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Fecal transplantation for treatment of inflammatory bowel disease (Review)

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[Intervention Review]

Fecal transplantation for treatment of inflammatory bowel disease

Aamer Imdad[1], Natasha G Pandit[2], Muizz Zaman[2], Nathan Zev Minkoff[3], Emily E Tanner-Smith[4], Oscar G Gomez-Duarte[5], Sari Acra[6], Maribeth R Nicholson[6]

[1]Department of Pediatrics, Division of Pediatric Gastroenterology, Hepatology and Nutrition, SUNY Upstate Medical University, Syracuse, New York, USA. [2]Norton College of Medicine, SUNY Upstate Medical University, Syracuse, New York, USA. [3]Pediatric Gastroenterology, Hepatology and Nutrition, Valley Children's Hospital, Madera, CA, USA. [4]Counseling Psychology and Human Services, University of Oregon, Eugene, Oregon, USA. [5]Division of Pediatric Infectious Diseases, Department of Pediatrics, University at Buffalo, State University of New York, Buffalo, New York, USA. [6]Department of Pediatrics, D. Brent Polk Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

Contact: Aamer Imdad, aamer08@gmail.com.

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ABSTRACT

Background

Inflammatory bowel disease (IBD) is a chronic, relapsing disease of the gastrointestinal (GI) tract that is thought to be associated with a complex interplay between the immune system, the GI tract lining, the environment, and the gut microbiome, leading to an abnormal inflammatory response in genetically susceptible individuals. An altered composition of the gut's native microbiota, known as dysbiosis, may have a major role in the pathogenesis of ulcerative colitis (UC) and Crohn disease (CD), two subtypes of IBD. There is growing interest in the correction of this underlying dysbiosis using fecal microbiota transplantation (FMT).

Objectives

To evaluate the benefits and safety profile of FMT for treatment of IBD in adults and children versus autologous FMT, placebo, standard medication, or no intervention.

Search methods

We searched CENTRAL, MEDLINE, Embase, two clinical trial registries, and the reference sections of published trials through 22 December 2022.

Selection criteria

We included randomized controlled trials that studied adults and children with UC or CD. Eligible intervention arms used FMT, defined as the delivery of healthy donor stool containing gut microbiota to a recipient's GI tract, to treat UC or CD.

Data collection and analysis

Two review authors independently screened studies for inclusion. Our primary outcomes were: 1. induction of clinical remission, 2. maintenance of clinical remission, and 3. serious adverse events. Our secondary outcomes were: 4. any adverse events, 5. endoscopic remission, 6. quality of life, 7. clinical response, 8. endoscopic response, 9. withdrawals, 10. inflammatory markers, and 11. microbiome outcomes. We used the GRADE approach to assess the certainty of evidence.

Main results

We included 12 studies with 550 participants. Three studies were conducted in Australia; two in Canada; and one in each of the following: China, the Czech Republic, France, India, the Netherlands, and the USA. One study was conducted in both Israel and Italy. FMT was administered in the form of capsules or suspensions and delivered by mouth, nasoduodenal tube, enema, or colonoscopy. One study delivered FMT by both oral capsules and colonoscopy. Six studies were at overall low risk of bias, while the others had either unclear or high risk of bias.

Ten studies with 468 participants, of which nine studies focused on adults and one focused on children, reported induction of clinical remission in people with UC at longest follow-up (range 6 to 12 weeks) and showed that FMT may increase rates of induction of clinical remission in UC compared to control (risk ratio (RR) 1.79, 95% confidence interval (CI) 1.13 to 2.84; low-certainty evidence). Five studies showed that FMT may increase rates of induction of endoscopic remission in UC at longest follow-up (range 8 to 12 weeks); however, the CIs around the summary estimate were wide and included a possible null effect (RR 1.45, 95% CI 0.64 to 3.29; low-certainty evidence). Nine studies with 417 participants showed that FMT may result in little to no difference in rates of any adverse events (RR 0.99, 95% CI 0.85 to 1.16; low-certainty evidence). The evidence was very uncertain about the risk of serious adverse events (RR 1.77, 95% CI 0.88 to 3.55; very low-certainty evidence) and improvement in quality of life (mean difference (MD) 15.34, 95% CI −3.84 to 34.52; very low-certainty evidence) when FMT was used to induce remission in UC.

Two studies, of which one also contributed data for induction of remission in active UC, assessed maintenance of remission in people with controlled UC at longest follow-up (range 48 to 56 weeks). The evidence was very uncertain about the use of FMT for maintenance of clinical remission (RR 2.97, 95% CI 0.26 to 34.42; very low-certainty evidence) and endoscopic remission (RR 3.28, 95% CI 0.73 to 14.74; very low-certainty evidence). The evidence was also very uncertain about the risk of serious adverse events, risk of any adverse events, and improvement in quality of life when FMT was used to maintain remission in UC.

None of the included studies assessed use of FMT for induction of remission in people with CD.

One study with 21 participants reported data on FMT for maintenance of remission in people with CD. The evidence was very uncertain about the use of FMT for maintenance of clinical remission in CD at 24 weeks (RR 1.21, 95% CI 0.36 to 4.14; very low-certainty evidence). The evidence was also very uncertain about the risk of serious or any adverse events when FMT was used to maintain remission in CD. None of the studies reported data on use of FMT for maintenance of endoscopic remission or improvement in quality of life in people with CD.

Authors' conclusions

FMT may increase the proportion of people with active UC who achieve clinical and endoscopic remission. The evidence was very uncertain about whether use of FMT in people with active UC impacted the risk of serious adverse events or improvement in quality of life. The evidence was also very uncertain about the use of FMT for maintenance of remission in people with UC, as well as induction and maintenance of remission in people with CD, and no conclusive statements could be made in this regard. Further studies are needed to address the beneficial effects and safety profile of FMT in adults and children with active UC and CD, as well as its potential to promote longer-term maintenance of remission in UC and CD.

PLAIN LANGUAGE SUMMARY

Stool transplantation for treatment of inflammatory bowel disease

Key messages

• Ulcerative colitis (UC) and Crohn disease (CD) are two forms of inflammatory bowel disease (IBD). IBD is an autoimmune disease affecting the gut, as the body's immune system mistakenly attacks healthy cells, tissues, and organs.

• Fecal transplantation may increase the proportion of people with active UC who achieve control of the disease, defined as clinical remission (disease control defined based on clinical symptoms) and endoscopic remission (disease control defined based on endoscopic findings), and may have little to no effect on rates of any adverse events (unwanted events that causes harm to the person).

• The evidence was very uncertain about the risk of serious adverse events and improvement in quality of life when fecal transplantation was used for control of active UC.

• The evidence was also very uncertain about the use of fecal transplantation for induction of remission in people with active CD and maintenance of remission in people with UC or CD.

• Fecal transplantation is an evolving therapy and further studies are needed to evaluate its benefits and risks in both adults and children with active UC or CD, as well as its potential use for long-term control of UC and CD.

What is inflammatory bowel disease?

UC and CD are two forms of IBD that can cause weight loss, abdominal pain, and blood loss due to inflammation (pain and swelling) in the gastrointestinal (GI) tract, affecting an estimated 6.8 million people worldwide. The exact reasons that people develop IBD are still to be

determined, but are thought to involve a complex interaction between the immune system, the GI tract lining, the environment, and the gut microbiome, leading to an abnormal inflammatory response in genetically susceptible individuals. Evidence suggests that an unhealthy composition of the gut microbiota is associated with development of IBD, and its correction may help to control the inflammation seen in IBD. Stool administration from healthy donor to patient, called fecal microbiota transplantation (FMT), may restore a healthy balance of gut microbiota and control IBD-related inflammation both in active disease (called induction of remission) and on a long-term scale (called maintenance of remission).

What did we want to assess?

We wanted to assess the benefits and risks of FMT for treatment of IBD (UC and CD).

What did we do?

We searched multiple databases for randomized controlled trials (RCTs), a study design considered to be superior for assessment of clinical interventions, that compared FMT to control therapies for IBD. We combined the data from multiple studies when possible and rated our confidence in the evidence based on factors such as study methods, participants' awareness of the treatment they received, and sample sizes.

What did we find?

Ten studies (nine in adults and one in children) showed that FMT may increase rates of induction of clinical remission and endoscopic remission and may result in little to no difference in rates of any adverse events in people with active UC. The data on risk of serious adverse events and improvement in quality of life were very uncertain, and no conclusions could be drawn regarding these outcomes.

Two studies reported data on use of FMT for maintenance of remission in adults with controlled UC. Overall, the evidence was very uncertain about the use of FMT to maintain clinical or endoscopic remission in controlled UC, as well as the associated risk of adverse events and improvement in quality of life.

None of the included studies reported data on use of FMT for control of active CD.

One study reported data on use of FMT for maintenance of remission in adults with controlled CD, and the evidence was very uncertain about the benefits and risks of FMT when used to maintain clinical remission in controlled CD.

The studies varied in their methods, dosages, and frequencies of FMT administration, as well as the types of donors and baseline severity of disease. The FMT administration methods included oral capsule, nasoduodenal tube (a tube that travels from the nose to small bowel via the stomach), rectal enema, colonoscopy (a tube inserted into the colon via the anus), and combinations of these methods.

What are the limitations of the evidence?

Our confidence in the evidence was limited due to the small numbers of participants, concerns regarding how the studies were conducted, and variations of effect among studies in some of the analyses. Additional studies are needed to address the benefits and risks of FMT in adults and children with IBD.

How up-to-date is this evidence?

This review is an update of our previous review that was published in 2018. The evidence is up-to-date as of 22 December 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Fecal microbiota transplantation compared to control for induction of remission in ulcerative colitis

Patient or population: people with active UC

Setting: inpatient or outpatient

Intervention: FMT

Comparison: control

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence	What happens
	Risk with control	Risk with FMT				
Induction of clinical remission in UC at longest follow-up (RR > 1 favors FMT) Follow-up: range 6–12 weeks	174 per 1000	**312 per 1000** (197 to 494)	**RR 1.79** (1.13 to 2.84)	468 (10 RCTs)	⊕⊕⊖⊖ **Low**[a,b,c]	FMT may increase induction of clinical remission in UC at longest follow-up.
Serious adverse events with use of FMT for induction of remission in UC (RR > 1 favors control) Follow-up: range 6–12 weeks	54 per 1000	**95 per 1000** (47 to 190)	**RR 1.77** (0.88 to 3.55)	468 (10 RCTs)	⊕⊖⊖⊖ **Very low**[a,d]	The evidence is very uncertain about the effect of FMT on serious adverse events in people with UC.
Any adverse events with use of FMT for induction of remission in UC (RR > 1 favors control) Follow-up: range 6–12 weeks	455 per 1000	**450 per 1000** (386 to 527)	**RR 0.99** (0.85 to 1.16)	417 (9 RCTs)	⊕⊕⊖⊖ **Low**[a,e]	FMT may result in little to no difference in any adverse events in people with UC.
Induction of endoscopic remission in UC at longest follow-up (RR > 1 favors FMT) Follow-up: range 8–12 weeks	98 per 1000	**143 per 1000** (63 to 324)	**RR 1.45** (0.64 to 3.29)	285 (5 RCTs)	⊕⊕⊖⊖ **Low**[f,g,h]	FMT may result in an increase in induction of endoscopic remission in UC at longest follow-up; however, the CIs around the summary estimate were wide and included a possibility of no effect.
Quality-of-life scores: IBDQ with use of FMT for induction of remission in UC (MD > 0 favors FMT) Follow-up: range 8–12 weeks	The mean quality of life score: IBDQ was 150 QOL-IBDQ score in control group	MD **15.34 QOL-IBDQ scores higher** (3.84 lower to 34.52 higher)	—	131 (3 RCTs)	⊕⊖⊖⊖ **Very low**[i,j,k]	The evidence is very uncertain about the effect of FMT on quality-of-life scores: IBDQ in UC.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FMT:** fecal microbiota transplantation; **IBDQ:** Inflammatory Bowel Disease Questionnaire; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **UC:** ulcerative colitis.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

[a] Downgraded one level due to risk of bias. Three studies were at high risk of bias due to lack of blinding of participants or outcome assessors. Two studies had significant attrition.
[b] Not downgraded for inconsistency. The direction of effect was in favor of the intervention in eight of 10 studies. I^2 = 48%.
[c] Downgraded one level due to imprecision. We acknowledge that the overall absolute effect was 138 per 1000 or 13.8% higher for FMT, which is clinically meaningful (we considered an absolute effect of 10% to 15% as a minimally important difference); however, the CIs were wide and included an absolute effect as low as 2.3%, which might not be clinically meaningful.
[d] Downgraded two levels for very serious imprecision because the numbers of events were very small (total 26) and the CIs around the summary estimate were wide. The ratio of upper limit of CI to lower limit of CI exceeded four, indicating that the current pooled sample size is lower than optimal information size.
[e] Downgraded one level due to imprecision because the CIs around the summary estimate were wide and included a null effect.
[f] Not downgraded for risk of bias even though one study was at high risk of bias due to lack of allocation concealment and lack of blinding of participants; we considered these factors as less likely to cause significant risk of bias due to the objective nature of the outcome.
[g] Not downgraded for inconsistency (I^2 = 38%).
[h] Downgraded two levels for very serious imprecision. Overall number of events was small and the CIs around the summary estimate were very wide.
[i] Not downgraded for risk of bias. Even though one study had high attrition, it was balanced between groups.
[j] Downgraded one level for inconsistency and I^2 = 56%.
[k] Downgraded two levels for very serious imprecision because the CIs around the summary estimate were very wide and almost included a null effect. In addition, the ratio of upper CI to lower CI exceeded 3, indicating that optimal information size was not achieved.

Summary of findings 2. Fecal microbiota transplantation compared to control for maintenance of remission in ulcerative colitis

Patient or population: people with UC in remission

Setting: inpatient or outpatient

Intervention: FMT

Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens

	Risk with control	Risk with FMT				
Maintenance of clinical remission in UC (RR > 1 favors intervention) Follow-up: 48–56 weeks	556 per 1000	**1000 per 1000** (144 to 1000)	**RR 2.97** (0.26 to 34.42)	71 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a,b,c]	The evidence is very uncertain about the effect of FMT on maintenance of clinical remission in UC.
Serious adverse events with use of FMT for maintenance of remission in UC (RR > 1 favors control) Follow-up: 48–56 weeks	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	71 (2 RCTs)	⊕⊖⊖⊖ **Very low**[d,e]	The evidence is very uncertain about the effect of FMT on serious adverse events when FMT was used for maintenance of remission in UC.
Any adverse events with use of FMT for maintenance of remission in UC (RR > 1 favors the control) Follow-up: 48–56 weeks	556 per 1000	**644 per 1000** (472 to 883)	**RR 1.16** (0.85 to 1.59)	71 (2 RCTs)	⊕⊖⊖⊖ **Very low**[f,g]	The evidence is very uncertain about the effect of FMT on any adverse events when FMT was used for maintenance of remission in UC.
Maintenance of endoscopic remission in UC (RR > 1 favors FMT) Follow-up: 48–56 weeks	222 per 1000	**729 per 1000** (162 to 1000)	**RR 3.28** (0.73 to 14.74)	71 (2 RCTs)	⊕⊖⊖⊖ **Very low**[h,i,j]	The evidence is very uncertain about the effect of FMT on maintenance of endoscopic remission in UC.
Quality-of-life scores with use of FMT for maintenance of remission in UC Follow-up: mean 56 weeks	The mean quality-of-life score was 164 in control group when FMT was used for maintenance of remission in UC	MD **38.2 IBDQ score higher** (19.3 higher to 57.1 higher)	—	10 (1 RCT)	⊕⊖⊖⊖ **Very low**[h,k]	The evidence is very uncertain about the effect of FMT on quality-of-life scores when FMT was used for maintenance of remission in UC.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FMT:** fecal microbiota transplantation; **IBDQ:** Inflammatory Bowel Disease Questionnaire; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **UC:** ulcerative colitis.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

[a] Downgraded one level for risk of bias. One study addressed induction of clinical remission and maintenance of clinical remission (Haifer 2022). The portion of maintenance of remission was open-label and there was significant attrition for this portion of the study.
[b] Downgraded one level for inconsistency. The magnitude of effect differed widely between the two studies. I^2 = 72%.
[c] Downgraded two levels for imprecision. The number of events was small and the CIs around the summary estimate were very wide.
[d] Downgraded one level for risk of bias. One study was open-label and had significant attrition when FMT was used for maintenance of remission, so the assessment of risk of serious adverse events could have been biased (Haifer 2022).
[e] Downgraded two levels for very serious imprecision. There were no events in either study.
[f] Downgraded one level for risk of bias. One study was open-label and had significant attrition when FMT was used for maintenance of remission, so the assessment of risk of adverse events could have been biased (Haifer 2022).
[g] Downgraded two levels for severe imprecision. The CIs around the summary estimate were very wide.
[h] Downgraded one level for risk of bias. One study was open-label and had significant attrition when FMT was used for maintenance of endoscopic remission.
[i] Not downgraded for inconsistency as both studies had an effect in favor of the intervention.
[j] Downgraded two levels for very serious imprecision. The number of events was small and CIs around the summary estimate were very wide.
[k] Downgraded two levels for very serious imprecision. There was a low number of participants (10) and the CIs around the summary estimate were very wide.

Summary of findings 3. Fecal microbiota transplantation compared to control for induction of remission in Crohn disease

Patient or population: people with active CD

Setting: inpatient or outpatient

Intervention: FMT

Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk with control	Risk with FMT				
Induction of clinical remission in CD	—	—	Not estimable	(0 studies)	—	No study reported data on use of FMT for induction of clinical remission in CD.
Serious adverse events with use of FMT for induction of remission in CD	—	—	Not estimable	(0 studies)	—	No study reported data for serious adverse events when FMT was used for induction of remission in CD.
Any adverse events with use of FMT for induction of remission in CD	—	—	Not estimable	(0 studies)	—	No study reported data for any adverse events when FMT was used for induction of remission in CD.
Induction of endoscopic remission in CD	—	—	Not estimable	(0 studies)	—	No study reported data on use of FMT for induction of endoscopic remission in CD.

Quality-of-life scores with use of FMT for induction of remission in CD	—	—	Not estimable	(0 studies)	—	No study reported data for quality-of-life scores when FMT was used for induction of remission in CD.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CD: Crohn disease; **CI:** confidence interval; **FMT:** fecal microbiota transplantation; **MD:** mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Summary of findings 4. Fecal microbiota transplantation compared to control for maintenance of remission in Crohn disease

Patient or population: people with CD in remission

Setting: inpatient or outpatient

Intervention: FMT

Comparison: control

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence	What happens
	Risk with control	Risk with FMT				
Maintenance of remission in CD Follow-up: 24 weeks	300 per 1000	**363 per 1000** (108 to 1000)	**RR 1.21** (0.36 to 4.14)	21 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	The evidence is very uncertain about the effect of FMT on maintenance of remission in CD.
Serious adverse events with use of FMT for maintenance of remission in CD Follow-up: 24 weeks	—	—	Not estimable	(1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	The evidence is very uncertain about the effect of FMT on serious adverse events in people with CD in remission. The number of events was very small and the data were reported in such a way that an effect size could not be calculated from the only included study for this outcome.

Any adverse events with use of FMT for maintenance of remission in CD Follow-up: 24 weeks	—	—	Not estimable	(1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	The evidence is very uncertain about the effect of FMT on any adverse events in people with CD in remission. The number of events was very small and the data were reported in such a way that an effect size could not be calculated from the only included study for this outcome.
Maintenance of endoscopic remission in CD	—	—	—	(0 studies)	—	No data reported for this outcome.
Quality-of-life scoreswith use of FMT for maintenance of remission in CD	—	—	—	(0 studies)	—	No data reported for this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CD: Crohn disease; **CI:** confidence interval; **FMT:** fecal microbiota transplantation; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

[a] Downgraded one level for risk of bias. The only included study was at high risk of bias due to lack of blinding of outcome assessors and high attrition.
[b] Downgraded two levels due to imprecision. The number of events was very small and the data were reported in such a way that an effect size could not be calculated from the only included study for this outcome.

