25 mg/kg/day).²⁴

Duration of disease, history of prior *C. difficile* infection or prior/current medication history will not be considered for patient eligibility beyond what has been outlined earlier.

Sample size

The proposed sample size for our study is 45. As this is a pilot study, we seek to establish feasibility and information to be used for determining power calculations for future studies. Our proposed sample size was informed by (1) the number of potentially eligible patients with CD through McMaster and CHU-SJ paediatric IBD clinics, (2) the study team's recruitment experience with their previous paediatric FMT UC study²⁴ and (3) the number of clinic patients with CD who have already expressed interest at McMaster.

Randomisation

All patients who meet eligibility criteria will be approached for participation by the research coordinator. Patients will be randomised 2:1 to the intervention and control groups, respectively. Randomisation will involve computer-generated block randomisation (block size=6).

Intervention arm

Thirty patients were randomised to undergo FMT infusion into the terminal ileum via colonoscopy at week 0+OMC therapy two times per week for 6 weeks.

Control arm

Fifteen patients were randomised to undergo normal saline (NS) infusion into the terminal ileum via colonoscopy at week 0+microcrystalline cellulose-containing (MCC) oral placebo capsule (OPC) therapy two times per week for 6 weeks.

Open-label arm

Patients randomised to the control group (max n=15) will be given the option of entering the open-label arm on completion or withdrawal from the trial (ie, due to disease exacerbation or adverse event). Patients will be

reassessed by their primary gastroenterologist to determine eligibility. Patients will repeat the same protocol as the intervention group, but without blinding. Open-label patients' outcomes will not be included with blinded, randomised patients' analyses, as this pilot study is not powered for any of the outcomes.

Colonoscopic infusion product

Colonoscopies will be conducted per standard endoscopy procedure at the local study site. Infusions of 150 mL will be delivered into the terminal ileum (or most distally reached segment) on colonoscopy by the LPI.

The intervention study arm will receive RBX2660,⁵⁴ a faecal microbiota suspension prepared from human stool consisting of 150 mL ($\geq 10^7$ live microbes/mL of suspension). RBX2660 is delivered fresh-frozen by Rebiotix to the investigator in a single-dose enema bag. The 150 mL colonoscopic infusion will be drawn up from the RBX2660 enema bag using a 500 mL syringe. The syringe is concealed with an opaque bag to ensure contents are blinded to the patient, non-study personnel and the LPI administering the colonoscopic infusion during the colonoscopy.

The control study arm will have the identical procedure performed as previously mentioned, but with 150 mL NS infused through the colonoscope instead (NS+polyethylene glycol 3350). Blinding will be preserved by identical concealment of the 500 mL syringe used to withdraw and infuse contents through the colonoscope. For the placebo infusion, the research coordinator will add 0.75 mL of commercially available (Club House brand), food-grade food colouring (two drops red, three drops green and seven drops yellow) to confer a brown colour to maintain blinding.

A Simple Endoscopic Score for Crohn's Disease (SES-CD) will be measured at each endoscopy by the study team.⁵⁵ Endoscopies will be video recorded to allow for central reporting of the SES-CD. This will be completed by two members of the Clinical Trial Steering Committee (CTSC) following the procedure.

Oral capsule product

Following the baseline colonoscopic infusion, all patients will undergo oral capsular therapy two times per week for six consecutive weeks. Patients will be instructed to take four oral capsules in the morning and four oral capsules in the evening with at least 4 oz of water on an empty stomach (defined as not having had anything to eat or drink for 1 hour before and 2 hours after administration, aside from water). Patients who are unable to take the required number of oral capsules, who spit out a capsule or vomit a capsule will be asked to take the remaining pills as tolerated. No additional oral capsules will be given to make up for what has been lost.

Patients randomised to the intervention arm will receive RBX7455 (OMC),⁴⁷ a lyophilised, orally administered capsule containing live, human-derived faecal bacteria obtained from Rebiotix. The daily OMC dose

contains the equivalent of approximately 4g of human stool ($\geq 1.04 \times 10^9$ colony-forming unit, approximately eight capsules). RBX7455 has Clinical Trial Application (CTA) and Investigational New Drug Application (IND) approvals to conduct clinical trials in patients with recurrent *C. difficile* infection, and CTA approval to conduct a clinical trial of RBX7455 in patients with paediatric CD.⁴⁷

Patients randomised to the control arm will receive OPC. The capsules will contain MCC, a bulking agent commonly used in commercial food preparation.

The appearance, storage requirements, expiration, administration instructions and labels are the same for the OMC and OPC. OPC and OMC are both double encapsulated in size 00 enteric capsules, indistinguishable in size, colour and weight.

Preservation of double blinding

Patient, non-study personnel and LPI blinding will be accomplished by study personnel and Rebiotix facilitating matched concealment of all FMT and placebo materials used in the intervention and control groups. Food colouring of the control enema will be performed by the research coordinator only. The concealment process will involve the research coordinator adding food colouring to the placebo enema bag in a separate room, then an opaque covering applied around the bag. This will ensure the control enema appears identical to the intervention enema preparation at all times. The colonoscopic infusions will be prepared by the research coordinator. The oral capsules will be indistinguishable between the intervention and control groups. Unblinding to the LPI, patient and non-study personnel may occur at the end of the study or following patient withdrawal.

Patient and public involvement

The study design was informed by a prior trial conducted by the investigators assessing the feasibility and safety of FMT in paediatric UC (NCT02487238). The design was also informed by a follow-up study on patient and parent perceptions of FMT. Manuscripts for both studies are currently in preparation.

STATISTICAL ANALYSIS

Outcomes

Subjects will have outcome measures performed at 15 timepoints (figure 1). In addition to study outcome measures, patients in each randomisation arm will receive usual medical care. Outcome measurements are divided into (1) feasibility outcomes and (2) clinical outcomes measured at baseline and weeks 3, 6, 12, 18 and 24.

Feasibility outcomes include (1) patient eligibility, (2) patient recruitment, (3) patient retention, (4) completeness of blood, stool and urine sample collections, (5) completeness of PCDAI scores, (6) completeness of analysis on all microbiome samples and (7) rate of adverse events or hospitalisations throughout the study.

Clinical outcomes include (1) rate of clinical remission, (2) rate of clinical response, (3) rate of biological improvement, (4) change in urine metabolomics profile and (5v) change in intestinal microbiome.

Bloodwork collection will be performed during the intervention period (weeks 0, 3 and 6) and at scheduled clinic follow-up visits (weeks 12 and 24). Standard paediatric CD bloodwork to monitor for systemic inflammation will be collected: complete blood count, CRP, alanine transaminase, aspartate transaminase and alkaline phosphatase. Routine laboratory protocols and assays for obtaining and measuring samples will follow.⁵

Clinical disease activity scores will be objectively assessed using the internationally validated PCDAI clinical symptom score.^{53 56} Scores will be obtained at each clinical assessment during the intervention period (two times on weeks 0, 3 and 6) and follow-up period (once on weeks 12, 18 and 24).

Stool samples will be collected for microbiome 16S rRNA sequencing, additional microbial assays (including metagenomic assays, viral, fungal and bacteriophage assays) and faecal calprotectin at weeks 0, 3, 6, 12, 18 and 24. The assays will assess how microbial composition and diversity influence disease activity. With the exception of faecal calprotectin, all stool sequencing and analyses will be performed centrally through McMaster University. Samples collected from CHU-SJ will be transported to McMaster Children's Hospital for analysis.

Faecal microbiome, metagenomics assays, identification of faecal viruses, fungi and bacteriophage activity will be conducted through the laboratory of Dr Michael Surette (collaborator) within the McMaster University Farncombe Metagenomics Facility. Bacterial community profiling of 16S rRNA genes will be performed on part of each stool sample using 250 nucleotide paired-end reads of the V3 (or V3 and V4) region using MiSeq Illumina sequencer.⁵⁷ Analysis will be performed using an in-house bioinformatics pipeline that generates clusters of operational taxonomic units, taxonomic assignment and various measures of alpha diversity and beta diversity. If required at the bioinformatics stage, additional control microbial data will be obtained through the National Institute of Health Human Microbiome Project's published databanks.⁵⁸

All primary and secondary outcomes will be assessed using both intention-to-treat and per protocol as outlined previously.²⁴ The remission rates between the groups will be analysed with support from departmental statistical support personnel. Proportions and percentages will be reported to determine if all feasibility outcomes were achieved. Clinical outcomes will be measured as preliminary estimates of efficacy, through reporting of ORs, mean differences and 95% CIs (table 2).

SAFETY MONITORING

FMT product

Safety monitoring will be conducted as previously described, with donor material undergoing the same safety

Table 2 Trial outcomes (feasibility and clinical outcomes)