BACKGROUND

Description of the condition

Ulcerative colitis (UC) and Crohn disease (CD), two subtypes of inflammatory bowel disease (IBD), are chronic, relapsing conditions of the gastrointestinal (GI) tract. One of the proposed mechanisms for the development of IBD involves the interplay between the gut microbiome and the immune system, which may lead to an abnormal inflammatory response in genetically susceptible individuals (Abraham 2009; Cleynen 2016). UC is characterized by inflammation of the colonic mucosa and can affect variable lengths of the colon. CD is characterized by transmural inflammation and can affect any part of the GI tract from mouth to anus, with a particular predilection for the terminal ileum (Abraham 2009; Ananthakrishnan 2015). While there is regional variation in the prevalence of IBD, with the highest rates in North America, recently its prevalence has been trending upwards globally (Ahuja 2010; Dahlhamer 2016; GBD 2020; Molodecky 2012; Weintraub 2014). The Global Burden of Disease study estimated that the prevalence of IBD increased from 3.7 million to 6.8 million between 1990 and 2017 (GBD 2020). IBD is associated with poor quality of life, significant economic burden, and increased morbidity, including the need for hospitalizations and surgical procedures (Abraham 2009; Abraham 2012; Mehta 2016). Current treatment strategies for IBD focus on the control of inflammation with medications, including corticosteroids; 5-aminosalicylic acid (5-ASA) preparations; immune-modulating drugs such as azathioprine, 6-mercaptopurine, and methotrexate; and immune-modulating monoclonal antibodies such as infliximab, adalimumab, vedolizumab, and ustekinumab (Abraham 2009; Vindigni 2016). Unfortunately, these medical therapies have the potential to cause significant adverse effects. Moreover, while these therapies provide some benefit in many cases (Abraham 2009; Vindigni 2016), there remains a significant number of people who either do not respond to any of these treatment modalities or become refractory to them over time. Ultimately, some people may require surgical bowel resection (Vindigni 2016). The severity of IBD and poor outcomes justify the need for alternative treatment strategies that target known pathogenic factors to supplement or replace existing interventions.

Description of the intervention

There is growing evidence to suggest that 'dysbiosis' is one of the key elements in the pathogenesis of IBD and could be a potential therapeutic target (Assa 2016; Bejaoui 2015; Kostic 2014; Vindigni 2016). Dysbiosis is defined as any alteration in the composition of commensal microbial communities relative to those found in healthy individuals (Petersen 2014). In IBD, a decrease in alpha diversity, an increase in pathobionts (species of resident bacteria that activate the immune system), altered production of microbial metabolites, and an altered functional core of gut microbiota relative to that of healthy individuals have been reported (Chow 2011; De Preter 2012; Kostic 2014; Vindigni 2016).

Fecal microbiota transplantation (FMT) from healthy donors is one of the interventions used to correct dysbiosis (Cammarota 2017). While FMT is increasingly studied, most of the published literature relates to the treatment of recurrent *Clostridioides difficile* (formerly known as *Clostridium difficile*) infection (rCDI), for which its efficacy is greater than 90% (Austin 2014; Cammarota 2015; Kassam 2013; Kelly 2016; Lee 2016; Leffler 2015; van Nood 2013; Youngster 2014).

The US Food and Drug Administration (FDA) considers FMT as a 'biologic product' and a 'drug' under its regulations and has labeled it as an investigational new drug, with exceptions for the treatment of rCDI where the FDA exercises enforcement discretion (FDA 2022; Moore 2014). Although FMT methods are evolving, a typical FMT procedure involves selection and screening of the donor, collection and preparation of the donor stool for infusion, preparation of the patient to receive the stool infusion, and administration of the stool via the upper or lower GI tract (Cammarota 2017). There is no single tool that has been universally agreed upon for donor screening; however, most studies have adopted a screening strategy similar to that used for a human tissue donor (Austin 2014; Cammarota 2017; Moore 2014; Owens 2013). The donor is screened via interview, and then blood and stool studies are conducted to rule out chronic diseases and active infections. After the donor is screened, the stool is collected either to be used immediately for infusion or frozen for later use. At least 30 g to 50 g of feces are typically collected and mixed with normal saline or sterile water in preparation for infusion, and the patient is usually prepared with a colonic lavage. The donor feces can be administered via an upper GI route, such as nasoduodenal tube and orally ingested capsules, or a lower GI route, such as colonoscopy and enema. Since the publication of the last version of this review, guidelines have been updated for both children and adults regarding the use of FMT for treatment of rCDI (Davidovics 2019; Kelly 2021; McDonald 2018). All modalities have been studied with overall comparable efficacy, although the colonic route is considered the most efficacious (Cammarota 2017; Lee 2016; van Nood 2013; Youngster 2014). Per published international standards, infection control precautions should be adopted during FMT preparation and administration (Cammarota 2017).

How the intervention might work

The exact mechanism by which FMT might work for inducing remission in IBD is not well-established. However, the prevailing hypothesis is that FMT might correct the dysbiosis associated with IBD, leading to a reversal or improvement of the associated inflammation (Moayyedi 2015; Paramsothy 2017; Rossen 2015; Shi 2016; Sun 2016; Vindigni 2016). Knowledge around the use of FMT for treatment of IBD has been evolving. FMT impacts not only the composition of gut bacteria, but also the complex interconnected communities of viruses, fungi, protists, and archaea within the GI tract and their various by-products (Lam 2022).

Currently, there is no consensus on the volume, timing, route, and frequency of fecal administration necessary to achieve remission (Cammarota 2017; Kelly 2015; Moore 2014). While a single infusion of feces is often enough to treat rCDI in most cases (Austin 2014; Cammarota 2015; Kassam 2013), multiple infusions might be required for the induction of remission in IBD, as suggested by the FOCUS trial in Australia (Paramsothy 2017). Similarly, the response to FMT in people with rCDI may not vary much with the choice of donor (Osman 2016). However, donor selection might have a significant impact on the induction of remission in UC as reported by Moayyedi 2015, in which seven of nine people who achieved clinical remission had received stool from a single donor.

The short- and long-term safety of FMT in people with IBD is not well-established (Cammarota 2017; Kelly 2015; Moore 2014). Some studies report relatively minor adverse effects such as diarrhea, abdominal bloating, abdominal cramping, and fever in the immediate postprocedure period (Khoruts 2016; Kunde 2013). In addition, FMT may increase the risk of a flare in people with IBD

(Kelly 2014; Khoruts 2016). Concerns remain that the transplanted feces may contain pathogenic microorganisms and that the change in the functional core of bacteria may confer an undesirable and unanticipated outcome (Alang 2015; Cammarota 2017). Animal models of FMT have demonstrated undesired weight changes that accompanied changes in the microbiome (Blanton 2016; Ridaura 2013). Serious adverse events have been reported in individual cases, including mortality (Kelly 2014), septic shock and toxic megacolon (Solari 2014), and aspiration pneumonia (Link 2016). The FDA issued a safety alert in 2020 about the use of FMT and risk of serious adverse events, including the transmission of enteric pathogens and risk of mortality (FDA 2020a). Additionally, the FDA provided guidance about the use of FMT and risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (FDA 2020b).

Why it is important to do this review

As the literature increasingly alludes to dysbiosis in the pathogenesis of IBD, there have been efforts to correct the dysbiosis and assess whether its correction can improve IBD-associated outcomes (Chassaing 2011; Fuentes 2017; Morgan 2012; Nagao-Kitamoto 2016; Rapozo 2017; Schulberg 2016; Vindigni 2016). Some interventions that might target the gut microbiota include the use of probiotics, prebiotics, synbiotics, nutrition therapy (including exclusive enteral nutrition), and FMT (Anderson 2012; Colman 2014; Paramsothy 2017; Vindigni 2016). Most of these interventions have been the subject of Cochrane Reviews (Iheozor-Ejiofor 2020; Kaur 2020; Nguyen 2019), including the previous version of this updated review (Imdad 2018). Since the last version of this review (Imdad 2018), additional studies on this topic have been published (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Haifer 2022; Pai 2021; Paramsothy 2017; Sarbagili Shabat 2022; Sokol 2020; Sood 2019a; Zhao 2020). Therefore, we aimed to update the existing review to further assess the benefits and risks of FMT for treatment of IBD.

OBJECTIVES

To evaluate the benefits and safety profile of FMT for treatment of IBD in adults and children versus autologous FMT, placebo, standard medication, or no intervention.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs). We excluded case reports, case series, case-control studies, single-arm cohort studies, and non-randomized studies with a comparator arm.

Types of participants

Eligible studies included participants who were diagnosed with UC or CD based on their history, physical examination, and gross endoscopic and histologic evaluations. We excluded studies in which the diagnosis of IBD was made without endoscopic or histologic evaluation, as these two measures were considered key initial diagnostic studies for IBD (Mowat 2011). There were no age restrictions for participants. Included studies must have followed participants for at least six weeks after FMT (Feakins 2013). We excluded studies that used FMT for the treatment of pouchitis. We also excluded studies in which participants had active enteric infections such as *C. difficile,* as these conditions may mimic IBD. Furthermore, we excluded studies in which FMT was performed for rCDI in people with IBD and not for induction or maintenance of remission of IBD.

Types of interventions

Eligible interventions evaluated FMT for the treatment of IBD. FMT for this review was defined as, "the administration of fecal material containing distal gut microbiota from a healthy individual (donor) to a patient with a disease or condition related to dysbiosis, or an alteration in their normal gut microbiota" (Kelly 2015). Control arms used autologous FMT, placebo, standard medication, or no intervention. We included studies irrespective of the type of stool (liquid or frozen), volume, route, frequency, and timing of the transplant (e.g. at initial diagnosis, to treat a flare, or to maintain remission). We excluded studies that used selective microbes rather than whole stool from the donor, as this intervention does not fulfill the definition of FMT (Kelly 2015).

Types of outcome measures

We measured both clinical and laboratory-based outcomes.

Primary outcomes

- Induction of clinical remission in UC or CD at longest follow-up
- Maintenance of clinical remission in UC or CD at longest follow-up
- Serious adverse events in UC or CD as defined by study authors

We measured the primary outcomes using the number of participants achieving clinical remission, maintaining remission, or experiencing serious adverse events, expressed as a proportion of the number of participants randomized to each group in a given trial. Further details on how data were extracted for primary outcomes are provided in the Measures of treatment effect section.

We analyzed the data separately for primary outcomes in the induction and maintenance phases of treatment of UC and CD. The primary outcome of induction of clinical remission was measured at week eight and week 12 of follow-up, and at the longest follow-up. For the remaining primary outcomes, the longest follow-up time was considered before the trial was open for analysis.

Secondary outcomes

- Any adverse events in UC or CD as defined by study authors
- Endoscopic remission in UC or CD at longest follow-up
- Quality of life (i.e. Inflammatory Bowel Disease Questionnaire [IBDQ] scores) at the time of measurement of the primary outcomes
- Clinical response in UC or CD at longest follow-up
- Endoscopic response in UC or CD at longest follow-up
- Withdrawals in studies on UC or CD
- Laboratory measures of inflammation, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fecal calprotectin (FC), all of which were recorded as continuous outcomes, in UC or CD at longest follow-up
- Microbiome outcomes

We analyzed the data separately for secondary outcomes in the induction and maintenance phases of remission in UC and CD.

Search methods for identification of studies

Electronic searches

For this update, we searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 11, 2022) in the Cochrane Library;
- MEDLINE Ovid (1946 to 22 December 2022);
- Embase Elsevier (1974 to 22 December 2022);
- International Standard Registered Clinical/Social Study Number registry (ISRCTN; 22 December 2022).

We applied no limits on our searches. The search strategies are available in Appendix 1.

Searching other resources

For both the 2018 version (Imdad 2018) and current version of this review, we searched ClinicalTrials.gov (www.clinicaltrials.gov) and the ISRCTN metaRegister of Controlled Trials (mRCT; www.isrctn.com/page/mrct) for ongoing trials. We also searched the reference sections of previously published RCTs and meta-analyses on this topic.

In the previous version of this review (Imdad 2018), we searched the Conference Proceedings Citation Index database for conference abstracts. However, for the present review, Embase covers proceedings of the above conferences from the year 2010 onward.

Data collection and analysis

Selection of studies

For this update, at least two review authors (AI, NP, MZ, and NZM) conducted the initial screening to select potentially eligible studies by reviewing titles and abstracts. After the initial title and abstract screening, two review authors from the study team (AI, NP, MZ, and NZM) reviewed the full texts of selected studies and then made final decisions regarding inclusion or exclusion. At each stage of the screening process, we resolved any discrepancies by discussion and consensus.

Data extraction and management

At least two review authors (AI, NP, MZ, and NZM) independently extracted and updated data in the pretested Microsoft Excel sheet (available on request) that had been maintained since the first version of this review. We extracted information on the characteristics of included studies such as authors, date of publication, journal, study site, study design, age of participants, study population (inclusion/exclusion criteria), details of intervention (type, volume, route, and frequency of administration), outcomes (primary and secondary), and risk of bias. Then, we extracted the raw values of event occurrences (numerators) in the case and control groups, along with the total number of participants randomized (denominators) to each group. We extracted data on an intention-to-treat (ITT) basis, which considers the initial allocation of participants to the case or control groups, irrespective of whether they received the intervention or completed follow-up (Gupta 2011). When data for continuous outcomes were reported as medians with interquartile ranges (IQR), we converted the values to means with standard deviations (SD) using methods given in Hozo 2005, which assume a normal distribution of data

Assessment of risk of bias in included studies

We used the Cochrane RoB 1 tool to assess the risk of bias in the included RCTs (Higgins 2011). Briefly, these assessments were based on six criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, publication bias, and other bias. Each category was judged at 'low,' 'high,' or 'unclear' risk of bias.

Measures of treatment effect

We expected that the authors of included studies would report a range of clinical, endoscopic, and histologic outcomes in response to treatment with FMT. The most important of these outcomes was 'induction of clinical remission,' which was a primary outcome of our systematic review. We considered clinical remission as defined by the included studies (e.g. Mayo score for UC studies and Crohn's Disease Activity Index for CD studies). If the primary outcome was reported as a combination of clinical and endoscopic or histologic assessment, we extracted data for the combined or 'composite' outcome.

We considered the outcomes related to induction of remission in UC and CD at week eight, week 12, and the longest follow-up point post-FMT. If a primary outcome in a study was not reported at exactly eight weeks but between six and 10 weeks post-FMT, it was included as an outcome at eight weeks. Similarly, if a primary outcome was not reported at exactly 12 weeks but between 10 and 14 weeks post-FMT, it was included as an outcome at 12 weeks. Regardless of the number of weeks at which the primary outcome was measured, we analyzed the data reported at the time point farthest from the intervention as 'the longest follow-up' to accommodate as many studies as possible into a single analysis. However, we considered the data at the longest follow-up only up to the time point before the trial was open for analysis.

For maintenance of remission in UC and CD, we considered outcomes from studies in which all the participants were in remission at the time of randomization, and we considered these data at the longest follow-up.

We calculated the risk ratio (RR) and corresponding 95% confidence interval (CI) for all dichotomous outcomes. We calculated the mean difference (MD) and corresponding 95% CI for continuous outcomes.

Unit of analysis issues

For studies that had multiple intervention groups (e.g. factorial design), the data were extracted in such a way that the only difference between the case and control groups was administration of FMT. Similarly, if a study had more than one intervention or control group, the groups were combined in a single comparison of 'donor-based FMT versus control' (including autologous FMT). Co-interventions were permitted if they were uniformly applied to both the intervention and control groups. We only considered the effect of the first treatment attempt as defined by the authors. The treatment may have included multiple infusions of FMT; however, if a patient received study treatment (intervention or control) more than once, we ignored the subsequent attempts. Such a scenario might occur if the authors decided to treat all participants in the control group with the study intervention at the end of a randomized trial. Adverse events were considered as reported by the study authors, and we assumed that each adverse event

was an independent event unless the published report indicated otherwise.

Dealing with missing data

Attrition is an important factor that may affect the validity of studies, and differential dropout rates between study groups can lead to biased estimates of effect size (Dumville 2006). We described missing data, including withdrawals and reasons for withdrawal, as reported by the study authors. We contacted the authors if data were missing and no reasons were provided. When authors applied complete data to withdrawn participants (e.g. imputed using regression methods), we extracted the latter. If data were not available for the primary outcomes of this review, we contacted the authors for additional information. All data from the RCTs were analyzed on an ITT basis. Specifically, we conducted our analyses using the total number of participants originally randomized to each study group, rather than the number of participants who completed each study and for whom data were reported. As such, we assumed that participants with missing values for the primary outcomes did not develop the outcome of interest in either arm of the study and experienced treatment failure.

Assessment of heterogeneity

We assessed clinical, methodologic, and statistical heterogeneity across the included studies. Clinical heterogeneity was assessed by comparing the distributions of important factors such as study population, dose, and frequency of FMT. Methodologic heterogeneity was assessed by comparing data included in the risk of bias tables. Statistical heterogeneity was assessed by visual inspection of the forest plots, the I^2 statistic, and the P value of the Chi^2 test. If the forest plot was indicative of a heterogeneous effect (opposite direction or prominent difference in magnitude of effect), while the I^2 values were greater than 50% and P values for the Chi^2 test were less than 0.1, statistical heterogeneity was considered to be substantial. We explored potential explanations for heterogeneity using subgroup analyses.

Assessment of reporting biases

We aimed to assess potential publication bias based on symmetry of the funnel plots. We planned to construct funnel plots if at least 10 studies were included in the pooled analysis and investigate asymmetry in the funnel plots with Egger's test as appropriate.

Data synthesis

We synthesized data from individual trials using meta-analysis when the interventions, participant groups, and outcomes were sufficiently similar (as determined by consensus) using Review Manager Web (RevMan Web 2023). We planned to conduct separate meta-analyses for use of FMT in the induction and maintenance phases of remission in UC and CD. For dichotomous outcomes, we calculated pooled RRs and corresponding 95% CIs. We combined RRs (number of participants who experienced the event) and rate ratios (number of participants who experienced the event-days/months/years) for two reasons: studies were expected to be completed in a relatively short duration, and the primary outcome (induction of clinical remission) was not expected to be a recurrent event. All meta-analyses were conducted using the log RR, with all reported results transformed back into the RR metric for ease of interpretability. We considered a risk of difference of at least 10% to 15% to be a minimally important clinical difference (MICD) between the two groups for the primary outcome.

For continuous outcomes, data were combined to obtain pooled MDs and corresponding 95% CIs. When studies used different scales to measure the same underlying construct, we calculated the standardized mean difference (SMD; Hedges' g value) and corresponding 95% CI. We used a random-effects model to conduct all meta-analyses. The rationale for using a random-effects model was that we expected possible heterogeneity in the effects of FMT due to factors such as dosage, frequency, or donor source (e.g. single donor or pooling of multiple donors), as noted in the results of published studies.

Subgroup analysis and investigation of heterogeneity

We planned the following a priori subgroup analyses:

- Route of administration: upper GI tract (i.e. oral capsules; nasogastric, nasoduodenal, nasojejunal tube) versus lower GI tract (i.e. colonoscopy, enema);
- Type of donor: single donor (i.e. one person's stool administered per dose) versus multiple donors (i.e. more than one person's stool blended per dose);
- Age of participants: children versus adults;
- Frequency of FMT administration: single infusion versus multiple infusions during treatment period.

We used the Chi^2 test to determine any statistical significance between the subgroup analyses.

The subgroup analyses were considered separately for use of FMT in the induction and maintenance phases of remission in UC and CD. Subgroup analyses were conducted when at least 10 studies were available for analysis.

Sensitivity analysis

The following a priori sensitivity analysis was performed:

- choice of statistical model: random-effects versus fixed-effect models for primary outcomes.

Given that we performed an ITT analysis, which included randomized participants who may not have received the intervention and completed follow-up, we also performed post-hoc available case analyses for the primary outcomes, in which only those participants who completed follow-up were included. We also updated the post-hoc analysis conducted in the last version of this review for studies that defined induction of remission with a combination of clinical and endoscopic/histologic criteria (Imdad 2018).

The sensitivity and subgroup analyses were conducted for the primary outcomes only, but separately for use of FMT in the induction and maintenance phases of remission in UC and CD.