	Outcome	Measure	Analysis
Feasibility outcomes	Patient recruitment	Recruitment/month	≥20 patients/year recruited across all sites*
	Patient retention	Per cent withdrawal post recruitment	<50% of patients†
	Patient eligibility	Per cent meeting eligibility	>50% of patients
	Adverse events	Per cent disease exacerbation (↑PCDAI ≥20×2 consecutive measures) or hospitalisation	<50% of patients†
	Oral capsule adherence	Patient ingests all required capsules	>50% of patients
	Blood specimens	Patient provides all required blood samples	>75% of patients
	Stool specimens	Patient provides all required stool samples	>75% of patients
	Urine specimens	Patient provides all required urine samples	>75% of patients
	Microbiome	Microbiome analyses (16S rRNA profile and metagenomics) performed for patient at all required timepoints	>90% of patients
	PCDAI	Patient provides information to calculate all required PCDAI scores	>90% of patients
Clinical outcomes	Clinical remission (3 weeks)	PCDAI≤10	OR (95% CI)
	Clinical remission (6 weeks)	PCDAI≤10	OR (95% CI)
	Clinical remission (24 weeks)	PCDAI≤10	OR (95% CI)
	Sustained clinical remission (6–24 weeks)	Sustained PCDAI<10	OR (95% CI)
	Clinical improvement (3 weeks)	↓ PCDAI≥15 from baseline (week 0 PCDAI)	OR (95% CI)
	Clinical improvement (6 weeks)	↓ PCDAI≥15 from baseline (week 0 PCDAI)	OR (95% CI)
	Sustained Clinical improvement (6–24 weeks)	Sustained ↓ PCDAI≥15 from baseline (week 0 PCDAI)	OR (95% CI)
	Biological improvement (3 weeks)	↓ C reactive protein	Mean Δ (95% CI)
	Biological improvement (3 weeks)	↓ Faecal calprotectin	Mean Δ (95% CI)
	Biological improvement (6 weeks)	↓ C reactive protein	Mean Δ (95% CI)
	Biological improvement (6 weeks)	↓ Faecal calprotectin	Mean Δ (95% CI)
	Biological improvement (24 weeks)	↓ C reactive protein	Mean Δ (95% CI)
	Biological improvement (24 weeks)	↓ Faecal calprotectin	Mean Δ (95% CI)
	Change in urine (3 weeks)	Δ Urine metabolomics profile from baseline (week 0)	Mean Δ (95% CI), αβ diversity
	Change in urine (6 weeks)	Δ Urine metabolomics profile from baseline (week 0)	Mean Δ (95% CI), αβ diversity
	Change in urine (24 weeks)	Δ Urine metabolomics profile (week 0)	Mean Δ (95% CI), αβ diversity
	Change in microbiome (6 weeks)	Δ 16S rRNA profile, metagenomics profile from baseline (week 0)	Mean Δ (95% CI), αβ diversity
	Change in microbiome (6 weeks)	Δ 16S rRNA profile, metagenomics profile from baseline (week 0)	Mean Δ (95% CI), αβ diversity
	Change in microbiome (24 weeks)	Δ 16S rRNA profile, metagenomics profile from baseline (week 0)	Mean Δ (95% CI), αβ diversity

*Patients may be recruited to any group: control, intervention or open-label group.

†At least 33% of the patients will be expected to withdraw from the trial or to show some degree of adverse events due to having active Crohn's disease and undergoing placebo treatment through the control group.
PCDAI, Paediatric Crohn's Disease Activity Index.

screening protocol.²⁴ The two investigational products, RBX7455 and RBX2660, have obtained US Food and Drug Administration (FDA) IND approval for clinical trial use in patients with recurrent *C. difficile* infections, and RBX2660 has obtained an FDA IND approval for clinical trial use in patients with paediatric UC.^{47 54 59} Approval

to conduct this trial has also been obtained from Health Canada's Biologics and Genetic Therapies Directorate.⁶⁰

Study risks involve complications of FMT and route of delivery. High-quality data gathered over the course of the last past 10 years involving patients undergoing FMT with significant comorbidities (haematopoietic stem-cell