Summary of findings and assessment of the certainty of the evidence

We assessed the overall certainty of the evidence supporting the primary outcomes and selected secondary outcomes using GRADE (Guyatt 2011). This method takes into consideration the impact of the types of studies (i.e. randomized versus observational), risk of bias, imprecision, inconsistency (i.e. unexplained heterogeneity),

indirectness, and potential publication bias. The overall certainty of the evidence was rated as 'high,' 'moderate,' 'low,' or 'very low.' We presented the results of the GRADE evaluation in summary of findings tables for all primary outcomes (i.e. induction and maintenance of remission and serious adverse events) and the following secondary outcomes: any adverse events, induction of endoscopic remission, and quality of life. We reported the GRADE evaluations separately for use of FMT for induction of remission in UC, maintenance of remission in UC, induction of remission in CD, and maintenance of remission in CD at longest follow-up, along with the follow-up time ranges.

RESULTS

Description of studies

Results of the search

In the previous version of this review (Imdad 2018), a search conducted on 19 March 2018 identified 1020 studies, and after removal of duplicates, 665 studies were retained for the title and abstract screening. Out of 34 studies reviewed by full-text, eight reports of four studies were included (Costello 2019; Moayyedi 2015; Paramsothy 2017; Rossen 2015), of which one was an abstract version of what has subsequently become a full-length paper (Costello 2019). That search identified 13 ongoing studies. For this updated version of the review, we included the four full studies from the previous review (Figure 1).

Figure 1. Study flow diagram.

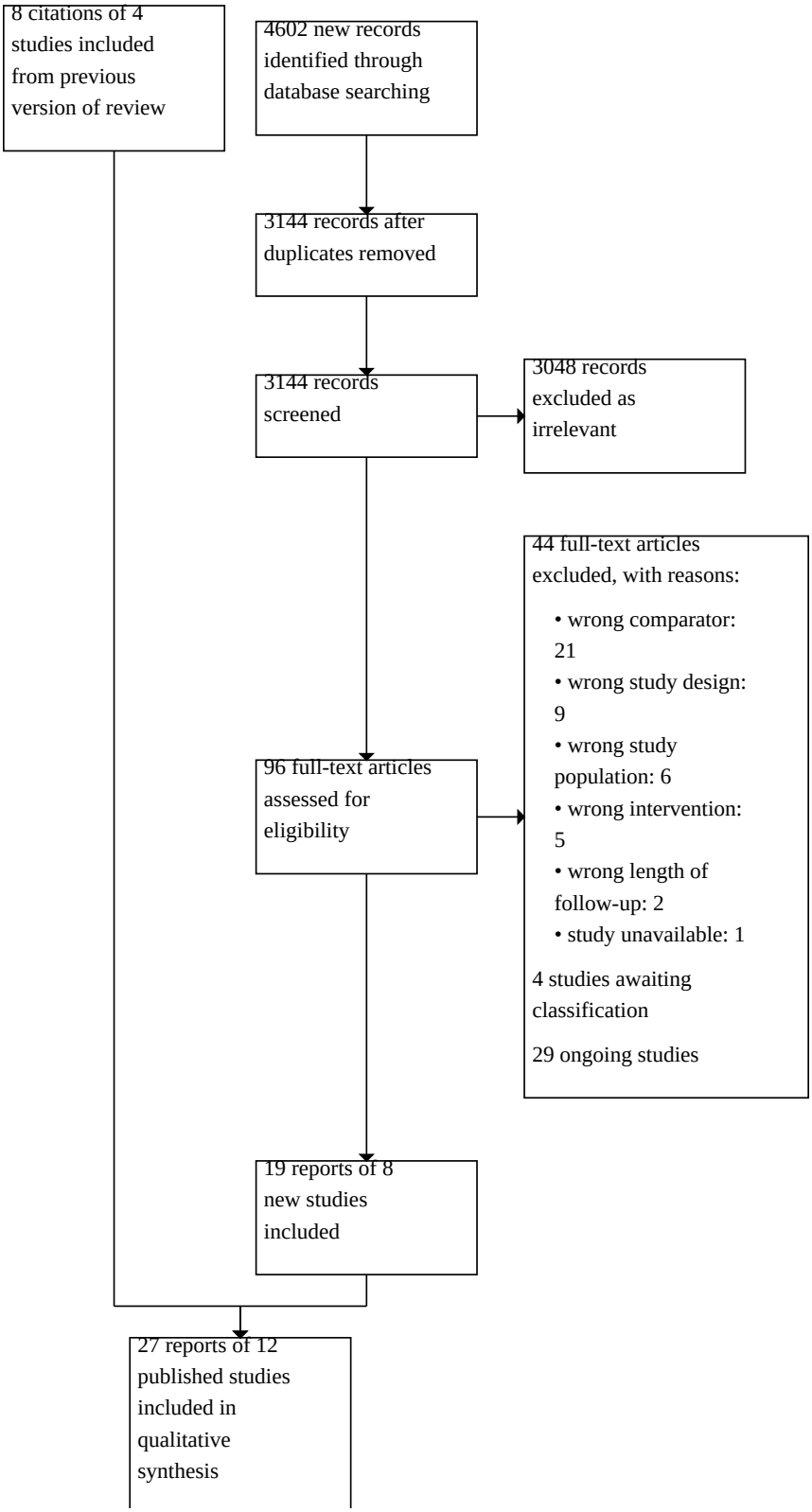
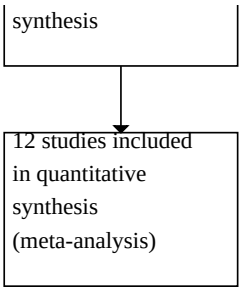


Figure 1. (Continued)



A literature search was conducted on 15 January 2022 and updated on 22 December 2022, which identified 4602 studies (Figure 1). After removal of duplicates, 3144 studies were retained for the title and abstract screening, and 96 studies met the criteria for full-text review. We excluded 44 studies for reasons outlined in the Characteristics of excluded studies table, four studies are awaiting classification (Characteristics of studies awaiting classification table), and 29 studies are ongoing (Characteristics of ongoing studies table).

In summary, four studies were carried over from the last version of this review and eight studies were newly included, of which two were previously ongoing and are now completed and published, for a total of 12 studies published in 27 reports in this systematic review (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022; Sokol 2020; Sood 2019a).

Included studies

Twelve RCTs assessed FMT for the treatment of IBD in peer-reviewed journals (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022; Sokol 2020; Sood 2019a).

Eleven studies assessed FMT for the treatment of UC, of which eight studies assessed FMT for induction of clinical remission in adults with UC (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Moayyedi 2015; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022). One study assessed FMT for induction of clinical remission in children with UC (Pai 2021). One study assessed FMT for both induction and maintenance of remission in UC (Haifer 2022), while one study assessed FMT for only maintenance of remission in UC (Sood 2019a). None of the included studies assessed the use of FMT for induction of remission in CD. One study assessed FMT for maintenance of remission in CD (Sokol 2020). The complete details of these studies can be found in the Characteristics of included studies table.

Country

Three studies were conducted in Australia (Costello 2019; Haifer 2022; Paramsothy 2017), two in Canada (Moayyedi 2015; Pai 2021), one in China (Fang 2021), one in the Czech Republic (Březina 2021), one in France (Sokol 2020), one in India (Sood 2019a), one in Israel and Italy (Sarbagili Shabat 2022), one in the Netherlands (Rossen 2015), and one in the US (Crothers 2021). Five studies were conducted at a single center (Březina 2021; Crothers 2021; Fang 2021; Rossen 2015; Sood 2019a), and seven were conducted at multiple centers (Costello 2019; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Sarbagili Shabat 2022; Sokol 2020).

Study population

Age and gender

The percentages of males in the included studies ranged from 20% (Fang 2021) to 72.5% (Sarbagili Shabat 2022). The ages of participants ranged from children (Pai 2021) to adults with a mean age of 48 years (Fang 2021).

History of prior medication treatment

All studies included participants who had previously received some form of treatment for IBD (i.e. no studies included only treatment-naive participants), and only one study excluded people who had previously received biologic therapy as part of their treatment (Fang 2021).

Duration of disease

The mean duration of disease in the studies on adults with UC ranged from 4.29 years (Sood 2019a) to 9.35 years (Crothers 2021). The mean duration of disease in the study on participants with CD was nine years (Sokol 2020).

Severity of disease

All 10 studies on FMT for induction of remission in UC reported the severity of disease during enrollment, of which nine studies included people experiencing mild-to-moderate UC with correlating Mayo scores at the time of inclusion (Březina 2021; Costello 2019; Crothers 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022), and one study included people with mild, moderate, and severe UC (Fang 2021). The two studies that assessed FMT for maintenance of remission in UC included people who were induced into remission with FMT (Haifer 2022; Sood 2019a), while one study that assessed FMT for maintenance of remission in CD included people who were induced into remission with steroids (Sokol 2020).

Indications for fecal microbiota transplantation

Ten studies used FMT for induction of remission in participants with active UC (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022). Two studies used FMT for maintenance of remission in UC (Haifer 2022; Sood 2019a), and one study used FMT for maintenance of remission in CD (Sokol 2020).

Intervention

Donors

All 12 studies used feces from apparently healthy donors. In nine studies, the donors were not related to the study participants receiving FMT (Březina 2021; Costello 2019; Crothers 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Sokol 2020; Sood 2019a). In one study, all donors were related to the recipient (Fang 2021), and in another study, there was a mixture of related and unrelated donors (Rossen 2015). One study did not specify whether the donors were related to the recipients (Sarbagili Shabat 2022).

Route

Two studies administered FMT to the upper GI tract only, of which one used oral capsules (Haifer 2022) and one used nasoduodenal tubes (Rossen 2015). Nine studies administered FMT to the lower GI tract only, of which three used enemas (Březina 2021; Moayyedi 2015; Pai 2021), four used colonoscopies (Fang 2021; Paramsothy 2017; Sokol 2020; Sood 2019a), and two used a combination of enemas and colonoscopy (Costello 2019; Sarbagili Shabat 2022). One study used a combination of oral capsules and colonoscopy (Crothers 2021).

Number of administrations

The number of FMT administrations varied across studies. Two studies gave only a single administration (Fang 2021; Sokol 2020), whereas the other studies gave multiple administrations, with a maximum of 85 FMT doses in Crothers 2021.

Weight of stool

The weight of stool used in each FMT administration ranged from 0.35 g per capsule (Haifer 2022) to 120 g via nasoduodenal tube (Rossen 2015).

Volume of stool

The volume of FMT delivered in each administration ranged from 50 mL (Moayyedi 2015) to 500 mL (Rossen 2015). One study that used oral capsules administered six capsules four times daily for one week, then six capsules twice daily for one week, followed by six capsules daily for another six weeks to induce remission and two capsules daily for another 48 weeks to maintain remission in UC (Haifer 2022).

Colon preparation

Nine studies used colon preparation before FMT (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Haifer 2022; Rossen 2015; Sarbagili Shabat 2022; Sokol 2020; Sood 2019a), while the others did not.

Comparison

Two studies used autologous FMT as the comparator (Costello 2019; Rossen 2015), seven used sham placebo that may have contained saline or water (Crothers 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Sokol 2020; Sood 2019a), one used mesalamine via enema (Březina 2021), one used the UC Exclusion Diet (Sarbagili Shabat 2022), and one used 'routine therapy' that varied depending on the severity of disease but potentially included mesalamine, corticosteroids, or both (Fang 2021). The volume, frequency of administration, and colon preparation were similar between the FMT and control groups in the respective studies except for Fang 2021 and Sarbagili Shabat 2022. Fang 2021 used 'routine therapy' as the comparator as opposed to placebo, so these control participants did not have colon preparation, whereas the treatment group that received FMT via colonoscopy did have colon preparation. Similarly, Sarbagili Shabat 2022 placed the control participants on the UC Exclusion Diet, so they did not receive colon preparation either.

Outcomes

All 12 studies reported data for at least one of the primary outcomes in this review. For the outcome of induction of clinical remission, two studies defined the outcome of clinical scores only (Pai 2021; Sarbagili Shabat 2022), while eight studies reported the composite of clinical and endoscopic remission (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Haifer 2022; Moayyedi 2015; Paramsothy 2017; Rossen 2015). Three studies reported on maintenance of remission in IBD, of which one study reported on maintenance of steroid-free remission in CD at week 24 (Sokol 2020), while two studies reported on maintenance of steroid-free clinical remission in UC at week 48 (Sood 2019a) and at week 56 (Haifer 2022). The outcome of 'induction of clinical remission' was defined by the study authors as:

- Březina 2021: Total Mayo score 2 or less with no subscore greater than 1 at week 12;
- Costello 2019: Total Mayo score 2 or less with endoscopic Mayo score 1 or less at week eight; clinical remission as a non-composite outcome was defined by Simple Clinical Colitis Activity Index (SCCAI) score;
- Crothers 2021: Modified Mayo score 2 or less including Rectal Bleeding (RB) subscore of 0, Stool Frequency (SF) subscore of 0 or with at least 1-point decrease from baseline to achieve SF subscore 1 or less, and endoscopic subscore 1 or less at week 12;
- Fang 2021: Mayo score 2 or less with each subscore 1 or less at week eight;
- Haifer 2022: Total Mayo score 2 or less, with all Mayo subscores 1 or less, and at least 1-point reduction of Mayo endoscopic subscore from baseline endoscopy at week eight;
- Moayyedi 2015: Full Mayo score less than 3 and endoscopic Mayo score of 0 at week seven;
- Pai 2021: Pediatric Ulcerative Colitis Activity Index (PUCAI) less than 15 at week six (actual longest follow-up was week 30, but it appeared that trial first opened for analysis at week six);
- Paramsothy 2017: Total Mayo score 2 or less, with all subscores 1 or less, and at least 1-point reduction from baseline in endoscopy subscore at week eight;
- Rossen 2015: composite of clinical remission (SCCAI score 2 or less) in combination with at least 1-point improvement on combined Mayo endoscopic score of sigmoid and rectum versus baseline sigmoidoscopy at week 12;
- Sarbagili Shabat 2022: clinical steroid-free remission (SCCAI less than 3) at week eight.

Follow-up

The follow-up time for measurement of induction of remission in UC ranged from six weeks (Pai 2021; Rossen 2015) to 12 weeks (Březina 2021; Crothers 2021; Rossen 2015). Five studies measured induction of clinical remission in UC at eight weeks (Costello 2019; Fang 2021; Haifer 2022; Paramsothy 2017; Sarbagili Shabat 2022). Among the two studies that assessed maintenance of remission in

UC, one reported outcomes after 48 weeks (Sood 2019a) and the other reported after 56 weeks (Haifer 2022). The study that assessed use of FMT for maintenance of remission in CD reported data after 26 weeks (Sokol 2020).

Excluded studies

We excluded 44 studies for reasons given in the Characteristics of excluded studies table. In summary, 21 studies had ineligible comparators (i.e. the comparison groups received FMT or did not have IBD), nine studies had ineligible study designs, six studies had ineligible study populations (i.e. five studies used FMT for treatment of rCDI rather than IBD and one study used FMT for treatment of pouchitis), five studies had ineligible interventions, two studies had incompatible lengths of follow-up, and one study was not available for review.

Studies awaiting classification

Four studies are awaiting classification for one of the following reasons: the study was terminated; despite our best efforts to gather data or clarify the study's status with the authors, it was unclear whether it was terminated, ongoing, or temporarily on hold; an English version of the study was not available; or the study had been completed but the author(s) had not published or granted access to their data (Caenepeel 2022; Jitsumura 2022; NCT02272868; Zhang 2019). We attempted to contact the listed authors of all studies awaiting classification to inquire about their status and whether any potential publications were pending.

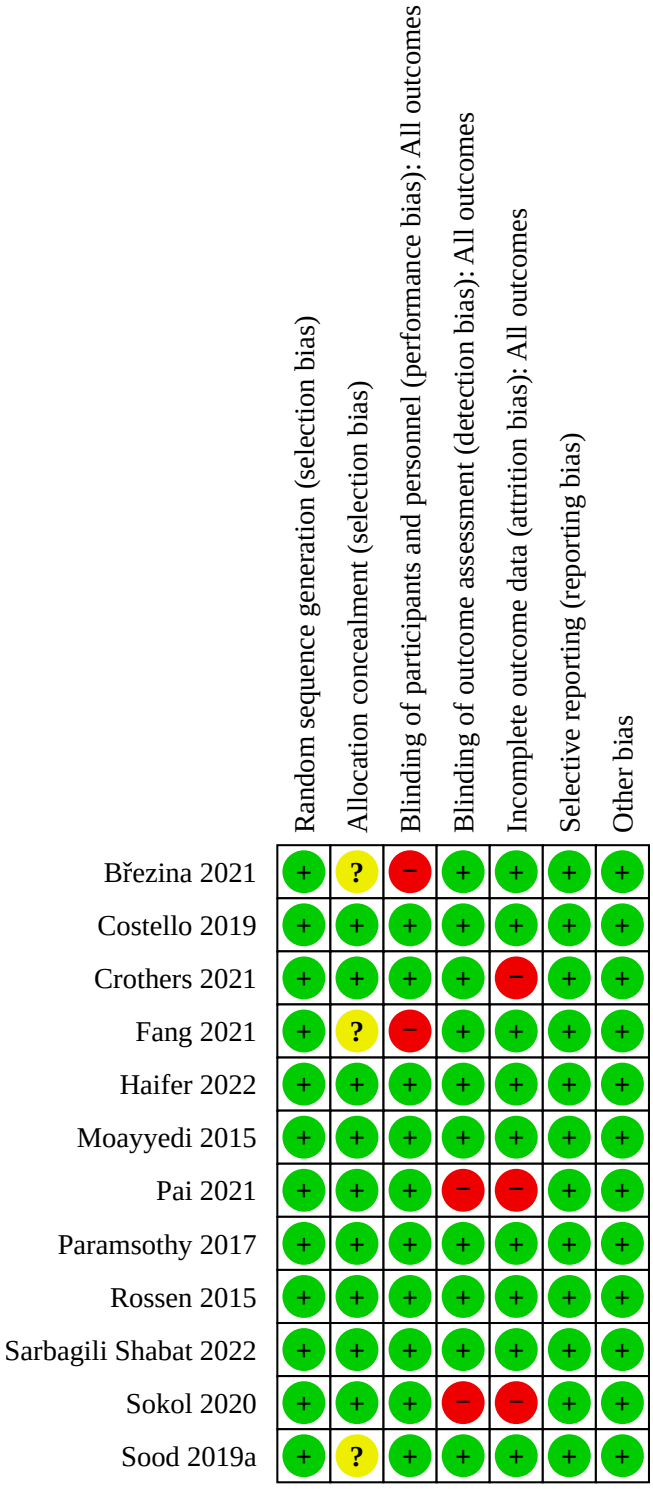
Ongoing studies

Twenty-nine studies are ongoing (CTRI/2021/03/032131; EUCTR 2019-003816-29; NCT01961492; NCT02335281; NCT02998112; NCT03078803; NCT03110289; NCT03273465; NCT03483246; NCT03561532; NCT03582969; NCT03716388; NCT03804931; NCT03998488; NCT04034758; NCT04202211; NCT04328922; NCT04373473; NCT04434872; NCT04521205; NCT04637438; NCT04924270; NCT04970446; NCT04997733; NCT05030064; NCT05538026; Pai 2019; Stallmach 2022; UMIN000033127). We attempted to contact the listed authors of all ongoing studies to inquire about their status and whether any potential publications were pending.

Risk of bias in included studies

A summary of the risk-of-bias assessments is reported in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All 12 studies adequately described the methods for random sequence generation and were at low risk of bias (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022; Sokol 2020; Sood 2019a). Fang 2021 did not explicitly address random sequence generation in the study text but specified the method in the published protocol and therefore was considered at low risk.

Nine studies were at low risk of bias in the domain of allocation concealment (Costello 2019; Crothers 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022; Sokol 2020), and three studies were at unclear risk (Březina 2021; Fang 2021; Sood 2019a).