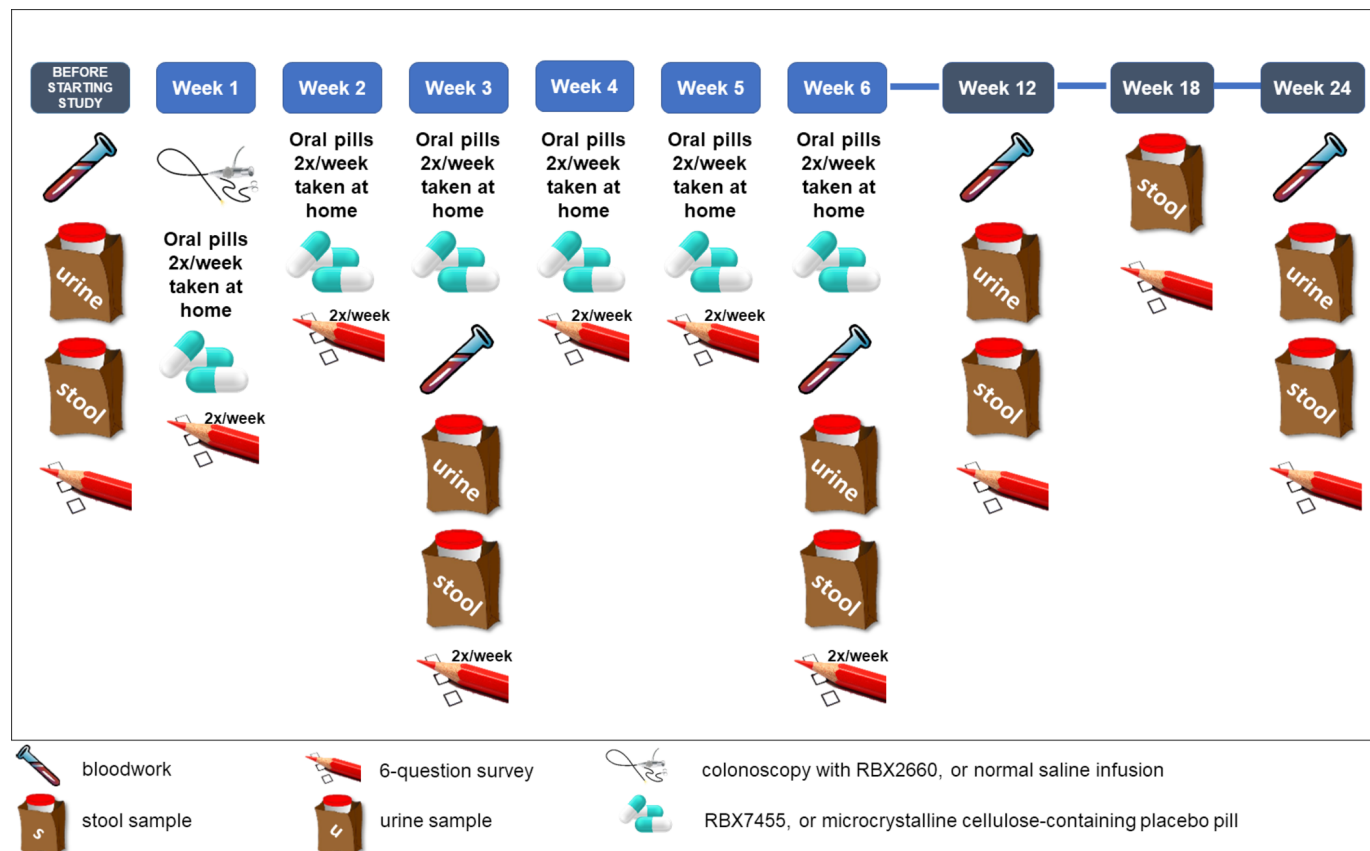


Figure 2 Collection timepoints of clinical study outcomes.

transplant, solid organ transplant and other immunosuppressed states) suggest low rates of directly attributable adverse events to FMT inoculation⁶¹; however, IBD flares have been reported in 3.6% of paediatric patients undergoing FMT for recurrent *C. difficile* infection, and short-term gastrointestinal complaints (bloating, flatulence and diarrhoea) are most common.⁶¹ Known risks associated with colonoscopy and general anaesthesia include a 0.2% risk in patients of infection, perforation, haematoma, hypoxia, aspiration and bleeding.⁶² Administrations of OMC carry a low risk of vomiting, nausea and pulmonary aspiration.⁶¹ Patients will be enrolled only if they are able to confidently swallow pills. Advanced coaching through hospital-designated child life specialists will be offered to patients who experience challenges with pill swallow.

STUDY PARTICIPANTS

Study participants will be monitored for signs of clinical deterioration over 15 timepoints (figure 2). PCDAI scores will be measured at defined trial timepoints (figure 1). Any increase in disease activity score of ≥ 20 from previous will be classified as 'disease progression'.^{53 56} Reassessment of PCDAI scoring will occur within 1 week, and any further increase of ≥ 20 will warrant removal from the study for implementation of standard IBD management.

Patients will be monitored during the trial through investigator-led and patient-led surveillance methods:

1. Patient-led safety monitoring. Patients who contact study coordinators reporting fever or worsening vomiting, abdominal pain, rectal pain, diarrhoea or haematochezia will have PCDAI scores measured to evaluate for disease progression. Participants with PCDAI scores of ≥ 20 at successive measurements will be removed from the study. Participants may be removed from the study at the discretion of the patient's primary paediatric gastroenterologist and/or the CTSC. Patients may also voluntarily withdraw from the study at any time, as outlined at the time of informed consent. Unblinding will be performed if the patient withdraws or is removed from the study.
2. Investigator-led safety monitoring. An online questionnaire is sent to patients two times per week during the intervention and once a week during the follow-up period. Patients are asked to provide responses to calculate a PCDAI score.⁵² Patients are also contacted once a week by the research coordinator to discuss how the trial is going and to assess any unreported symptoms in patients that may prompt review by the principal investigator.

External study monitoring

Three external study monitors will be assembled for the study: (1) Data, Safety and Monitoring Board (DSMB), (2) CTSC and the (3) Local Research Office Internal Audit.

The DSMB will perform an interval assessment of preliminary study data approximately midway through the trial's recruitment. The DSMB will be composed of experts in the fields of paediatric gastroenterology, paediatric IBD management and clinical trial statistical analyses, and will operate independently of the investigators and collaborators for the trial. The CTSC will meet at least once per year to review ongoing trial conduct. It will comprise local experts. Both study sites will involve the support of their respective institutional research offices to conduct an internal audit by a member unaffiliated with the study team, approximately midway through the trial at each centre.

ETHICS AND DISSEMINATION

Ethics

The study will be conducted in accordance with the described study protocol, Helsinki declaration,⁶³ Canadian Tri-Council Policy Statement on research ethics,⁶⁴ Hamilton Integrated Research Ethics Board,⁶⁵ CHU-SJ Research Ethics Board⁶⁶ and Health Canada Biologics and Genetic Therapies Directorate.⁶⁰ All amendments to the trial protocol will be obtained through approval by both institutions' Research Ethics Boards, updated through the clinical trials registry (ClinicalTrials.gov)⁶⁷ and filed as amendments with Health Canada. All patients who meet eligibility criteria and choose to take part in the trial will need to sign approved consent and assent forms prior to enrolment. Patients will be permitted to withdraw from the trial at any time.

Data sharing

Anonymised data about patient outcomes will be shared with Rebiotix for assessment of RBX2660 and RBX7455 efficacy. The information shared will be limited to

1. Patient age, height and weight.
2. Patient medication history (previous and ongoing).
3. Dates of FMT treatments, amount administered and reported adverse effects of delivery.
4. PCDAI scores, results of bloodwork, faecal calprotectin and urine metabolomics.

Deidentified patient stool samples may be sent to Rebiotix in accordance with the US National Institutes of Health-endorsed Human Microbiome Project Data Release and Resource Sharing Guidelines statement.⁶⁸

As Rebiotix is located in the USA, US regulatory bodies will also have permission to access information from these samples.

Follow-up

Results from this pilot will inform several future research goals. Pilot data will be used to inform a definitive multi-centre randomised controlled trial using a larger paediatric patient population. Data will be used to support additional research funding for a multicentre trial through a Canadian Institute of Health Research operating grant. Our data may also support further crossover studies between human

and mouse models to ascertain host-microbial influences underlying observed changes.

Reporting

Results of the study will be reported as previously outlined.²⁴

FUTURE DIRECTIONS

The results of this trial will provide preliminary evidence for feasibility and therapeutic use of FMT in paediatric CD. Furthermore, these results will serve as a platform for informing larger trials in the future, which will be powered appropriately to assess true therapeutic benefit by way of primary and secondary outcomes.

Primary outcomes

- ▶ Evaluation of the feasibility of administering FMT via colonoscopic infusion and oral capsules two times per week in a paediatric population.
- ▶ Evaluation of the safety of employing colonoscopic and oral FMT modalities in a paediatric CD population.

Secondary outcomes

- ▶ Evaluation of efficacy of inducing clinical improvement and/or remission in paediatric CD using stool from anonymous donors via colonoscopic and oral modalities.
- ▶ Evaluation of long-term clinical improvement and/or remission and mucosal healing post-FMT treatment.
- ▶ Evaluation of changes in the faecal microbiome.
- ▶ Evaluation of systemic changes as measured by urine metabolomics profile.

DISCUSSION

Five case series have been published on the use of FMT in paediatric UC and CD. Protocols varied between all studies, and four main routes of administration were used: serial enemas,⁴⁰ serial enemas with supplementary colonoscopic administration,³⁹ nasogastric tube^{37 38} and nasojejunal tube.⁴¹ While three of the studies demonstrated promising results,³⁷⁻³⁹ their methods were heterogeneous; sample sizes were small; and they lacked a rigorous placebo-controlled design. A recent series involving nasojejunal infusion of a single FMT treatment included 21 patients with paediatric CD aged <16 years. Cumulative response and remission rates were reported as 71% and 57%, respectively, across all patients in the cohort (n=139), but these results were not stratified by age; clinical efficacy was assessed 1 month postintervention; and patients were unblinded.⁴¹ While results were promising, FMT trials demand blinded study protocols, particularly given that patients who enrol in FMT studies may have a stronger confirmation bias towards believing in the therapeutic value of 'natural' treatments. IBD has well-described associations between clinical symptoms, mucosal disease activity and underlying stressors; this patient confirmation bias therefore may have a significant confounding effect on self-reported clinical disease

activity scores, and potentially even biological markers of inflammation.