Blinding

Ten studies were at low risk of bias in the domain of blinding of participants (Costello 2019; Crothers 2021; Haifer 2022; Moayyedi 2015; Pai 2021; Paramsothy 2017; Rossen 2015; Sokol 2020; Sood 2019a), and two studies were at high risk (Březina 2021; Fang 2021). Ten studies were at low risk of bias in blinding of outcome assessors and study investigators (Březina 2021; Costello 2019; Crothers 2021; Fang 2021; Haifer 2022; Moayyedi 2015; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022; Sood 2019a), and two studies were at high risk (Pai 2021; Sokol 2020). Březina 2021 was at low risk of bias in blinding of outcome assessors as the endoscopy pictures were read at a central location. However, this study may be at high risk of bias for other outcomes such as adverse events.

Incomplete outcome data

Nine studies were at low risk of bias related to attrition (Březina 2021; Costello 2019; Fang 2021; Haifer 2022; Moayyedi 2015; Paramsothy 2017; Rossen 2015; Sarbagili Shabat 2022; Sood 2019a). Three studies were at high risk of bias based on incomplete data, as they had high attrition rates (Crothers 2021; Pai 2021; Sokol 2020).

Selective reporting

All included studies were at low risk of bias in selective reporting.

Other potential sources of bias

We did not identify any other major risks of bias in the included studies.

Effects of interventions

See: **Summary of findings 1** Fecal microbiota transplantation compared to control for induction of remission in ulcerative colitis; **Summary of findings 2** Fecal microbiota transplantation compared to control for maintenance of remission in ulcerative colitis; **Summary of findings 3** Fecal microbiota transplantation compared to control for induction of remission in Crohn disease; **Summary of findings 4** Fecal microbiota transplantation compared to control for maintenance of remission in Crohn disease

In this section, we describe the results of our review of studies on FMT for treatment of IBD, separately for: induction of remission in UC, maintenance of remission in UC, induction of remission in CD, and maintenance of remission in CD.

Comparison 1: fecal microbiota transplantation for induction of remission in ulcerative colitis

Primary outcomes

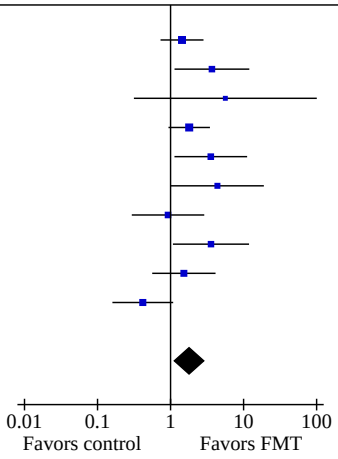
Induction of clinical remission in ulcerative colitis at longest follow-up

Ten studies reported data on the use of FMT for induction of clinical remission in 468 participants with UC. Two studies used mesalamine as the control, two used autologous FMT, five used sham therapy such as water and isotonic saline, and one used the UC Exclusion Diet. The combined results at longest follow-up showed that FMT may increase rates of induction of clinical remission in participants with UC (RR 1.79, 95% CI 1.13 to 2.84; low-certainty evidence; Analysis 1.1; Figure 3). We downgraded the certainty of evidence due to risk of bias and imprecision (Summary of findings 1).

Figure 3. Forest plot of comparison: 1 Fecal microbiota transplantation (FMT) versus control for treatment of inflammatory bowel disease, outcome: 1.1 Induction of clinical remission in ulcerative colitis at longest follow-up.

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	12	23	8	22	15.3%	1.43 [0.73 , 2.82]
Costello 2019	12	38	3	35	9.2%	3.68 [1.13 , 11.98]
Crothers 2021	2	7	0	8	2.3%	5.63 [0.31 , 100.52]
Fang 2021	9	10	5	10	15.7%	1.80 [0.94 , 3.46]
Haifer 2022	8	15	3	20	9.5%	3.56 [1.13 , 11.18]
Moayyedi 2015	9	38	2	37	6.9%	4.38 [1.01 , 18.94]
Pai 2021	4	13	4	12	9.5%	0.92 [0.29 , 2.89]
Paramsothy 2017	11	41	3	40	9.0%	3.58 [1.08 , 11.88]
Rossen 2015	7	23	5	25	11.1%	1.52 [0.56 , 4.13]
Sarbagili Shabat 2022	6	36	6	15	11.5%	0.42 [0.16 , 1.09]
Total (95% CI)		**244**		**224**	**100.0%**	**1.79 [1.13 , 2.84]**
Total events:	80		39			

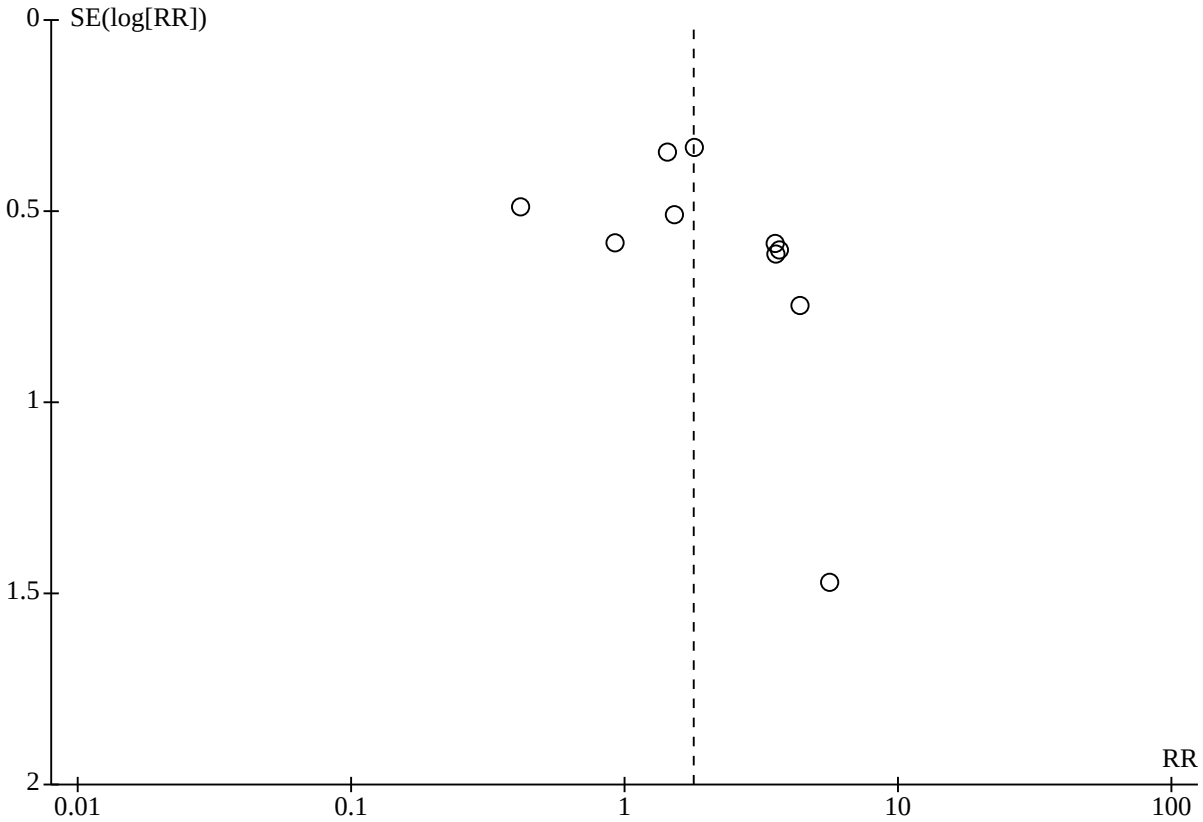
Heterogeneity: Tau² = 0.24; Chi² = 17.15, df = 9 (P = 0.05); I² = 48%
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Not applicable



Publication bias

The funnel plot was symmetrical (Figure 4).

Figure 4. Funnel plot: FMT for induction of clinical remission for UC. The graph appears symmetrical.



Subgroup analyses

We performed subgroup analyses based on the route of FMT administration (Analysis 1.4), type of donor (Analysis 1.5), age of participants (Analysis 1.6), and frequency of FMT (Analysis 1.7). The number of included studies in each subgroup analysis was small and the CIs of the summary estimates overlapped, indicating similar effects across all subgroups.

Sensitivity analyses

A fixed-effect model for induction of clinical remission in UC showed similar results compared to the primary random-effects model used in this review (RR 1.88, 95% CI 1.37 to 2.57; 10 studies, 468 participants; Analysis 1.8; compare with Analysis 1.1).

Our primary analysis was based on ITT, in which we considered all participants randomized to the case and control groups irrespective of whether they received the intervention or completed follow-up. A post-hoc sensitivity analysis that considered only participants who received the intervention and completed follow-up yielded similar results (RR 1.77, 95% CI 1.07 to 2.94; 382 participants; Analysis 1.9).

We decided a priori that the primary outcome of 'clinical remission' would be based on a clinical score (e.g. Mayo score or SCCAI). However, there was also interest in examining composite clinical outcomes in which both clinical and endoscopic/histologic criteria were considered. A random-effects meta-analysis of studies that reported a composite outcome for induction of remission showed that FMT may increase rates of induction of remission by about two times compared to control (RR 2.13, 95% CI 1.51 to 3.02; 8 studies, 392 participants; Analysis 1.10).

Induction of clinical remission in ulcerative colitis at weeks eight and 12

FMT may increase induction of remission after eight weeks in participants with active UC (RR 1.68, 95% CI 0.93 to 3.05; 8 studies, 408 participants; Analysis 1.2). FMT may also increase induction of remission after 12 weeks; however, the CIs around the summary estimate were wide and included a possibility of no effect (RR 1.54, 95% CI 0.89 to 2.66; 3 studies, 108 participants; Analysis 1.3).

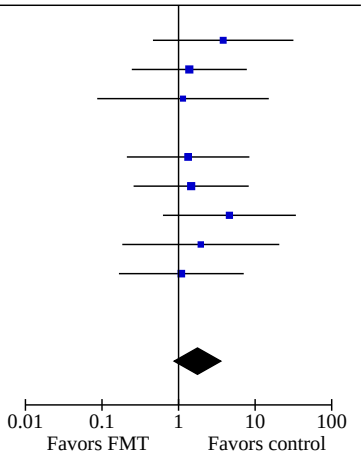
Serious adverse events

Ten studies reported data on serious adverse events when FMT was used for induction of remission in participants with active UC. The evidence was very uncertain about the risk of serious adverse events with use of FMT in active UC (RR 1.77, 95% CI 0.88 to 3.55; 468 participants; very low-certainty evidence; Analysis 1.11; Figure 5). We downgraded the certainty of evidence due to risk of bias and very serious imprecision of the summary estimate (Summary of findings 1). Serious adverse events included worsening of UC necessitating intravenous steroids or surgery, infection, small bowel perforation, and pneumonia.

Figure 5. Forest plot of comparison: 1 Fecal microbiota transplantation versus control for participants with ulcerative colitis, outcome: 1.8 Serious adverse events.

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	4	23	1	22	10.9%	3.83 [0.46 , 31.62]
Costello 2019	3	38	2	35	16.3%	1.38 [0.25 , 7.79]
Crothers 2021	1	7	1	8	7.3%	1.14 [0.09 , 15.08]
Fang 2021	0	10	0	10		Not estimable
Haifer 2022	2	15	2	20	14.4%	1.33 [0.21 , 8.41]
Moayyedi 2015 (1)	3	38	2	37	16.3%	1.46 [0.26 , 8.25]
Pai 2021	5	13	1	12	12.2%	4.62 [0.63 , 34.05]
Paramsothy 2017	2	41	1	40	8.7%	1.95 [0.18 , 20.68]
Rossen 2015	2	23	2	25	13.8%	1.09 [0.17 , 7.10]
Sarbagili Shabat 2022	0	36	0	15		Not estimable
Total (95% CI)		**244**		**224**	**100.0%**	**1.77 [0.88 , 3.55]**
Total events:	22		12			

Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 7 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable



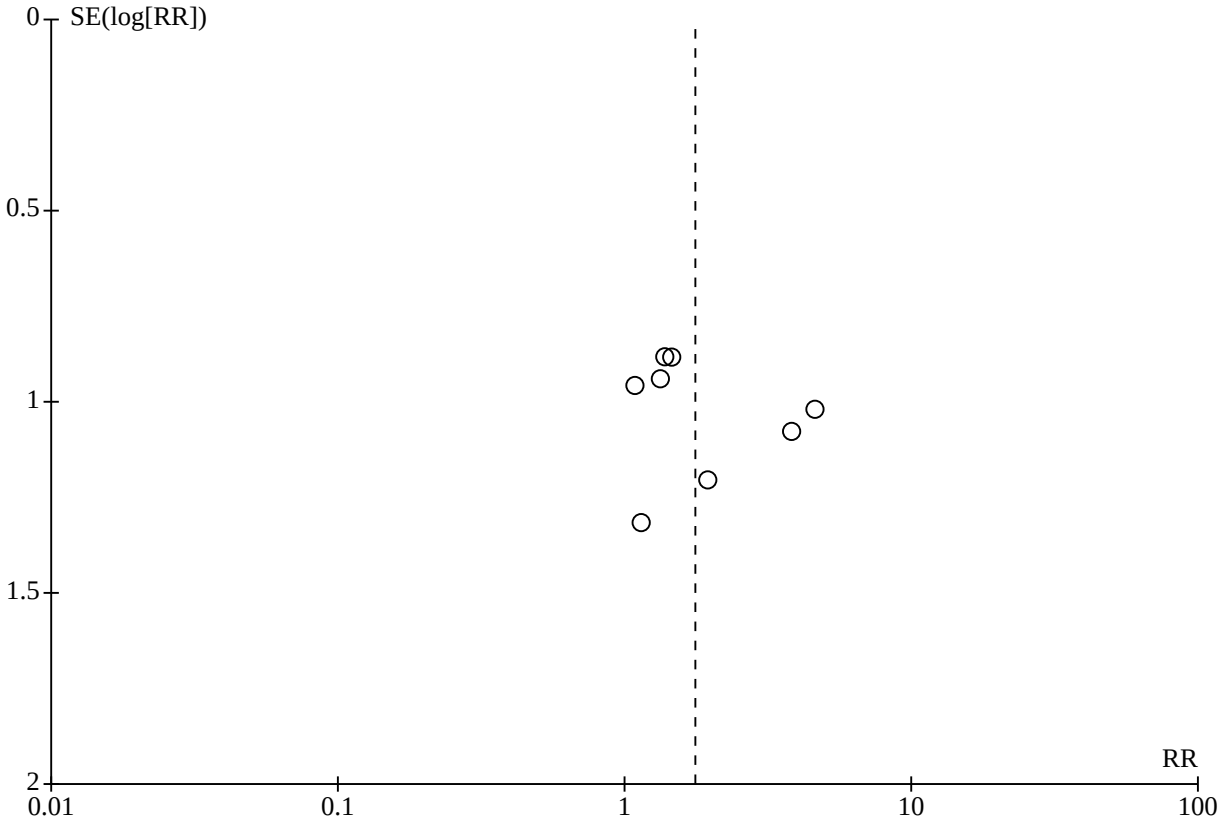
Footnotes

(1) FMT, 2 diagnoses changed to Crohn's colitis and 1 positive for *C difficile* toxin at end of therapy; control, 1 diagnosis changed to Crohn's colitis and 1 h

Publication bias

The funnel plot was symmetrical (Figure 6).

Figure 6. Funnel plot: serious adverse events for use of FMT for induction of remission in UC. The graph appears symmetrical.



Subgroup analyses

We performed subgroup analyses for the risk of serious adverse events after FMT based on route of administration (Analysis 1.12), type of donor (Analysis 1.13), and age of participants (Analysis 1.14). The number of included studies in each subgroup analysis was small and the CIs overlapped the line of no effect, indicating similarity of subgroup summary estimates.

Sensitivity analyses

A sensitivity analysis based on the use of a fixed-effect model showed similar results (RR 1.87, 95% CI 0.95 to 3.68) to those reported using a random-effects model (Analysis 1.15). A post-hoc sensitivity analysis based on available cases showed similar results (RR 1.74, 95% CI 0.88 to 3.47; 382 participants, Analysis 1.16).

Secondary outcomes

Any adverse events

There was little to no difference in any adverse events between the FMT and control groups of participants with active UC (RR 0.99, 95% CI 0.85 to 1.16; 9 studies, 417 participants; low-certainty of evidence; Analysis 1.17). We downgraded the certainty of evidence due to risk of bias and imprecision of the summary estimate (Summary of findings 1). Common adverse events included abdominal pain, nausea, flatulence, bloating, headaches, and dizziness.

Induction of endoscopic remission in ulcerative colitis at longest follow-up

FMT may increase rates of induction of endoscopic remission in UC at longest follow-up; however, the CIs around the summary estimate were wide and included a possibility of no effect (RR 1.45, 95% CI 0.64 to 3.29; 5 studies, 285 participants; low-certainty evidence; Analysis 1.18). We downgraded the certainty of evidence due to very serious imprecision of the summary estimate (Summary of findings 1).

Quality of life at longest follow-up

Five studies reported quality of life (IBDQ) scores in UC at the longest follow-up for FMT versus control groups. However, two of these studies were excluded from the quantitative analysis because one provided means without SD values (Moayyedi 2015) and one provided data in the form of box plots (Rossen 2015). Thus, the meta-analysis of final IBDQ scores was based on three studies with 131 participants. The evidence was very uncertain about whether FMT in participants with active UC increased quality of life at longest follow-up. The CIs were wide and included the possibility of no effect (MD 15.34, 95% CI −3.84 to 34.52; very low-certainty evidence; Analysis 1.19). We downgraded the certainty of evidence due to inconsistency and very serious imprecision of the summary estimate (Summary of findings 1). One study reported data as medians and IQR (Haifer 2022), which we converted to means and SDs using a calculator based on methods by Hozo 2005. A sensitivity analysis without this study showed similar results but with a more

imprecise CI around the summary estimate (MD 22.20, 95% CI 0.63 to 43.78; Analysis 1.20).

Induction of clinical response in ulcerative colitis at longest follow-up

FMT may increase rates of clinical response in participants with UC at the longest follow-up (RR 1.33, 95% CI 0.96 to 1.84; 10 studies, 468 participants; Analysis 1.21).

Induction of endoscopic response in ulcerative colitis at longest follow-up

FMT may increase rates of endoscopic response in participants with active UC; however, the CIs around the summary estimate were imprecise and a null effect could not be ruled out (RR 1.48, 95% CI 0.79 to 2.76; 3 studies, 164 participants; Analysis 1.22).

Withdrawals in studies on induction of remission in ulcerative colitis

There was little to no difference in withdrawal rates between the FMT and control groups of participants with active UC (RR 0.91, 95% CI 0.62 to 1.34; 10 studies, 468 participants; Analysis 1.23).

Erythrocyte sedimentation rate at longest follow-up

There was no evidence of a difference in ESR at longest follow-up between FMT and control groups of participants with active UC (MD 2.98 mm/hour, 95% CI −0.38 to 6.34; 2 studies, 113 participants; Analysis 1.24).

C-reactive protein at longest follow-up

There was no evidence of a difference in CRP at longest follow-up between FMT and control groups of participants with active UC (MD 1.11 mg/L, 95% CI −1.85 to 4.08; 3 studies, 128 participants; Analysis 1.26). Another study, Pai 2021, also measured CRP, but the data were not reported as final means and SDs and could not be combined with data from the other three studies.

Fecal calprotectin at longest follow-up

Three studies of 131 participants with UC reported data on FC at longest follow-up for the FMT versus control groups (Crothers 2021; Haifer 2022; Paramsothy 2017). FMT may decrease FC levels; however, the CIs were wide and included the possibility of no effect (MD −69.49 µg/mg, 95% CI −260.62 to 121.65; 3 studies, 131 participants; Analysis 1.28). Two other studies also measured FC (Costello 2019; Pai 2021), but their data were not reported as final means and SDs and could not be combined with data from the other three studies. One study reported data as medians and IQR (Haifer 2022), which we converted to means and SDs using a calculator based on methods by Hozo 2005.

Microbiome outcomes

Table 1 provides the summary of methods used to assess microbiome-related outcomes and the summary of key findings.

Comparison 2: fecal microbiota transplantation for maintenance of remission in ulcerative colitis

Primary outcomes

Maintenance of clinical remission in ulcerative colitis at longest follow-up

Two studies assessed FMT for maintenance of remission in 71 participants with UC, all of whom had achieved remission with FMT before randomization to the FMT versus control groups (Haifer 2022; Sood 2019a). The evidence was very uncertain about the effect of FMT on maintenance of clinical remission in participants with UC (RR 2.97, 95% CI 0.26 to 34.42; very low-certainty evidence; Analysis 2.1). We downgraded the certainty of evidence due to risk of bias, inconsistency, and very serious imprecision (Summary of findings 2).

Sensitivity analyses

A sensitivity analysis using a fixed-effect model showed that FMT may lead to a small increase in rates of maintenance of remission in participants with controlled UC (RR 1.53, 95% CI 1.13 to 2.07; Analysis 2.2). A sensitivity analysis based on participants who completed follow-up showed similar results (RR 1.66, 95% CI 0.47 to 5.81; Analysis 2.3).

Publication bias and subgroup analyses

The number of studies was fewer than 10, so we did not draw funnel plots for publication bias or perform subgroup analyses.

Serious adverse events

Two studies reported no serious adverse events in 71 participants with UC for whom FMT was used for maintenance of remission (Analysis 2.4). Overall, the evidence was very uncertain (Summary of findings 2). We downgraded the certainty of evidence due to risk of bias and very serious imprecision.

Publication bias, subgroup analyses, and sensitivity analyses

None of the subgroup or sensitivity analyses were performed as the number of events was zero in both studies. The funnel plot was not drawn because there were fewer than 10 studies.

Secondary outcomes

Any adverse events

The data from two studies showed very uncertain evidence about the risk of any adverse events when FMT was used for maintenance of remission in UC (RR 1.16, 95% CI 0.85 to 1.59; very low-certainty of evidence; Analysis 2.5). We downgraded the certainty of evidence due to risk of bias and very serious imprecision (Summary of findings 2).

Maintenance of endoscopic remission in ulcerative colitis at longest follow-up

The evidence was very uncertain about the use of FMT for maintenance of remission in people with UC (RR 3.28, 95% CI 0.73 to 14.74; very low-certainty evidence; Analysis 2.6). We downgraded the certainty of evidence due to risk of bias and very serious imprecision (Summary of findings 2).

Quality of life at longest follow-up

Haifer 2022 reported quality-of-life (IBDQ) scores after use of FMT for maintenance of remission in people with UC and the evidence was very uncertain, so no conclusive statement could be made (MD 38.2, 95% CI 19.3 to 57.1; 10 participants; very low-certainty evidence). The data in this study were reported in such a way that an effect size could not be calculated. We downgraded the certainty of evidence due to risk of bias and very serious imprecision (Summary of findings 2).

Withdrawals in studies on maintenance of remission in ulcerative colitis

There was little to no difference in withdrawal rates between the FMT and control groups after use of FMT for maintenance of remission in UC (RR 0.30, 95% CI 0.05 to 1.73; 2 studies, 71 participants; Analysis 2.7).

Erythrocyte sedimentation rate at longest follow-up

One study reported low levels of ESR at the end of follow-up after use of FMT for maintenance of remission in UC (MD −10.40 mm/hour, 95% CI −12.54 to −8.26; 61 participants; Analysis 2.8).

C-reactive protein at longest follow-up

One study reported low levels of CRP at the end of follow-up after use of FMT for maintenance of remission in UC (MD −2.70 mg/L, 95% CI −3.82 to −1.58; 61 participants; Analysis 2.9).

Microbiome outcomes

Table 1 provides the summary of methods used to assess microbiome-related outcomes and the summary of key findings.

Comparison 3: fecal microbiota transplantation for induction of remission in Crohn disease

None of the included studies reported data on use of FMT for induction of remission in CD.

Comparison 4: fecal microbiota transplantation for maintenance of remission in Crohn disease

Primary outcomes

Maintenance of clinical remission in Crohn disease at longest follow-up

One study reported data on maintenance of remission in people with CD after FMT versus control (Sokol 2020). The evidence was very uncertain and no conclusive statement could be made about the use of FMT for maintenance of remission in CD (RR 1.21, 95% CI 0.36 to 4.14; 21 participants; very low-certainty of evidence; Analysis 4.1; Summary of findings 4).

Serious adverse events

One study of 21 participants reported 13 serious adverse events in people with CD (Sokol 2020). However, the paper did not specify an exact breakdown of events between the FMT and control groups that totaled 13 events, so we did not calculate an effect size from these data. Overall, the evidence was very uncertain and no conclusive statement could be made about the risk of serious adverse events with FMT in people with CD (Summary of findings 4).

Secondary outcomes

Any adverse events

One study of 21 participants provided examples of adverse events experienced by participants, but the total number of any adverse events and corresponding breakdown between the FMT and control groups were not specified (Sokol 2020). It was also unclear whether the events reported were per person or if one participant experienced more than one event. Therefore, we did not calculate an effect size from these data. Overall, the evidence was very uncertain and no conclusive statement could be made about the risk of any adverse events with FMT in people with CD (Summary of findings 4).

Quality of life at longest follow-up

No studies reported data on quality of life (IBDQ scores) in people with CD.

Withdrawals in studies on maintenance of remission in Crohn disease

In one study, the withdrawal rate was 54.5% (6/11) in the FMT group versus 40.0% (4/10) in the control group (RR 1.36, 95% CI 0.54 to 3.46; 21 participants; Analysis 4.2).

Erythrocyte sedimentation rate at longest follow-up

No studies reported ESR levels after use of FMT in people with CD.

C-reactive protein at longest follow-up

One study reported CRP levels at six weeks after use of FMT as median values, which were lower in the FMT group (median 3.0 mg/L, IQR 3.0 to 14.2) than the control group (median 6.9 mg/L, IQR 4.0 to 8.7; Sokol 2020).

Fecal calprotectin at longest follow-up

One study reported FC levels at six weeks after use of FMT and the results were similar between the FMT and control groups (Sokol 2020).

Microbiome outcomes

Table 1 provides the summary of methods used to assess microbiome-related outcomes and the summary of key findings.

DISCUSSION

Summary of main results

This review synthesized findings from 11 studies that assessed FMT for treatment of UC and one study that assessed FMT for treatment of CD. Eight new studies were added to this updated version of our previous review (Imdad 2018). FMT may increase the rates of clinical and endoscopic remission in people with active UC, with little to no difference in any adverse events. The evidence was very uncertain about the risk of serious adverse events and improvement in quality of life when FMT was used for control of active UC. The evidence was also very uncertain about the use of FMT for maintenance of remission in UC and for both induction and maintenance of remission in CD.

Overall completeness and applicability of evidence

In this update, we added eight studies of participants with UC, which contributed to the analyses of FMT for induction of clinical remission, induction of endoscopic remission, serious adverse events, any adverse events, clinical response, endoscopic response, and quality of life. The addition of new data increased the overall number of events and size of the study population, which improved the precision of the summary estimates. However, the summary estimate was still very wide for most outcomes and the lower intervals of CIs around the summary estimate either showed a very small effect or crossed the null effect. More data will be required before the efficacy and safety of FMT for treatment of IBD can be established. It is important to note that the FDA issued safety alerts related to the use of FMT and risk of serious adverse events,

including the transfer of multiple drug-resistant organisms, SARS-CoV-2 transmission, and mortality (FDA 2020a; FDA 2020b).

Most studies included in this review assessed the use of FMT for induction of remission in people with active UC and showed low-certainty evidence that FMT may increase rates of clinical and endoscopic remission. The potential benefit of FMT for treatment of UC seems to be biologically plausible, based on earlier observations suggesting that people with UC have dysbiosis of the gut (Bejaoui 2015; Kostic 2014; Vindigni 2016), and that those who respond to FMT demonstrate reversal of this dysbiosis (Costello 2019; Paramsothy 2017). In addition, other therapeutic agents that target the microbiome, such as probiotics, have demonstrated efficacy in maintenance of remission in UC (Kaur 2020). A causal association between dysbiosis and UC seems to be further supported by the studies in this review, as microbiome analyses suggested differential responses in the microbiota of responders versus non-responders, highlighted by a shift towards the donor community microbiota in FMT responders (Crothers 2021; Moayyedi 2015; Paramsothy 2017; Rossen 2015; Sokol 2020). Notably, Paramsothy 2017 was also able to identify several taxa that were associated with induction of remission and the presence of other taxa that were associated with a lack of effect. Similarly, increased alpha diversity was associated with increased likelihood of a positive response.

Most of the participants with active UC in the included studies had mild-to-moderate UC, and it is not clear whether the efficacy would be similar, better, or worse in participants with severe UC. Also, it is not clear whether a combination of interventions, such as the use of antibiotics, nutritional therapy, or probiotics with FMT, has advantages over FMT alone. Furthermore, all the studies on active UC included participants who have failed at least one drug and none of the participants were treatment-naive.

There was notable clinical heterogeneity in the use of FMT among participants with active UC in terms of route, dosage, frequency, donor type, and pooling of stool from multiple donors. We updated the subgroup analyses for people with UC, but the number of studies in each subgroup analysis remained small, so no conclusive statement could be made about a differential effect of FMT on induction of clinical remission in UC based on age, route, frequency, or donor.

The number of studies on FMT for treatment of CD was small, and no conclusive statement could be made about the use of FMT for induction or maintenance of remission in CD.

Quality of the evidence

In the previous version of this review (Imdad 2018), the certainty of the evidence for most outcomes was low. With the addition of eight new studies to the analysis on induction of remission among participants with active UC, the evidence remained of low certainty for most outcomes. The most common reasons for downgrading the certainty of the evidence were risk of bias and imprecision due to a low number of studies and participants in a given analysis. Even though the overall precision of the summary estimate improved with the addition of new studies, the variation of effect around the summary estimate included a possibility of little or no effect. For example, the risk difference for the effect of FMT on induction of clinical remission in UC was about 15%; however, the lower limit of the CIs showed a risk difference of only 5%, which might not be clinically meaningful. We considered a minimal important difference of at least 10% to 15% for induction of remission in people with active UC, which is a conservative target compared to those of other trials on treatment of IBD (Bahnam 2023; Gordon 2021). We might revise our certainty assessment with the addition of newer studies in future updates.

We prioritized five outcomes to be included in the summary of findings tables in this version of the review, compared to seven outcomes included in the last version of the review. We included quality-of-life scores and excluded clinical and endoscopic response from the summary of findings tables based on the clinical importance of these outcomes. We generated separate summary of findings tables for induction and maintenance of remission in each subtype of IBD. We think that this approach is clinically meaningful for clinicians to access the most up-to-date evidence-based information on use of FMT for induction and maintenance of remission in UC and CD. As the body of evidence on this topic grows, more data will be reported in these tables, especially as we noted 29 ongoing studies.

Potential biases in the review process

This review was conducted following the standardized methods of Cochrane. We searched for both published and ongoing studies, and two review authors extracted data from each published study. In the previous version of this review, we had aimed to include non-randomized cohort studies with control arms, but no such studies were available. In this update, we did not consider any observational studies and only included randomized trials.

Three included studies were stopped early due to futility issues (Moayyedi 2015; Rossen 2015; Sarbagili Shabat 2022), and one trial enrolled approximately half of its goal participant number (Pai 2021). One trial was discontinued because the primary endpoint, remission of UC, was deemed unlikely to be achieved by the institution's Data Monitoring and Safety Board (DMSB), but enrolled participants were allowed to complete the trial (Moayyedi 2015). Similarly, another trial was advised by its DMSB to terminate early due to serious adverse events, less-than-expected treatment effect, and the need to expand its sample size uncovered during interim analysis (Rossen 2015). This study collected three months of data prior to its termination and an ITT analysis of its reported outcomes has been included in the current review. A third trial was also stopped early by the DMSB upon review of interim data after more than half of the intended participants had been enrolled (Sarbagili Shabat 2022). However, the *Cochrane Handbook for Systematic Reviews of Interventions* guidelines do not consider these studies to be at high risk of bias (Higgins 2011).

There is a debate on which outcome is most important to define the efficacy of an intervention for induction of remission in people with IBD (Armuzzi 2012; Auzoux 2017; Dave 2012; Dulai 2015; Peyrin-Biroulet 2011). The most commonly used outcome is 'clinical remission,' which is based on clinical symptom scores. The literature has suggested the need to assess mucosal healing as part of the response to therapy in IBD, as it might better predict long-term outcomes, including the risk of surgery (Auzoux 2017; De Preter 2012; Dulai 2015). In the protocol (Imdad 2017) of the first published version of this review (Imdad 2018), we had decided a priori that the primary outcome of 'clinical remission' would be based on definitions derived from clinical scores. In this updated version of the review, we updated the same analysis but also

considered composite outcomes, if available, and results continued to favor FMT versus control for induction of remission in people with active UC (Analysis 1.10). Therefore, we consider that the observed effect of FMT on induction of remission in people with active UC seems to hold regardless of how remission is defined.

We conducted ITT analyses with the assumption that all participants who were randomized to a group would be analyzed in the same group irrespective of whether they received the intervention or completed follow-up. Participants lost to follow-up were considered to have experienced treatment failure in both the intervention and control groups. Some experts advocate for analysis of only those participants who completed follow-up to avoid attrition bias. Thus, we performed a post-hoc sensitivity analysis using available cases, which had similar results for the use of FMT for induction of clinical remission in people with active UC (Analysis 1.9).

Agreements and disagreements with other studies or reviews

Since the publication of the original version of this review (Imdad 2018), multiple meta-analyses have been published on the safety and efficacy of FMT for treatment of either UC or CD (Caldeira 2020; Fehily 2021; Zhao 2020). The systematic reviews on use of FMT for induction of remission in people with UC mirrored the results noted in our review (Caldeira 2020; Zhao 2020). However, these reviews also included single-arm cohort studies that we did not include here. The systematic review on use of FMT for treatment of CD also included both RCTs and cohort studies (Fehily 2021). That review included two RCTs that we screened (Sokol 2020; Yang 2020), of which we only included Sokol 2020 and excluded Yang 2020 because it compared use of FMT via gastroscopy versus colonoscopy but both groups received FMT, which did not qualify as an eligible comparison under our inclusion criteria. Overall, the results were similar in these RCTs, and no conclusive statements could be made about FMT for treatment of CD.

AUTHORS' CONCLUSIONS

Implications for practice

Fecal microbiota transplantation (FMT) may increase the proportion of people with mild-to-moderate active ulcerative colitis (UC) who achieve clinical and endoscopic remission with little to no difference in any adverse events. The evidence was very uncertain about the risk of serious adverse events or improvement in quality of life when FMT was used for induction of remission in active UC. The evidence was also very uncertain about the use of FMT for maintenance of remission in both UC and Crohn disease (CD), and no conclusive statements could be made in this regard. We found no randomized trials on use of FMT for induction of remission in CD.

Implications for research

Additional studies are needed to further assess the use of FMT for treatment of UC and CD, especially in people with severe disease, as most studies in this review assessed the use of FMT for induction of remission in adults with mild-to-moderate UC. Only one small study assessed the use of FMT to treat UC in children, so more studies are needed in the pediatric population as well. Further evaluations of the microbiome and metabolome are also needed to establish the exact mechanism of action of FMT in treatment of inflammatory bowel disease (IBD). It is important to note that the composition of human microbiota is highly heterogeneous with high interindividual variability. Thus, more in-depth analyses exploring the functional impact of FMT on the microbiota of people with IBD are needed. Furthermore, the included studies did not explore other components of the microbiome such as the virome or fungome, which have been recently appreciated as important factors in health and disease (Carding 2017; Witherden 2017). Also, it is unclear whether non-microbial components of stool, such as bile acids, have any impact on treatment outcomes. Finally, socioeconomic status and other barriers to participation in clinical trials could potentially bias the population that is enrolled and studied. Future clinical trials on the use of FMT for treatment of IBD should try to recruit a diverse and representative population. However, we acknowledge that it is very challenging to recruit people into studies in which the intervention needs an extensive regulatory process, such as FMT. Multiple factors make enrollment of a diverse sample challenging in the USA, such as distrust among African-American communities towards academic research (Nooruddin 2020), language barriers among immigrant communities (Nageswaran 2022), and poor access to health care among Native-American and rural communities (Ghebre 2014). We hope that the data synthesized in this Cochrane Review will help future research in creating an 'evidence-based' study design to take full advantage of the efforts to recruit participants into FMT trials.

The strongest evidence for use of FMT comes from its use in the treatment of recurrent *Clostridioides difficile* infection (rCDI), in which a single dose from a single donor might be effective in about 60% to 80% of patients, and the proportion increases to over 90% with follow-up treatment in those who did not respond to the first treatment (Cammarota 2015; Cammarota 2017; Kelly 2021). The characteristics of FMT administration for treatment of IBD might be different from those for treatment of rCDI. For example, the two largest studies in this review, which showed promising results, used stool from multiple donors and their frequency of administration ranged from three times in an eight-week period (Costello 2019) to 40 times in an eight-week period (Paramsothy 2017). Further data are needed to delineate aspects of FMT use for treatment of IBD in terms of route (upper versus lower gastrointestinal tract), frequency, type of donor (single versus pooled), timing (primary induction versus rescue therapy), preparation of stool (aerobic versus anaerobic; frozen versus fresh), and duration of therapy (for induction of remission). Another important aspect to assess in use of FMT is whether it can be used as an adjuvant therapy to increase the rates of induction of remission and to avoid treatment failures such as development of antibodies to biologics.

The use of FMT for maintenance of remission in UC and CD might pose unique challenges related to long-term safety of this intervention. Data from observational studies indicate that a single dose of FMT may change the microbiome and have long-term effects including the risk of developing chronic diseases (Alang 2015; Saha 2021). Similarly, each dose of FMT may increase the risk of transmission of infection, and this risk might increase significantly in the setting of multiple doses given over longer periods of time. Thus, future studies that aim to evaluate the use of FMT for maintenance of remission in UC or CD should plan for long-term follow-up of these patients to assess for any adverse effects with long-term consequences.

We noted 29 ongoing studies that reflect the scientific community's interest in investigating the role of FMT for treatment of IBD (see Characteristics of ongoing studies table). However, we anticipate challenges with adoption and conduct of this intervention as a 'drug' in clinical practice due to variation in production and quality control of each FMT specimen. The US Food and Drug Administration (FDA) has issued guidelines to help with appropriate development of FMT-based products used in clinical studies, and the guidance includes information on donor screening and blood testing, stool testing, as well as appropriate preparation and administration of the FMT product (Carlson 2020). The FDA also emphasized the need to develop potency assays of the FMT product and perform stability studies to ensure that individual species within the product's microbiota are viable and to assess any potential impact of the donor microbiome on the product's safety and effectiveness (Carlson 2020). There is also growing interest in other microbiome-based therapies, such as modified stool products that may reduce the concentration of potentially harmful bacteria (Feuerstadt 2022), and the administration of laboratory-grown bacteria without using any stool product (Rode 2021) for treatment of rCDI. Future studies may focus on some of these newer microbiome-based therapies to investigate their role in the treatment of IBD.