This double-blind, placebo-controlled trial will resolve the shortcomings in the currently available literature. It will test the hypothesis that inoculation with FMT from anonymous, non-household donors using a colonoscopic infusion at baseline, followed by oral FMT administration two times per week for 6 weeks, will result in mucosal healing in a paediatric CD population. In contrast to previous studies, this trial will use a double-blind research design, a standardised number of FMT inoculations for every patient, and active surveillance of patients during the intervention and follow-up periods to monitor clinical, biochemical and mucosal markers of inflammation.

The results of this trial will inform future studies of the feasibility and safety of using FMT in patients with paediatric CD using both, colonoscopic and oral modalities. Further, they will provide preliminary evidence for the therapeutic benefit of FMT in inducing mucosal healing in paediatric CD.

Acknowledgements We thank Drs Paul Moayyedi and Christine Lee for their mentorship and support with the study design; Dr Lehana Thabane for his statistical review of the manuscript; our valued co-investigators: Drs Kelly Grzywacz, David Godin, Waliul Khan, Philip Britz-McKibbin, Michael Surette; our research assistants: Ms. Melanie Figueredo and Michal Moshkovich; and finally, our exceptional patients, families and colleagues at McMaster Children's Hospital's and Centre Hospitalier Universitaire Sainte-Justine.

Collaborators Paul Moayyedi, Christine Lee, Kelly Grzywacz, David Godin, Lehana Thabane, Waliul Khan, Philip Britz-McKibbin and Michael Surette.

Contributors NP and JP: substantial contributions to the conception and design of the trial, drafting of the manuscript, final approval of the protocol to be published and agreement to be accountable for all aspects of the work. LH: substantial contributions to drafting of the manuscript, final approval of the protocol to be published and acquisition of trial data. EH: substantial contributions to the drafting of the manuscript, final approval of the protocol to be published and acquisition of trial data.

Funding This work was supported by Hamilton Health Sciences New Investigator Fund (2018, Spring), and Hamilton Academic Health Sciences Organization Alternate Funding Plan Innovation Grant (2018/2019).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Nikhil Pai <http://orcid.org/0000-0002-7537-6059>

REFERENCES

- Bessissow T, Reinglas J, Aruljothy A, *et al.* Endoscopic management of Crohn's strictures. *World J Gastroenterol* 2018;24:1859–67.
- Lowe A-M, Roy P-O, B-Poulin M, *et al.* Epidemiology of Crohn's disease in Québec, Canada. *Inflamm Bowel Dis* 2009;15:429–35.
- Benchimol EI, Guttman A, Griffiths AM, *et al.* Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data. *Gut* 2009;58:1490–7.
- Rocchi A, Benchimol EI, Bernstein CN, *et al.* Inflammatory bowel disease: a Canadian burden of illness review. *Can J Gastroenterol* 2012;26:811–7.
- Talley NJ, Abreu MT, Achkar J-P, *et al.* An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol* 2011;106:S2–25.
- Mann G, Greer M-L, Nadel H. Paediatric Crohn's Disease. In: Greer M-L, Nadel H, Mann G, eds. *Crohn's Disease*. Cham: Springer International Publishing, 2015: 123–42.
- Hyams JS, Davis P, Grancher K, *et al.* Clinical outcome of ulcerative colitis in children. *J Pediatr* 1996;129:81–8.
- Benchimol EI, Fortinsky KJ, Gozdyra P, *et al.* Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;17:423–39.
- El Mouzan M, Al Mofarreh MA, Saadah OI. Impact of pediatric inflammatory bowel disease on linear growth: data from a national cohort study in Saudi Arabia. *Saudi J Gastroenterol* 2016;22:396–108.
- Sanderson IR. Growth problems in children with IBD. *Nat Rev Gastroenterol Hepatol* 2014;11:601–10.
- Agace WW, McCoy KD. Regionalized development and maintenance of the intestinal adaptive immune landscape. *Immunity* 2017;46:532–48.
- Pabst O, Pires da Cunha A, Weiner HL. Mechanisms of oral tolerance to soluble protein antigens. In: *Mucosal Immunology*. Elsevier 2015:831–48.
- Bischoff SC, Sampson HA. Food allergy and gastrointestinal syndromes. In: *Allergy: expert consult online and print*. 4th edn, 2012: 297–303.
- Murch S. Pediatric gastrointestinal and liver disease. (Murch S, ED.). Elsevier 2011.
- Horjus Talabur Horje CS, Smids C, Meijer JWR, *et al.* High endothelial venules associated with T cell subsets in the inflamed gut of newly diagnosed inflammatory bowel disease patients. *Clin Exp Immunol* 2017;188:163–73.
- McNamee EN, Rivera-Nieves J. Ectopic tertiary lymphoid tissue in inflammatory bowel disease: protective or Provocateur? *Front Immunol* 2016;7.
- Dignass A, Van Assche G, Lindsay JO, *et al.* The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010;4:28–62.
- Vernier-Massouille G, Balde M, Salleron J, *et al.* Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008;135:1106–13.
- von Roon AC, Karamountzos L, Purkayastha S, *et al.* Diagnostic precision of fecal calprotectin for inflammatory bowel disease and colorectal malignancy. *Am J Gastroenterol* 2007;102:803–13.
- Cunliffe RN, Scott BB. Monitoring for drug side-effects in inflammatory bowel disease. *Aliment Pharmacol Ther* 2002;16:647–62.
- Tavernier N, Fumery M, Peyrin-Biroulet L, *et al.* Systematic review: fertility in non-surgically treated inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:847–53.
- Vasseur F, Gower-Rousseau C, Vernier-Massouille G, *et al.* Nutritional status and growth in pediatric Crohn's disease: a population-based study. *Am J Gastroenterol* 2010;105:1893–900.
- Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. *Inflamm Bowel Dis* 2006;12:697–707.
- Pai N, Popov J. Protocol for a randomised, placebo-controlled pilot study for assessing feasibility and efficacy of faecal microbiota transplantation in a paediatric ulcerative colitis population: PediFETCh trial. *BMJ Open* 2017;7:e016698.
- Haberman Y, Tickle TL, Dexheimer PJ, *et al.* Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. *J Clin Invest* 2014;124:3617–33.
- Gevers D, Kugathasan S, Denson LA, *et al.* The Treatment-Naive Microbiome in New-Onset Crohn's Disease. *Cell Host Microbe* 2014;15:382–92.
- Conte MP, Schippa S, Zamboni I, *et al.* Gut-Associated bacterial microbiota in paediatric patients with inflammatory bowel disease. *Gut* 2006;55:1760–7.
- Tedelind S, Westberg F, Kjerrulf M, *et al.* Anti-Inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. *World J Gastroenterol* 2007;13:2826–32.
- Machiels K, Joossens M, Sabino J, *et al.* A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut* 2014;63:1275–83.
- Kassam Z, Lee CH, Yuan Y, *et al.* Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013;108:500–8.