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- Sign-off Editor (final editorial decision): Grigorios Leonitiadis; McMaster University, Canada; Co-ordinating Editor of the Cochrane Gut Group
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- Peer-reviewers (provided comments and recommended an editorial decision): Athos Bousvaros; Professor of Pediatrics Harvard Medical School Pediatric Gastroenterologist Boston Children's Hospital (clinical), George Lillington (consumer), Natalia Castaño-Rodríguez; School of Biotechnology and Biomolecular Sciences Faculty of Science UNSW Sydney Australia (clinical), Rachel Richardson; Associate Editor; Cochrane Evidence Production and Methods Directorate (methods), Sheila Wallace; Cochrane Incontinence (search)

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Březina 2021

Study characteristics	
Methods	Multicenter, open-label RCT conducted in the Czech Republic
Participants	**Inclusion criteria** • Adults age < 70 years, with clinically and endoscopically active left-sided UC for > 3 months, total Mayo score 4–10, and endoscopy subscore ≥ 2 • Participants were allowed to use oral 5-ASA (stable dose for 8 weeks, maximal dose 4 g), thiopurines (stable dose for 8 weeks), and oral prednisone (≤ 10 mg daily, stable for 4 weeks), if they maintained same dosage during study period **Exclusion criteria** • Use of anti-TNF medication and other biologic therapy in preceding 12 weeks, rectal corticosteroids or 5-ASA in preceding 4 weeks, calcineurin inhibitors in preceding 12 weeks, methotrexate in preceding 8 weeks, prednisone > 10 mg, antibiotics or probiotics in preceding 8 weeks • Indeterminate colitis, CD, IBS, impending risk of colectomy, history of bowel cancer • Positive stool culture for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *pathogenic Escherichia coli*; cytomegalovirus infection, *Clostridioides difficile* infection • Pregnancy, lactation
Interventions	**Experimental arm** n = 23 • Single donor feces (multiple donors recruited for study but each participant received feces from 1 donor only) • 50 g of stool in 150–170 mL infusion per treatment; administered via enema; 5 times in the first week and then once weekly for 5 more weeks **Control arm** n = 22 • Mesalamine 4 g; administered via enema; daily for 2 weeks and then every other day until end of week 6
Outcomes	**Primary outcome** • Clinical remission at week 12 (total Mayo score ≤ 2 with no subscore > 1)

Březina 2021 *(Continued)*

	Secondary outcomes • Clinical response at weeks 6 and 12 (reduction in total Mayo score ≥ 2 points) • Endoscopic remission at weeks 6 and 12 (endoscopic Mayo score of 0) • Adverse events at week 12 • Withdrawals
Notes	Data interpretation: study authors used mITT analysis, in which the number of participants who experienced treatment success in the primary outcome was analyzed out of the number of participants who received treatment. The latter did not equal the total number of participants originally randomized to each group. For our review, we considered the number of participants with treatment success in the primary outcome out of the number randomized to each group, and then we conducted sensitivity analyses using only participants with complete data. Funding: Ministry of Health of the Czech Republic, grant number 16-27449A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 1:1 using a computer-generated randomization list stratified by gender and the receipt of immunosuppressive therapy. The randomization was performed centrally at IKEM in Prague." (page 3) Comment: most likely done.
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomization was performed centrally at IKEM in Prague." (page 3) Comment: likely done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: study was open-label, so the participants likely knew the treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Endoscopies were performed and recorded at each study center and were then centrally assessed by two endoscopists blinded to the administered therapy." (page 3) Comment: most likely done for the primary outcome of induction of clinical remission. Other outcomes may be at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 participants randomized to the FMT group were not included in the analysis. Data were available for the remaining participants in the FMT and control groups. Results were less likely to be affected by attrition.
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported in the paper. Trial registered on ClinicalTrials.gov (NCT03104036).
Other bias	Low risk	Comment: no other risk of bias noted.

Costello 2019

Study characteristics

Costello 2019 *(Continued)*

Methods	Multicenter, double-blind RCT conducted in Australia
Participants	**Inclusion criteria** • Ages ≥ 18 years with active UC, total Mayo score 3–10, endoscopic subscore ≥ 2 • On stable dose of UC maintenance therapy prior to enrollment: 4 weeks for 5-ASA, 6 weeks for thiopurines and methotrexate, 8 weeks for biologic agents • Permitted to take oral prednisolone ≤ 25 mg, with mandatory taper of 5 mg per week (those unable to cease by week 8 were considered FMT non-responders) **Exclusion criteria** • People with severe disease: total Mayo score 11–12 or Truelove and Witts criteria (passing > 6 bloody stools/day plus ≥ 1 of: temperature > 37.8 °C, HR > 90 bpm, hemoglobin < 10.5 g/dL, ESR > 30 mm/hour) • Previous colonic surgery, gastrointestinal infection, pregnancy, anticoagulant therapy, current use of antibiotics or probiotics
Interventions	**Experimental arm** n = 38 • Multiple donor feces (each stool treatment was pooled and blended from 3 or 4 donors) • First treatment: 50 g stool administered in 200 mL infusion via colonoscopy • Each of next 2 treatments: 25 g stool administered in 100 mL infusion via enema, within 7 days following first treatment **Control arm** n = 35 • Autologous FMT • First treatment: 50 g stool administered in 200 mL infusion via colonoscopy • Each of next 2 treatments: 25 g stool administered in 100 mL infusion via enema, within 7 days following first treatment
Outcomes	**Primary outcomes** • Steroid-free remission at week 8 (total Mayo score ≤ 2 and endoscopic Mayo score ≤ 1) • Clinical remission at week 8 and month 12 (SCCAI score ≤ 2) **Secondary outcomes** • Clinical response at week 8 and month 12 (≥ 3-point reduction in total Mayo score) • Endoscopic remission at week 8 and month 12 (Mayo score < 1) • Adverse events at week 8 and month 12 • Withdrawals
Notes	Data extraction: study reported data for open-label maintenance of remission at month 12, but only the data at week 8 were included in the analysis because re-randomization was not done after week 8. Also, fecal calprotectin outcomes were reported as log-transformed values, which were not included in the analysis because we needed data in the form of means with SD. Data interpretation: study authors used an ITT analysis, in which all participants originally randomized to each group were included in the primary analysis, even though there were withdrawals during that 8-week period. Authors stated that for participants with missing Mayo score data at week 8, the missing values were imputed, with methods outlined in the 'Statistical analysis' section of their published paper. We used the data as reported in the main manuscript. Funding: National Health and Medical Research Council and the Gutsy Foundation.

Costello 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Accrued participants were randomized 1:1 using a computer-generated simple randomization algorithm (http://www.random.org) to receive either pooled donor stool FMT (dFMT) or autologous FMT (aFMT)." (page 157) Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization and blinding procedure was conducted by nursing staff who were not present at FMT administration. The randomization record was kept in a separate document to the patient record and other study data such that participants and clinicians performing the procedures and assessing the primary and secondary end points were blinded to the therapy received." (page 158) Comment: most likely done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The randomization and blinding procedure was conducted by nursing staff who were not present at FMT administration. The randomization record was kept in a separate document to the patient record and other study data such that participants and clinicians performing the procedures and assessing the primary and secondary end points were blinded to the therapy received." (page 158) Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The randomization and blinding procedure was conducted by nursing staff who were not present at FMT administration. The randomization record was kept in a separate document to the patient record and other study data such that participants and clinicians performing the procedures and assessing the primary and secondary end points were blinded to the therapy received." (page 158) Comment: most likely done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The primary and secondary outcomes at week 8 between treatment groups were assessed on an intention-to-treat basis." (page 161) Comment: 3/38 participants withdrew in experimental group and 1/35 withdrew in control group, so less than 10% were lost to follow-up in both groups (page 159); there were no major concerns related to attrition in this study.
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported in the paper. Trial was registered at www.anzctr.org.au (ACTRN12613000236796).
Other bias	Low risk	Comment: no other risk of bias noted.

Crothers 2021

Study characteristics	
Methods	Single-center, double-blind RCT conducted in the US
Participants	**Inclusion criteria**

Crothers 2021 *(Continued)*

- Adults with established diagnosis of UC and inflammation extending proximally to at least the rectosigmoid junction; with baseline total Mayo score 4–10, Endoscopic Mayo subscore ≥ 1, Rectal Bleeding subscore ≥ 1, Stool Frequency subscore ≥ 1
- On stable dosing of UC-specific medications (e.g. anti-TNFα, oral immunomodulators, oral and topical 5-ASA, methotrexate) for ≥ 6 weeks prior to screening

Exclusion criteria

- People who were asymptomatic or had severe, refractory disease (Mayo score ≥ 10, endoscopic subscore ≥ 3), proctitis only, infectious colitis, exacerbation of baseline symptoms
- History of colectomy, gastrointestinal motility disorder, limited life expectancy (< 12 months), pregnancy, lactation, severe immunodeficiency, history of anaphylaxis
- Corticosteroid use; antibiotic use within 6 weeks or probiotics use within 4 weeks of enrollment
- Modification to eligibility criteria after trial began, to increase recruitment: probiotic use permitted up to 1 week prior to enrollment

Interventions

Experimental arm

n = 7

- Single donor feces for induction therapy via colonoscopy (120 mL at concentration of 1 g stool/2.5 mL)
- 2 alternating donors' feces for maintenance therapy via capsule (1 daily 550 µL FMT capsule, about 0.5 g stool) for 12 weeks

Control arm

n = 8

- Sham colonoscopy and sham capsules that resembled the intervention in experimental group

Outcomes

Primary outcome

- Adverse events, measured by telephone call 24 hours after induction therapy, at 4 clinic visits (weeks 4, 8, 12, 18), and by telephone call at week 36

Secondary outcomes

- Clinical remission at week 12 (modified Mayo Score ≤ 2, including Rectal Bleeding subscore of 0, Stool Frequency subscore 0 or ≥ 1 point decrease from baseline to achieve Stool Frequency subscore ≤ 1, Endoscopic subscore ≤ 1)
- Clinical response at week 12 (decrease in total Mayo score (Stool Frequency, Rectal Bleeding, physical global assessment, Endoscopic Mayo scores) from baseline by ≥ 3 points with Rectal Bleeding subscore of 0 or 1, or decrease in Rectal Bleeding subscore by ≥ 1 point)
- Serum CRP at week 12
- Fecal calprotectin at week 12
- IBDQ total score at week 12

Notes

Data extraction: participants in both groups were pretreated with antibiotics (ciprofloxacin 250 mg orally every 12 hours and metronidazole 500 mg orally every 8 hours for 7 days prior to FMT or placebo). Even though the study reported outcomes of maintenance of remission, we did not consider these data as the participants received FMT during the active disease phase and were not re-randomized after achieving remission. We only considered the outcomes of induction of remission.

Data interpretation: study authors used an mITT analysis, in which only participants who received ≥ 1 study dose were considered, rather than the total number of participants randomized to each group. They report that the latter included participants who were deemed ineligible after randomization. In our review, we considered the total number of participants randomized to each group in order to remain consistent with our methods used for other studies, and then we conducted a sensitivity analysis with only complete data.

Crothers 2021 *(Continued)*

Funding: University of Vermont Larner College of Medicine, the Departments of Medicine and Pathology & Laboratory Medicine (University of Vermont Medical Center), the National Institutes of Health (P30GM118228 [RCB]), (DK113800 [GMM]), the MIT Center for Microbiome Informatics and Therapeutics, and OpenBiome.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible subjects were randomized 1:1 by a computer-generated randomization list maintained off-site at OpenBiome (Cambridge, MA) to ensure concealment of allocation and double blinding." (page 3) Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote: "The treatment allocation was blinded to the subject, and all on-site investigators and staff." (page 3) Comment: most likely done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The treatment allocation was blinded to the subject, and all on-site investigators and staff." (page 3) Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The treatment allocation was blinded to the subject, and all on-site investigators and staff." (page 3) Comment: most likely done.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 1/7 (14.3%) were excluded from analysis in experimental group, while 2/8 (25%) were excluded from analysis in control group, though each group excluded 1 due to no evidence of disease and control group excluded 1 due to worsening symptoms of disease. (page 5)
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported in the paper. The trial was registered on ClinicalTrials.gov (NCT02390726).
Other bias	Low risk	Comment: no other risk of bias noted.

Fang 2021

Study characteristics

Methods	Single-center, open-label RCT conducted in China
Participants	**Inclusion criteria** • Adults ages 18–75 years with recurrent active UC, hospitalized at the study center; those with Mayo score 4–12, previously on stable dosing of 5-ASA for ≥ 4 weeks but no other therapy (e.g. immunosuppressive agents, biologics, surgery) **Exclusion criteria** • Pregnancy; history of abdominal surgery or FMT treatment; use of antibiotics, probiotics, or prebiotics within 4 weeks of study participation • Infections (e.g. *Clostridioides difficile*, CMV, EBV, extra-intestinal infections requiring antibiotics)

Fang 2021 *(Continued)*

	• Comorbidities, e.g. heart, lung, cerebrovascular disease; history of gastrointestinal malignancy, polyps, IBS, inability to undergo endoscopy
Interventions	**Experimental arm** n = 10 • Multiple donor feces; 50 g stool in 200 mL infusion administered via colonoscopy **Control arm** n = 10 • People with mild-to-moderate UC were treated with mesalazine • People with severe UC were treated with corticosteroids for induction therapy and mesalazine for maintenance therapy
Outcomes	**Primary outcomes** • Clinical remission at week 8 (Mayo score ≤ 2 with each subscore ≤ 1) • Mucosal remission at week 8 (Mayo Endoscopy subscore ≤ 1 compared with baseline) • Clinical response at week 8 (decrease in Mayo score of ≥ 30% and ≥ 3 points compared with baseline) **Secondary outcomes** • Maintenance of clinical and mucosal remission at weeks 2, 4, 8, 12, 24, and months 12 to 24 • Adverse events during long-term follow-up • Clinical relapse (exacerbation of diarrhea and purulent bloody stool that required drug initiation or replacement to induce remission)
Notes	It seems that the related FMT donors tended to be quite young, as young as 5 years old, while most studies use adult FMT donors. Ideal donors are not known, however, and children are studied for this purpose. Data extraction: data for induction of remission were included at week 8 of follow-up. The study also reported data for maintenance of remission up to month 24; however, these data were not included as re-randomization was not performed after the induction of remission. 'Quality-of-life scores' were reported as an outcome in this study, but the data were not evident in the paper. Data interpretation: study authors used an ITT analysis, in which all participants originally randomized to each group were accounted for in the final analysis. We included the data as reported in the primary study. Funding: Anhui Natural Science Foundation (grant number 1408085MH178).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The study was designed as an open-label, randomized, parallel-group comparison study. Eligible patients were randomized to the FMT monotherapy and control groups." (page 11) Published protocol stated, "A random number table and a random number remainder grouping method are adopted by PI [principal investigator]." Comment: most likely done.
Allocation concealment (selection bias)	Unclear risk	Comment: the exact method of allocation concealment was not available for review.

Fang 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was designed as an open-label, randomized, parallel-group comparison study." (page 11) Comment: study was open-label, so it likely did not have blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: published protocol stated, "Blind method for clinical efficacy evaluator and analysts."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "An intention-to-treat analysis was performed." (page 12) Comment: appeared that all 20 participants (10 in each group) were included in the analysis.
Selective reporting (reporting bias)	Low risk	Comment: a protocol was available for review of methods and a priori outcomes; all intended outcomes were reported in the paper. Trial was registered at www.chictr.org.cn (ChiCTR2000030080).
Other bias	Low risk	Comment: no other risk of bias noted.

Haifer 2022

Study characteristics	
Methods	Multicenter, double-blind RCT conducted in Australia
Participants	**Inclusion criteria** • Ages 18–75 years diagnosed with clinically and endoscopically active UC for > 3 months, total Mayo score 4–10, Mayo endoscopic subscore ≥ 1 • Must have been on stable dosing of concomitant medications: oral mesalazine (stable dose for ≥ 4 weeks); thiopurines or methotrexate (stable dose for ≥ 4 weeks), oral prednisolone or equivalent (dose ≤ 20 mg daily and stable dose for ≥ 2 weeks), or first-line biologic therapy with vedolizumab or anti-TNF agent (infliximab, adalimumab, golimumab; stable maintenance dose for ≥ 8 weeks) • Patients had to continue stable dosing of all UC therapies during trial period except for prednisolone, for which there was mandatory taper of 2.5 mg weekly until corticosteroid-free status by week 8 **Exclusion criteria** • Features of acute severe colitis (fevers, HR > 100, > 10 stools per day), CD, indeterminate colitis, isolated proctitis limited to < 5 cm from anal verge, *Clostridioidesdifficile* colitis or other infectious enterocolitis in the past 3 months, current or history of toxic megacolon, pregnancy, lactation, trying to conceive, significant gastrointestinal surgery (except appendectomy), previous FMT, significant medical comorbidities (e.g. cardiac, liver, renal failure), congenital or acquired immunodeficiency, immunosuppression treatment for another condition, another significant GI condition (e.g. irritable bowel syndrome, diverticulitis, neoplasm), steroid dependency requiring > 20 mg prednisone daily at time of enrollment, participation in any trial or experimental treatment in preceding 12 weeks; history of allergy to penicillin, doxycycline, metronidazole; prior loss of response (primary or secondary) to ≥ 2 biologic medications • Use of antibiotics, antimycobacteria therapy, antituberculosis medications, probiotics in preceding 4 weeks • Rectal preparations (e.g. steroid or 5-ASA suppositories/enemas) during study period or in preceding 2 weeks • Concomitant antibiotic treatment during study period or in preceding 4 weeks • Probiotics during study period or in preceding 4 weeks

Haifer 2022 *(Continued)*

	• Experimental/trial drug within past 12 weeks
Interventions	**Experimental arm** n = 15 • Single donor feces; 0.35 g of lyophilized stool administered via capsules • 6 capsules 3 time daily for 1 week, then 6 capsules twice daily for 1 week, then 6 capsules once daily for 6 weeks **Control arm** n = 20 • Administered via capsules identical to those used in experimental group
Outcomes	**Primary outcome** • Combined corticosteroid-free clinical remission with endoscopic remission or response (total Mayo score ≤ 2, with all Mayo subscores ≤ 1, and ≥ 1-point reduction of Mayo Endoscopic subscore from baseline endoscopy) at week 8 **Secondary outcomes** • Corticosteroid-free clinical remission (combined Mayo subscores for Rectal Bleeding and Stool Frequency ≤ 1) at week 8 • Corticosteroid-free clinical response (reduction in partial Mayo score of ≥ 3 or ≥ 50% reduction of Rectal Bleeding and Stool Frequency Mayo subscores) at week 8 • Corticosteroid-free Endoscopic Remission (UCEIS ≤ 1) at week 8 • Corticosteroid-free endoscopic response (reduction in UCEIS of ≥ 3 or ≥ 50% reduction from baseline UCEIS score) at week 8 • Maintenance of clinical remission at week 56 • Maintenance of endoscopic remission at week 56 • Change in IBDQ scores at weeks 8 and 56 • Change in fecal calprotectin levels at weeks 8 and 56 • Change in CRP • Rates of adverse events
Notes	Data extraction: data on quality-of-life scores and fecal calprotectin were reported as medians and IQR, so they were converted to mean and SD per methods described in Hozo 2005, with the help of the calculator at vassarstats.net/median_range.html. The paper reported that CRP levels were measured, but the data were not found. We only extracted data on clinical and endoscopic remission rates, adverse events, and withdrawals during the maintenance period. Data interpretation: the study authors used an mITT analysis, in which only the participants who received ≥ 1 study dose were considered, which included all participants who were originally randomized. The authors stated in the 'Statistical analysis' section of their published paper that any missing value was imputed using the last recorded value for that participant. Funding: St Vincent's Clinic Foundation, Gastroenterological Society of Australia, Gutsy Group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised centrally by the Centre for Digestive Diseases (Sydney, NSW, Australia) in a 1:1 ratio to receive either FMT or placebo, using a pre-established computer-generated randomisation list created by an online list generator with permutated blocks of eight. The individual who performed the randomisation was not otherwise involved in the trial." (page 143)

Haifer 2022 *(Continued)*

		Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote: "To ensure masking, placebo capsules were double encapsulated to replicate the lyophilised capsules and were indistinguishable from FMT capsules by taste, smell, or colour, and were stored in identical coded packaging. Packaged capsules were then dispensed to the patient by a separate investigator who was unaware of the treatment allocation … Endoscopic images and histology were both read centrally by an expert gastroenterologist and histopathologist, respectively, masked to the treatment allocation." (page 143) Comment: most likely done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To ensure masking, placebo capsules were double encapsulated to replicate the lyophilised capsules and were indistinguishable from FMT capsules by taste, smell, or colour, and were stored in identical coded packaging. Packaged capsules were then dispensed to the patient by a separate investigator who was unaware of the treatment allocation. We assessed the placebo preparation on two study investigators (CH and RWL) who were not able to distinguish between the preparations. Study investigators who played a part in patients' assessment did not see the investigational product at any time. At 8 weeks, investigators and patients were unmasked after the end of treatment sigmoidoscopy." (page 143) Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Endoscopic images and histology were both read centrally by an expert gastroenterologist and histopathologist, respectively, masked to the treatment allocation." (page 143) Comment: the assessors were not aware of the intervention received by the participants, so the risk of detection bias was low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: mITT analysis used; all randomized participants were included in induction follow-up 8 weeks after commencing FMT. (page 145)
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported in the paper; trial was registered with the Australian New Zealand Trial Registry (ACTRN 12619000611123).
Other bias	Low risk	Comment: no other risk of bias noted.