- 31 Moayyedi P, Surette MG, Kim PT, *et al.* Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology* 2015;149:102–9.
- 32 Paramsothy S, Kamm MA, Kaakoush NO, *et al.* Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017;389:1218–28.
- 33 Costello SP, Soo W, Bryant RV, *et al.* Systematic review with meta-analysis: faecal microbiota transplantation for the induction of remission for active ulcerative colitis. *Aliment Pharmacol Ther* 2017;46:213–24.
- 34 Narula N, Kassam Z, Yuan Y, *et al.* Systematic review and meta-analysis: fecal microbiota transplantation for treatment of active ulcerative colitis. *Inflamm Bowel Dis* 2017;23:1702–9.
- 35 Rossen NG, Fuentes S, van der Spek MJ, *et al.* Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology* 2015;149:110–8.
- 36 Goyal A, Yeh A, Bush BR, *et al.* Safety, clinical response, and microbiome findings following fecal microbiota transplant in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2018;24:410–21.
- 37 Suskind DL, Singh N, Nielson H, *et al.* Fecal microbial transplant via nasogastric tube for active pediatric ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2015;60:27–9.
- 38 Suskind DL, Brittnacher MJ, Wahbeh G, *et al.* Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease. *Inflamm Bowel Dis* 2015;21:556–63.
- 39 Kellermayer R, Nagy-Szakal D, Harris RA, *et al.* Serial fecal microbiota transplantation alters mucosal gene expression in pediatric ulcerative colitis. *Am J Gastroenterol* 2015;110:604–6.
- 40 Kunde S, Pham A, Bonczyk S, *et al.* Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013;56:597–601.
- 41 Wang H, Cui B, Li Q, *et al.* The Safety of Fecal Microbiota Transplantation for Crohn's Disease: Findings from A Long-Term Study. *Adv Ther* 2018;35:1935–44.
- 42 Zhang F. Standardized Fecal Microbiota Transplantation for Crohn's Diseases (NCT01793831). U.S. National Library of Medicine: Clinical Trials.
- 43 Youngster I, Gerding DN. Editorial: making fecal microbiota transplantation easier to swallow: freeze-dried preparation for recurrent *Clostridium difficile* infections. *Am J Gastroenterol* 2017;112:948–50.
- 44 Youngster I, Mahabamunuge J, Systrom HK, *et al.* Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent *Clostridium difficile* infection. *BMC Med* 2016;14.
- 45 Kao D, Roach B, Silva M, *et al.* Effect of Oral Capsule– vs Colonoscopy–Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection. *JAMA* 2017;318.
- 46 Jiang Z-D, Jenq RR, Ajami NJ, *et al.* Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent *Clostridium difficile* infection: a randomized clinical trial. *PLoS One* 2018;13:e0205064.
- 47 Rebiotix. RBX7455 clinical trials. Available: <https://www.rebiotix.com/clinical-trials/rbx7455-oral-c-diff-prevention/> [Accessed 1 Jul 2019].
- 48 OpenBiome. Available: <https://www.openbiome.org/> [Accessed 1 Jul 2019].
- 49 CIDsCaNN. The Canadian children inflammatory bowel disease network. Available: <http://www.cidscann.ca/>
- 50 Rebiotix. Microbiota restoration therapy. Available: <https://www.rebiotix.com/> [Accessed 1 Jul 2019].
- 51 Turner D, Otley AR, Mack D, *et al.* Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133:423–32.
- 52 Turner D, Griffiths AM, Walters TD, *et al.* 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.
- 53 Turner D, Levine A, Walters TD, *et al.* Which PCDAI version best reflects intestinal inflammation in pediatric Crohn disease? *J Pediatr Gastroenterol Nutr* 2017;64:254–60.
- 54 RBX R. *Clinical Trials*;2660 <https://www.rebiotix.com/clinical-trials/rbx2660-clinical-trials/>
- 55 Daperno M, D'Haens G, Van Assche G, *et al.* Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;60:505–12.
- 56 Hyams JS, Ferry GD, Mandel FS, *et al.* Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991;12:439–47 <http://www.ncbi.nlm.nih.gov/pubmed/1678008>
- 57 Illumina. MiSeq™ system. Available: <https://www.illumina.com/systems/sequencing-platforms/miseq.html> [Accessed 1 Jul 2019].
- 58 National Institutes of Health. Nih human microbiome project. National Institutes of health. Available: <https://hmpdacc.org/> [Accessed 1 Jul 2019].
- 59 Pai N, Popov J. Pediatric fecal microbiota transplant for ulcerative colitis (PediFETCh) (NCT02487238). U.S. National library of medicine: clinical trials.
- 60 Government of Canada. Biologics and genetic therapies Directorate. health products and food branch, 2019. Available: <https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/biologics-genetic-therapies-directorate.html> [Accessed 1 Jul 2019].
- 61 Cammarota G, Ianiro G, Tilg H, *et al.* European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 2017;66:569–80.
- 62 Thakkar K, El-Serag HB, Mattek N, *et al.* Complications of pediatric colonoscopy: a five-year multicenter experience. *Clin Gastroenterol Hepatol* 2008;6:515–20.
- 63 General Assembly of the World Medical Association. World Medical association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent* 2014;81:14–18.
- 64 Tri-Council policy statement: ethical conduct for research involving humans. Available: http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf
- 65 Hamilton Integrated Research Ethics Board. Forms & Downloads. Available: <https://www.hireb.ca/forms-downloads/> [Accessed 15 Jun 2018].
- 66 Research Centre of the Sainte-Justine University Hospital. Research ethics. Available: [https://research.chusj.org/en/Services/Comite-d-ethique-de-la-recherche-\(CER\)/Roles-du-CER](https://research.chusj.org/en/Services/Comite-d-ethique-de-la-recherche-(CER)/Roles-du-CER) [Accessed 1 Jul 2019].
- 67 Pai N, Hill L, Popov J. PediCRaFT: Pediatric Crohn's Disease Fecal Transplant Trial (PediCRaFT) (NCT03378167). U.S. National Library of Medicine: Clinical Trials.
- 68 National Institutes of Health. Hmp data release and resource sharing guidelines for human microbiome project data production grants. Available: <https://commonfund.nih.gov/hmp/datareleaseguidelines> [Accessed 22 Oct 2017].
- 69 Suskind D. Bacteriotherapy in pediatric inflammatory bowel disease (NCT01757964). U.S. National library of medicine: clinical trials.
- 70 Goyal A. Fecal microbiota transplantation in pediatric patients (FMT) (NCT02108821). U.S. National library of medicine: clinical trials.
- 71 Kahn S. Fecal Microbiota Transplant (FMT) in Pediatric Active Crohn's Colitis (NCT02330211). U.S. National Library of Medicine: Clinical Trials.
- 72 Hospital XFMMUXDD. Available: . [fmtBank.org](http://fmtbank.org/). <http://fmtbank.org/>. [Accessed 1 Jul 2019].
- 73 Michail S, Leong R. FMT in Pediatric Crohn's Disease (FMTPCD) (NCT03194529). U.S. National Library of Medicine: Clinical Trials 2017.