Moayyedi 2015

Study characteristics	
Methods	Single-center, double-blind RCT conducted in Canada
Participants	**Inclusion criteria** • Adults ages ≥ 18 years with active UC (Mayo score ≥ 4 with Endoscopic Mayo score ≥ 1) • Concomitant UC medications allowed if participants were on stable dosing for ≥ 12 weeks and disease remained active, e.g. mesalamine, glucocorticoids (4 weeks), immunosuppressants such as azathioprine, TNF antagonists **Exclusion criteria**

Moayyedi 2015 *(Continued)*

- Use of antibiotics or probiotics in last 30 days, concomitant infection with *Clostridioides difficile* or another enteric pathogen, disease severity requiring hospitalization, pregnancy

Interventions	**Experimental arm** n = 38 • Single donor feces • 50 g stool in 300 mL mixture; 50 mL treatments administered via enema once per week for 6 weeks **Control arm** n = 37 • Placebo consisting of water • 50 mL treatments administered via enema once per week for 6 weeks
Outcomes	**Primary outcome** • Clinical remission at week 7 (full Mayo score < 3, Endoscopic Mayo score = 0) **Secondary outcomes** • Clinical response at week 7 (reduction in full Mayo score ≥ 3 points) • Improvement in UC symptoms (defined as ≥ 3 improvement in full Mayo score) • Full Mayo score • IBDQ scores (mean values reported without SD) • Inflammatory markers (ESR and CRP) • Adverse events
Notes	The study was stopped early due to futility. Data interpretation: study authors reported that all analyses were conducted on an ITT basis, which considered all participants originally randomized to each group even though not every participant completed the trial. They also reported that the IBDQ data had missing values, which were imputed using their means. However, because the IBDQ means for each group were reported without SD values, we excluded this study from the corresponding analysis. Data extraction: data for ESR and CRP were given for a subset of participants and were used accordingly. We also think that Table 2 of the published manuscript reported SD for continuous outcomes and not SE. The continuous data in Table 1 were reported as mean and SD and when we converted the SE values in Table 2 to SD using the formula SE × √(n) = SD, the values obtained were implausible. Therefore, we extracted the data reported in Table 2 of the published manuscript as SD values. We also wrote to the authors to clarify these data. Funding: Hamilton Academic Health Sciences Organization (HAHSO) and Crohn's and Colitis Canada (CCC).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 1:1 according to a computer-generated randomization list that was stratified for patients with UC diagnosed within 1 year. The randomization was held centrally at the McMaster Gastroenterology Clinical Trials Unit to ensure concealment of allocation." (page 103) Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization was held centrally at the McMaster Gastroenterology Clinical Trials Unit to ensure concealment of allocation. The treatment lo-

Moayyedi 2015 *(Continued)*

		cation was masked to the patient, health care workers caring for the patient, and investigators. The technician administering FMT or placebo was aware of the treatment being administered, as the nature of the intervention meant that it was not possible to make it identical to the placebo." (page 103) Comment: most likely done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The randomization was held centrally at the McMaster Gastroenterology Clinical Trials Unit to ensure concealment of allocation. The treatment location was masked to the patient, health care workers caring for the patient, and investigators. The technician administering FMT or placebo was aware of the treatment being administered, as the nature of the intervention meant that it was not possible to make it identical to the placebo." (page 103) Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The randomization was held centrally at the McMaster Gastroenterology Clinical Trials Unit to ensure concealment of allocation. The treatment location was masked to the patient, health care workers caring for the patient, and investigators. The technician administering FMT or placebo was aware of the treatment being administered, as the nature of the intervention meant that it was not possible to make it identical to the placebo." (page 103) Comment: most likely done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1/38 (2.6%) participants withdrew from the experimental group and 3/37 (8.1%) withdrew from the control group.
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported in the paper. The trial was registered on ClinicalTrials.gov (NCT01545908).
Other bias	Low risk	Comment: trial was stopped early due to futility; however, data were completely described for included participants.

Pai 2021

Study characteristics	
Methods	Multicenter, single-blind RCT conducted in Canada
Participants	**Inclusion criteria** • Children ages ≥ 4 years, diagnosed with UC based on characteristic endoscopic and histologic evidence of chronic active inflammation • Children with IBD-unclassified (IBD-U) if primary gastroenterologist judged their disease features as most consistent with UC • Participants could remain on stable dosing of oral mesalamine, thiopurines, or methotrexate at study entry, and on stable dosing and frequency of biologic agents within 12 weeks of enrollment **Exclusion criteria** • Hospitalization or active *Clostridioides difficile* infection at study entry • Use of oral antibiotics or rectal therapies (e.g. corticosteroid suppositories/enemas or mesalamine suppositories/enemas) within 4 weeks of enrollment
Interventions	**Experimental arm**

Pai 2021 *(Continued)*

	n = 13 • Multiple donor feces (i.e. 1 participant would receive treatments from different donors at different time points in study, but no pooled treatments) • 150 mL/FMT (50 g stool, 1×10^7 colony-forming units/mL) over 12 infusions; 150 mL FMT administered via enema, twice per week for 6 weeks **Control arm** n = 12 • 150 mL placebo administered via enema, twice per week for 6 weeks
Outcomes	**Primary outcome** • Clinical remission at weeks 6 and 30 (PUCAI score < 15) **Secondary outcomes** • Clinical response at weeks 6 and 30 (improvement from baseline PUCAI) • CRP change from baseline at weeks 6 and 30 • Fecal calprotectin change from baseline at weeks 6 and 30 • Adverse events
Notes	Data extraction: study authors reported data for an open-label maintenance period up to week 30, which were not included in the analysis because the trial opened for analysis at week 6. They reported maintenance of remission data in-text for FMT participants, which were not analyzed as the intervention was given during the active disease phase and not during remission. Maintenance data were only considered if the participants in remission were randomized again. They also reported data on the number of participants who showed improvement from baseline in CRP and fecal calprotectin, as well as the quantified changes from baseline. However, they did not provide the final values and thus these data were not included in the analysis, as we only considered these outcomes as continuous data and not as binary outcomes. Data interpretation: the study authors used an mITT analysis, in which only the participants who received ≥ 1 study dose were considered. They also reported in a footnote for Table 1 in their published paper, which included data for the primary outcome of clinical remission, that missing values were excluded. We included the data for all randomized participants irrespective of whether they received the intervention or completed follow-up, and then we conducted a sensitivity analysis for only participants with complete data. Funding: this investigator-initiated study was supported by institutional grants from the Hamilton Health Sciences New Investigator Fund (NIF-15375) Hamilton Academic Health Sciences Organization (HAH-17-002), and Canadian Institutes of Health Research (RN279389 – 358033; Inflammation, Microbiome, and Alimentation: Gastro-Intestinal and Neuropsychiatric Effects (IMAGINE): A Strategy for Patient-Oriented Research CIHR Chronic Disease Network). The study's investigational therapeutic and placebo materials were provided by Rebiotix Inc, a Ferring Company.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 1:1 through an unstratified computer- generated block randomization list with permutated blocks of 4." (page 393) Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote: "Random sampling numbers were contained in a set of sealed envelopes per block and drawn at the moment of assignment by a study team member. Patients and caregivers were unaware of treatment allocation, but

Pai 2021 *(Continued)*

		study team members were not blinded due to study resource and ethics constraints." (page 393) Comment: most likely done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Random sampling numbers were contained in a set of sealed envelopes per block and drawn at the moment of assignment by a study team member. Patients and caregivers were unaware of treatment allocation, but study team members were not blinded due to study resource and ethics constraints." (page 393) Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Patients and caregivers were unaware of treatment allocation, but study team members were not blinded due to study resource and ethics constraints." (page 393) Comment: it appeared that the outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 9/25 (36%) participants were withdrawn from the study (5/12 of the experimental group and 3/13 of the control group had treatment failures).
Selective reporting (reporting bias)	Low risk	Comment: all a priori outcomes were reported in the paper. A published protocol is available and the trial was registered on ClinicalTrials.gov (NCT02487238).
Other bias	Low risk	Comment: no other risk of bias noted.

Paramsothy 2017

Study characteristics	
Methods	Multicenter, double-blind RCT conducted in Australia
Participants	**Inclusion criteria** • Adults ages 18–75 years with UC for > 3 months; clinically and endoscopically active UC with total Mayo score 4–10 (Mayo Endoscopy subscore ≥ 1 and Physician's Global Assessment subscore ≤ 2); any disease extent except proctitis confined to the distal 5 cm • People on stable dosing of oral 5-ASA (stable dose for 4 weeks), thiopurines and methotrexate (on medication for ≥ 90 days and stable dose for 4 weeks), oral prednisone (dose ≤ 20 mg daily and stable for 2 weeks) preceding enrollment; Participants had to remain on same dose of 5-ASA, thiopurine, methotrexate; oral prednisone mandatory taper of up to 2.5 mg per week until steroid-free by week 8 **Exclusion criteria** • Indeterminate colitis, major comorbid chronic disease, major food allergy, irritable bowel syndrome, history of bowel cancer, pregnancy, previous gastrointestinal surgery apart from appendectomy > 3 months before the study, gastrointestinal infection at study entry (e.g. parasitic and *Clostridioides difficile* infections) • No rectal therapies, including corticosteroids or 5-ASA (within 2 weeks of enrollment) • No antibiotics or probiotics (within 4 weeks of enrollment) • No biologic therapies or calcineurin inhibitors (within 12 weeks of enrollment)
Interventions	**Experimental arm** n = 41

Paramsothy 2017 *(Continued)*

- Multiple donor feces (blended from 3–7 donors); each participant received treatment from same donor batch
- 37.5 g stool in 150 mL infusion, administered first via colonoscopy; starting the next day, administered via enema 5 times per week for 8 weeks (total 40 enemas)

Control arm

n = 40

- Isotonic saline in 150 mL infusion, administered first via colonoscopy; starting the next day, administered via enema 5 time per week for 8 weeks (total 40 enemas)

Outcomes

Primary outcome

- Composite of steroid-free clinical remission and endoscopic remission or response at week 8 (total Mayo score ≤ 2, with all Mayo subscores ≤ 1, and ≥ 1-point reduction from baseline in endoscopy subscore)

Secondary outcomes

- Steroid-free clinical remission at week 8 (combined Mayo subscores of ≤ 1 for Rectal Bleeding plus Stool Frequency)
- Steroid-free clinical response at week 8 (either decrease of ≥ 3 points on Mayo score, ≥ 50% reduction from baseline in combined Rectal Bleeding plus Stool Frequency Mayo subscores, or both)
- Steroid-free endoscopic response at week 8 (Mayo Endoscopy subscore ≤ 1, with reduction of ≥ 1 point from baseline)
- Steroid-free endoscopic remission at week 8 (Mayo Endoscopy subscore 0)
- IBDQ scores
- Adverse events

Notes

Data extraction: data on quality-of-life scores were reported as medians and ranges, so these were converted to means and SDs by methods given in Hozo 2005.

Data interpretation: study authors used an mITT analysis, in which only the participants who received ≥ 1 study dose were considered. For each group, the postrandomization n values were reported on an mITT basis only, so those are the numbers we extracted. The study authors also report in the 'Statistical analysis' section of their published paper that missing values were imputed using the worst value in the cohort.

Funding: Broad Medical Research Program, Gastroenterological Society of Australia, Mount Sinai (New York) SUCCESS fund, University of New South Wales.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised centrally by the Centre for Digestive Diseases after screening in a 1:1 ratio to either faecal microbiota transplantation or placebo, using a pre-established computer-generated randomisation list with permutated blocks of four and stratified for study site and concomitant corticosteroid use." (page 1220) Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote: "Patients and investigators were unaware of treatment allocation." (page 1220) Comment: most likely done.

Paramsothy 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients and investigators were unaware of treatment allocation." (page 1220) Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Study investigators who played a part in patients' assessment did not see the investigational product at any time." (page 1220) Comment: most likely done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the overall attrition rate was > 20%; however, the dropout rates and reasons were similar between both groups.
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported in the paper. The trial was registered on ClinicalTrials.gov (NCT01896635).
Other bias	Low risk	Comment: no other risk of bias noted.

Rossen 2015

Study characteristics	
Methods	Single-center, double-blind RCT conducted in the Netherlands
Participants	**Inclusion criteria** • Adults with established UC according to Lennard-Jones criteria, participant-reported SCCAI 4–11, Endoscopic Mayo subscore ≥ 1 at baseline sigmoidoscopy • Stable medication dosing continued during study period (e.g. thiopurines, mesalamine, or corticosteroids ≤ 10 mg/day for 8 weeks before inclusion) **Exclusion criteria** • Infectious cause of UC disease flare, history of colectomy, current stoma, life expectancy < 12 months, pregnancy, hospital admission • Use of anti-TNF or methotrexate within 8 weeks before inclusion or cyclosporine within 4 weeks before inclusion; use of antibiotics or probiotics within 6 weeks before inclusion
Interventions	**Experimental arm** n = 23 • Multiple donor feces • 120 g stool in 500 mL suspension; administered via nasoduodenal tube once in first week and once 3 weeks later **Control arm** n = 25 • 120 g autologous stool in 500 mL suspension; administered via nasoduodenal tube once in first week and once 3 weeks later
Outcomes	**Primary outcome** • Composite of clinical remission (SCCAI score ≤ 2) in combination with ≥ 1-point improvement on combined Mayo Endoscopic score of sigmoid and rectum vs baseline sigmoidoscopy at weeks 6 and 12

Rossen 2015 *(Continued)*

Secondary outcomes

- Clinical response (reduction ≥ 1.5 points on SCCAI) at weeks 6 and 12
- Clinical remission (SCCAI ≤ 2) at weeks 6 and 12
- Endoscopic response at weeks 6 and 12
- Change in median IBDQ score from baseline to week 6
- Adverse events up to week 12

Notes	Study was stopped early due to futility. Multiple donors were recruited for the study, but each participant received feces from 1 donor only. Data extraction: data on quality-of-life scores were depicted in box plots and, therefore, were not included in our meta-analysis. Data interpretation: study authors used an mITT analysis, in which only the participants who received ≥ 1 study dose were considered. For each group, the postrandomization n values were reported on an mITT basis only, so those are the numbers we extracted. Funding: MLDS grant 2011 (WO 11-17) to Noortje G Rossen and NWO-Spinoza grant 2008 to Willem M de Vos.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from study protocol: "Alea software will be used to perform randomisation." Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote from study protocol: "Randomisation and preparation of the feces will be performed by one of the research nurses, she is the only person who will know which treatment the patient will be given and will have no role in further part of the study." Comment: most likely done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding of participants and trial members was guaranteed by collecting both donor and recipient feces on both treatment days." (page 111) Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Endoscopy videos and pictures recorded at baseline and 6 and 12 weeks after the first FMT were scored by the Critical Event Committee, who were not aware of the allocated treatment, in a random order." (page 111) Comment: most likely done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 17/23 participants in the intervention group and 20/25 in the control group completed the follow-up. Attrition was similar in both groups. Less likely that the findings were at high risk of bias due to attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: protocol was available for review, and all intended outcomes were reported in the paper. Trial was registered on ClinicalTrials.gov (NCT01650038).
Other bias	Low risk	Comment: trial was stopped early due to futility; however, the data were completely described for included participants.

Sarbagili Shabat 2022

Study characteristics	
Methods	Multicenter, single-blind RCT conducted in Israel and Italy
Participants	**Inclusion criteria** • Ages 18–70 years (inclusive) • Established diagnosis of UC, confined to the large intestine with rectosigmoid involvement for ≥ 3 months • Mild-to-moderate active disease, SCCAI score ≥ 5 and < 10 with Endoscopic subscore ≥ 2 • Refractory to mesalamine for 6 weeks, steroids > 14 days, or immunomodulator therapy for 12 weeks, biologics for ≥ 12 weeks • No use or stable use of medical cannabis for 2 weeks • Informed consent **Exclusion criteria** • Acute severe UC in past 3 months • Start of new biologic therapy in previous 12 weeks, FMT in last 6 months • Evidence of *Clostridioides difficile* infection, any confirmed current infection such as cytomegalovirus, positive stool culture, or parasite • Current extra-intestinal manifestation of UC such as active arthritis or primary sclerosing cholangitis • Immune deficiency (other than drug-induced) • Current use of calcineurin inhibitor • Pregnancy • Suspected toxic megacolon, guarding on palpation, or signs of peritoneal inflammation; presence of a pouch or pouchitis • Other IBD-unrelated disease such as autoimmune disorders, renal failure, fever (< 38 °C) or current infection (UTI, strep throat, pneumonia, etc.) • Prior or current neoplasia, active malignant disease or prior malignancy in past 5 years (excluding skin basal cell carcinoma) • Inability or reluctance to use enema • Anticipation of antibiotic use within the study period (such as for elective surgery or dental treatment) • Participation in another clinical interventional trial
Interventions	**Experimental arm** • FMT by colonoscopy on day 1 + 60 mL enemas on days 2 and 14 from the same donor, with dietary pre-conditioning of donor for 14 days and dietary treatment of patient for 12 weeks **Control arm 1** • FMT by colonoscopy on day 1 + 60 mL enemas on days 2 and 14 from the same donor, without dietary conditioning **Control arm 2** • Dietary treatment of participant for 12 weeks without FMT
Outcomes	**Primary outcome** • Clinical remission at week 8, determined by SCCAI score < 3 **Secondary outcomes** • Improvement in SCCAI score for each group at weeks 8 and 12 • Mayo Endoscopic score < 2 (for participants undergoing sigmoidoscopy) at week 8

Sarbagili Shabat 2022 *(Continued)*

- Fecal calprotectin < 250 µg/g at week 8
- Need for additional therapy or flare, based on physician's discretion, at week 12
- Change in microbiome from baseline at day 14 for donor and week 8 for recipient, based on analysis of fecal samples
- Endoscopic SCCAI score for each group at week 8

Notes	Data extraction: we combined the 2 FMT groups (experimental arm and control arm 1) and compared them with the control group (control arm 2). This study reported adverse events as individual events rather than the number of participants experiencing each event, so these data were not extracted. Furthermore, the study stated that CRP levels were obtained at study visits and that change in calprotectin at week 8 was a secondary endpoint, but these data were not found in the paper. Last, the study assessed SCCAI scores at week 12, but these data were not considered as it did not appear that the study groups were re-randomized after the trial opened for analysis at week 8. Funding: ECCO Pioneer Prize, Litwin IBD Pioneer grant, and the Azrieli, Solomon and Beker foundations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was started 1:1:1 for the first 60 patients until the first 20 patients in Group 3 were enrolled, and then was to continue as a two-arm study with Group 1 and Group 2 alone randomised 1:1 to complete at least 76 patients in the FT arms [effectively 2:2:1 by the end of the study]; the dietary arm was to have fewer patients [as this arm was designed to evaluate the independent role of diet on recipients' clinical state and their microbiome] in blocks of 6, provided by opaque randomisation envelopes handed to the patient during enrolment after consent." (page 372) Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was started … provided by opaque randomisation envelopes handed to the patient during enrolment after consent. In order to ensure physician blinding, a coordinator in each institution set up the study visits, met with the dietitians and patients, and ensured that patients received the appropriate donor sample and diet according their allocated group without the physicians' knowledge." (page 372) Comment: most likely done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Randomisation was started … provided by opaque randomisation envelopes handed to the patient during enrolment after consent. In order to ensure physician blinding, a coordinator in each institution set up the study visits, met with the dietitians and patients, and ensured that patients received the appropriate donor sample and diet according their allocated group without the physicians' knowledge." (page 372) Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomisation was started … provided by opaque randomisation envelopes handed to the patient during enrolment after consent. In order to ensure physician blinding, a coordinator in each institution set up the study visits, met with the dietitians and patients, and ensured that patients received the appropriate donor sample and diet according their allocated group without the physicians' knowledge." (page 372) Comment: most likely done.

Sarbagili Shabat 2022 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Patients who did not achieve remission or required additional therapy were considered failures in the intention to treat analysis." (page 372) Comment: most likely done.
Selective reporting (reporting bias)	Low risk	All intended outcomes were reported. Comment: most likely done.
Other bias	Low risk	No other risks of bias were noted. Comment: most likely done.

Sokol 2020

Study characteristics	
Methods	Multicenter, single-blind RCT conducted in France
Participants	**Inclusion criteria** • Adults ages 18–70 years with health insurance, with colonic or ileo-colonic involvement • People with active disease at screening (Harvey Bradshaw Index > 4) received oral prednisolone (minimum dose 40 mg/day, maximum dose 1 mg/kg/day); those who achieved clinical remission (Harvey Bradshaw Index < 5) within 3 weeks were randomized to receive either FMT or sham FMT by colonoscopy **Exclusion criteria** • Active fistulizing disease, perianal or abdominal abscesses, complications requiring surgery, pregnancy; use of anti-TNF agents (ongoing or stopped within month preceding randomization), immunosuppressants (started or stopped within 3 months preceding randomization), non-steroidal anti-inflammatory drugs (within 4 weeks preceding randomization), antibiotics or antifungals (within 4 weeks preceding colonoscopy), probiotics (within 4 weeks preceding colonoscopy), *Clostridioides difficile* infection within 10 days preceding randomization; any contraindication to colonoscopy or anesthesia
Interventions	**Experimental arm** n = 11 • Single donor feces (5 donors involved, but only 1 donor was used per participant) • 50–100 g stool in 300 mL infusion, administered via colonoscopy after achieving clinical remission with oral corticosteroids (FMT was performed within 5 weeks of starting the corticosteroids) **Control arm** n = 10 • Physiologic serum in sham infusion, administered via colonoscopy
Outcomes	• Maintenance of remission at week 24 • CRP • Fecal calprotectin • Adverse events
Notes	Data interpretation: the study authors reported that they used an ITT approach for their analysis, although upon further review of the published paper, it appeared that they used an mITT analysis in which only the participants who received ≥ 1 study dose were considered. For our review, we created

Sokol 2020 *(Continued)*

an ITT analysis for maintenance of remission at week 24 and considered the total number of participants randomized to each group.

The authors also reported that 13 "serious adverse events" occurred overall, but the breakdown provided did not add up to 13 events, and we were not sure if these were numbers of events or numbers of participants. Therefore, we did not analyze the data on serious adverse events for this study. The authors also evaluated CRP and fecal calprotectin levels, but they were reported in forms that could not be combined with those of other studies, so the results were narrated in the review text instead.

Funding: grant from Programme Hospitalier de Recherche Clinique - PHRC PHRCR-13-029 (Ministère de la Santé), Assistance Publique – Hôpitaux de Paris (CRC16), Fondation de France (fond Inkermann), and Association Francois Aupetit.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized in a 1:1 ratio. Centralized block randomization was performed by an independent statistician from the clinical research platform (URC- Est) and the size of the blocks was not communicated to the investigator." (page 4) Comment: most likely done.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized in a 1:1 ratio. Centralized block randomization was performed by an independent statistician from the clinical research platform (URC- Est) and the size of the blocks was not communicated to the investigator." (page 4) Comment: likely done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomized in a 1:1 ratio. Centralized block randomization was performed by an independent statistician from the clinical research platform (URC- Est) and the size of the blocks was not communicated to the investigator." (page 4) Comment: study was described as single-blind; control group received sham FMT, and we assumed that participants were not aware of the treatment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: blinding of the outcome assessment was not specifically mentioned in the paper.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 3/11 (27.3%) participants in the experimental group and 1/10 (10%) in the control group were not included in the ITT analysis. (page 6)
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported in the paper; the trial was registered on ClinicalTrials.gov (NCT02097797)
Other bias	Low risk	Comment: no other risk of bias noted.

Sood 2019a

Study characteristics

Methods	Single-center, double-blind RCT conducted in India

Sood 2019a *(Continued)*

Participants	**Inclusion criteria** • People with active UC (Mayo score 4–10) being treated with standard-of-care therapy (5-ASAs, corticosteroids, thiopurines) who achieved clinical remission (Mayo score ≤ 2, with each subscore ≤ 1) after 7 sessions of colonoscopic FMT and were on stable dosing of medications (5-ASA and azathioprine for 6 months) **Exclusion criteria** • People with proctitis (E1 disease) and receiving topical 5-ASAs
Interventions	**Experimental arm** n = 31 • Single donor feces; 100 g stool in 200 mL infusion, administered via colonoscopy at weeks 0, 8, 16, 24, 32, 40, and 48 **Control arm** n = 30 • Placebo consisting of preservative-free normal saline with added food grade color; in 200 mL infusion, administered via colonoscopy at weeks 0, 8, 16, 24, 32, 40, and 48
Outcomes	**Primary outcome** • Maintenance of steroid-free clinical remission at week 48 (Mayo score ≤ 2, all subscores ≤ 1) **Secondary outcomes** • Endoscopic remission at week 48 (Endoscopic Mayo score 0) • ESR and CRP at week 48 • Adverse events
Notes	Data extraction: the breakdown of adverse events was extracted with the assumption that 1 event occurred per participant. We only extracted data on clinical and endoscopic remission rates, adverse events, withdrawals, ESR, and CRP during the maintenance period. Data interpretation: study authors used an ITT approach, in which it appeared that all randomized participants received ≥ 1 study dose and were considered in the final analysis, even though some participants were lost to follow-up over the course of the maintenance period. Funding: none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients who consented were then randomised in a 1:1 ratio according to a computer-generated randomisation list, to receive either FMT or placebo by a colonoscopic route every 8 weeks, for a further 48 weeks." (page 1312) Comment: most likely done.
Allocation concealment (selection bias)	Unclear risk	Comment: the paper did not specifically mention allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both patients and treating physicians were blinded to the nature of intervention done." (page 1312)

Sood 2019a *(Continued)*

All outcomes		Comment: most likely done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The worst site of inflammation was assessed using the Mayo endoscopic subscore and a blinded review, and consensus scoring of endoscopic images [photographs] was done by two gastroenterologists [AjS, RM]." (page 1312) Comment: most likely done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: experimental group had 1 participant lost to follow-up and 3 relapses; the control group had 8 relapses, 1 colectomy, 1 death.
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported in the paper; the trial was registered at Clinical Trials Registry – India (CTRI/2018/02/012148).
Other bias	Low risk	Comment: no other risk of bias noted.

5-ASA: 5-aminosalicylic acid; bpm: beats per minute; CD: Crohn disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FMT: fecal microbiota transplantation; HR: heart rate; IBDQ: Inflammatory Bowel Disease Questionnaire; IQR: interquartile range; ITT: intention to treat; mITT: modified intention to treat; n: number; PUCAI: Pediatric Ulcerative Colitis Activity Index; RCT: randomized controlled trial; SCCAI: Simple Clinical Colitis Activity Index; SD: standard deviation; TNF: tumor necrosis factor; UC: ulcerative colitis; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adler 2019	Wrong comparator: included optional extension arm after colonoscopic FMT, in which participants received cap-FMT maintenance therapy
Allegretti 2016	Wrong study population: cohort study that included people with recurrent *Clostridioides difficile* infection
Borody 2003	Wrong study design: case series
Chen 2018	Wrong comparator: no comparator arm
Chen 2020	Wrong comparator: people with moderately to severely active UC were randomly assigned to undergo FMT 3 times on days 1, 3, and 5 by nasojejunal tube or transendoscopic enteral tubing.
Chin 2017	Wrong study population: included participants with IBD with recurrent *Clostridioides difficile* infection, for which FMT was used as treatment
Ding 2019	Wrong comparator: all participants received FMT
El-Nachef 2020	Wrong comparator: participants were randomized into 4 arms, all of which included FMT, no placebo arm
Fang 2017	Wrong comparator: of 5 participants, 2 were diagnosed with very early-onset CD, 2 had UC, and 1 had pseudomembranous colitis; they received FMT via nasojejunal tube or colonoscopy.
Fischer 2016	Wrong study population: included people with IBD who had recurrent *Clostridioides difficile* infection
Gionchetti 2000	Wrong intervention: used probiotics instead of FMT

Study	Reason for exclusion
Hourigan 2015	Wrong comparator: comparison group included children without IBD
Ishikawa 2017a	Wrong comparator: both study groups received FMT (with + without antibiotics)
Ishikawa 2017b	Wrong length of time for follow-up: 4 weeks
Ishikawa 2019	Wrong length of time for follow-up: 4 weeks
Ishikawa 2022	Wrong intervention: intervention of interest was alginate drink after FMT following triple antibiotic therapy with amoxicillin, fosfomycin, and metronidazole
Karolewska-Bochenek 2018	Wrong comparator: open prospective trial where all participants received FMT
Kedia 2022	Wrong intervention: intervention of interest included FMT and specialized diet, so it was not possible to assess if the effect noted was because of the FMT or the specialized diet.
Kump 2018	Wrong study design: not randomized
Landy 2013	Wrong study population: included people with pouchitis only
Li 2020	Wrong comparator: no comparator arm
Ma 2020	Wrong study design: murine study design
Mahajan 2018	Wrong comparator: historical controls treated without FMT
Mandalia 2016	Wrong study population: included people with IBD with recurrent *Clostridioidesdifficile* infection
Michail 2018	Wrong study design: retracted study
Mintz 2016	Wrong study population: no control arm, and included people with recurrent *Clostridioidesdifficile* infection and UC
NCT04436874	Wrong comparator: all groups received FMT
NCT05202990	Wrong comparator: both groups received FMT
Okahara 2020	Wrong study design: not randomized
Osaki 2021	Wrong study design: no control group
Quraishi 2019	Wrong comparator: all participants received FMT
Quraishi 2022	Wrong comparator: both groups received FMT
Rainer 2018	Wrong comparator: study assessed clinical efficacy of frozen vs fresh donor stool for FMT in UC
Silber 2022	Wrong intervention: intervention of interest was VE202 (live biotherapeutic product)
Smith 2022	Wrong comparator: all arms received FMT; 4 experimental groups differed on addition of pretreatment antibiotics or FMT capsules
Sood 2019b	Wrong comparator: prospective study of people treated with FMT
Steube 2019	Wrong study design: not randomized, not controlled, and all participants received FMT

Study	Reason for exclusion
Tian 2019	Wrong study design: not a randomized trial
UMIN000025846	Wrong comparator: not controlled, single-arm study
UMIN000026485	Wrong study design: not randomized, not controlled, single-arm, open study
UMIN000041968	Wrong intervention: alginate-combined FMT vs placebo-combined FMT
Wei 2016	Wrong comparator: both groups received FMT (FMT only vs FMT + pectin)
Xiang 2020	Wrong comparator: no comparator arm
Yang 2020	Study unavailable: conference abstract and full study unavailable

CD: Crohn disease; FMT: fecal microbiota transplantation; IBD: inflammatory bowel disease; UC: ulcerative colitis.

Characteristics of studies awaiting classification *[ordered by study ID]*

Caenepeel 2022

Methods	Multicenter, double-blind RCT conducted in Belgium
Participants	**Inclusion criteria** • Age > 18 years • Current mild-to-moderate active UC (Endoscopic Mayo subscore 2–3 and Total Mayo score 4–10) • Concomitant UC therapy allowed if restricted to current treatment and at stable dose (not in induction phase) • No topical therapy or trial medication • Maximum dose of methylprednisolone 15 mg • Negative coproculture (Salmonella, Shigella, Yersinia, Campylobacter, Entamoeba histolytica, *Clostridioides difficile* toxins and enteropathogenic *Escherichia coli*) • Use of reliable contraceptives during study participation for women • Written informed consent to participate via signature **Exclusion criteria** • Diagnosis of CD or indeterminate colitis • Profoundly immunosuppressive conditions, e.g. HIV, infectious diseases, bone marrow malignancies, liver cirrhosis, use of systemic chemotherapy • Use of antibiotics in previous 4 weeks • Surgery: total colectomy, presence of stoma or ileo-anal pouch • Presence of intra-abdominal fistula • Colon carcinoma • Diverticulitis • Steroid dependency and requirement of > methylprednisone 15 mg 2 weeks before start • Detection of gastrointestinal pathogen on stool analysis • Pregnancy or planning pregnancy • Inability or unwillingness to give informed consent
Interventions	**Experimental arm** n = 30 • 4 doses of anaerobic-prepared superdonor FMT

Caenepeel 2022 *(Continued)*

	Control arm n = 36 • 4 doses of autologous FMT
Outcomes	**Primary outcome** • Steroid-free clinical remission (Total Mayo ≤ 2, with no subscore > 1) assessed via sigmoidoscopy at week 8 **Secondary outcomes** • Steroid-free PRO-2 remission (combined Mayo subscores ≤ 1 for Rectal Bleeding + Stool Frequency) at week 8 • Steroid-free PRO-2 response (decrease of ≥ 3 points or ≥ 50% reduction from baseline (or both) in combined Mayo subscores for Rectal Bleeding + Stool Frequency) at week 8 • Steroid-free endoscopic remission (Mayo Endoscopy subscore ≤ 1) at week 8 • Steroid-free endoscopic response (Mayo Endoscopy subscore ≤ 1, with ≥ 1-point reduction from baseline) at week 8
Notes	

Jitsumura 2022

Methods	RCT conducted in the UK
Participants	**Inclusion criteria** • Newly diagnosed histologically confirmed UC with inflammation limited to rectum or rectosigmoid (within 40 cm of anal verge as measured by flexible sigmoidoscope) • Age ≥ 18 years • Ability to give full informed written consent • Willingness to return for sequential FMT dosing and endoscopic assessment • Not in receipt of standard medical treatment for colitis such as steroids or 5-ASA, i.e. treatment naive **Exclusion criteria** • No definitive diagnosis of UC (e.g. diagnosis of CD or infectious colitis) • Colitis extending beyond 40 cm from the anal verge • Severe acute colitis (defined as > 6 bloodstained stools per 24 hours with 1 of the following: pulse rate > 90, temperature > 37.8 °C, hemoglobin < 105 g/L, ESR > 30 mm/hour) • Abdominal tenderness on examination • Already commenced standard medical therapy for UC • Contraindication to oral bowel preparation • Allergy to study antibiotics • Age < 18 years • Patients belonging to vulnerable groups • Pregnancy • Immunosuppression, e.g. transplant patient • Known communicable disease; ≥ 2 weeks of full recovery from infectious disease, e.g. chickenpox • Systemic autoimmunity or atopic diseases • Previous prosthetic implant (e.g. metallic heart valve, joint replacement, ventriculoperitoneal shunt, cardiac stent) • Chronic pain syndromes (e.g. fibromyalgia, chronic fatigue)

Jitsumura 2022 *(Continued)*

- Neurologic, neurodevelopmental, or neurodegenerative disorders
- Depression (requiring therapy)
- Obesity (BMI > 35)
- Malignancy
- Use of antibiotics for any indication within past 3 months
- Foreign travel to areas with enteric disease prevalence within 3 months
- High-risk sexual behavior (e.g. sexual contact with anyone with HIV/HTLV/AIDS or hepatitis B/C carrier, men who have sex with men)
- Known exposure to HIV or hepatitis B/C
- Current/previous use of injected drugs or intranasal cocaine
- Tattoos, piercings, cosmetic botulinum toxin (Botox) or permanent makeup within 120 days (in line with Welsh Blood Transfusion guidelines)
- Recent transfusion, transplant, or skin graft
- Risk factors for variant Creutzfeldt-Jakob disease, e.g. blood transfusion or transplant after 1 January 1980

Interventions	**Experimental arm** • FMT administered by retention enema either once only (group 1) or on 5 consecutive days (group 2) **Control arm** • Bowel purgatives and antibiotic preparation without active administration of FMT (group 3)
Outcomes	**Primary outcomes** • Remission of UC (mucosal healing; Mayo score ≤ 2 with Endoscopic Mayo score of 0) at week 12, as assessed by sigmoidoscopy, participants' response, Mayo scoring system • Successful engraftment of donor fecal microbiota at week 12 as analyzed by 16S sequencing **Secondary outcomes** • Rate of recruitment of participants • Disease-specific severity scoring after treatment • Histologic grading of colitis severity after treatment • Mucosal immunologic response to treatment • Rate of development of adverse effects of FMT
Notes	Protocol article available Study results available in an abstract but insufficient details to include study in analysis.

NCT02272868

Methods	RCT conducted in the US
Participants	**Inclusion criteria** • Children and adolescents ages 12–21 years • Diagnosis of CD by primary gastroenterologist, based on history, physical exam, laboratory/radiologic studies and gastrointestinal histology • Mild or moderate disease activity, based on PCDAI score (15–45) • Ability of parent/guardian and child participant to comprehend consent and assent in English; and to attend study visits at baseline, and weeks 2, 6, and 12 • No changes in IBD medications for ≥ 1 month prior to enrollment

NCT02272868 *(Continued)*

	• Availability of stool donor from family • Patient's agreement to nasogastric tube placement **Exclusion criteria** • PCDAI score < 15 or > 45 • Active or history of intra-abdominal abscess, perianal abscess, perianal fistula, intra-abdominal fistula, stricturing CD • Other serious medical conditions (e.g. neurologic, liver, kidney, autoimmune, systemic disease) • Allergy to any product used in study (e.g. rifaximin, omeprazole, MiraLAX) • Pregnancy, lactation, child-bearing potential (unless abstinent or willing to use adequate birth control from screening to end of study) • Intolerance to nasogastric tube placement (e.g. due to recent surgery or trauma to nares) • Presence of condition or abnormality that may compromise patient safety or data quality, as deemed by investigator
Interventions	**Experimental arm** • Pretransplant regimen (rifaxamin + omeprazole + MiraLAX) + donor FMT **Control arm** • Pretransplant regimen (rifaximin + omeprazole + MiraLAX) + normal saline
Outcomes	**Primary outcome** • PCDAI at week 12
Notes	Trial completed on 1 October 2016 with actual enrollment of 7 participants; no results available.

Zhang 2019

Methods	RCT
Participants	**Inclusion criteria** • Unavailable **Exclusion criteria** • Unavailable
Interventions	**Experimental arm** • FMT **Control arm** • Standard medical treatment: sulfasalazine tablets
Outcomes	**Primary outcome** • Pre- and post-treatment inflammatory factors (CRP, interleukin-6, tumor necrosis factor-α) **Secondary outcomes** • Sutherland Index score • Intestinal flora score

Zhang 2019 *(Continued)*

	• Endoscopic score
Notes	Blinding information of the study not available. Abstract available in English. The study itself could not be translated.

5-ASA: 5-aminosalicylic acid; BMI: body mass index; CD: Crohn disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FMT: fecal microbiota transplantation; HTLV: human T-lymphotropic virus type; IBD: inflammatory bowel disease; n: number; PCDAI: Pediatric Crohn's Disease Activity Index; RCT: randomized controlled trial; UC: ulcerative colitis.

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2021/03/032131

Study name	Stool transplant for treatment of colitis and Crohn's disease
Methods	RCT conducted in India
Participants	**Inclusion criteria** • People with IBD ages ≥ 18 years at the time of enrollment with written informed consent to participate **Exclusion criteria** • Age < 18 years • Pregnancy • HIV-positive • Disseminated or advanced malignancy • Concomitant severe underlying systemic illness that, in the opinion of the investigator, would interfere with completion of follow-up • Active drug use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements • Any other condition which, in the opinion of the investigator, would impede compliance or hinder completion of study • Inability to provide informed consent
Interventions	**Experimental arm** • FMT via colonoscopy **Control arm** • Sham colonoscopy
Outcomes	**Primary outcome** • Efficacy of FMT in UC and CD at weeks 4, 12, 24, and 52 **Secondary outcomes** • Efficacy and safety of FMT in pouchitis and extra-intestinal manifestations of IBD at weeks 4, 12, 24, 52 • Microbiota profile of the donors and FMT recipients pre- and post-FMT, compared with donor microbiota profile, at weeks 4, 12, 24, and 52 • Safety of FMT in UC and CD at weeks 4, 12, 24, and 52
Starting date	1 April 2021

CTRI/2021/03/032131 *(Continued)*

Contact information	Ajit Sood Department of Gastroenterology, Third Floor Dayanand Medical College and Hospital, Ludhiana, Punjab, India; email: ajitsood10@gmail.com
Notes	

EUCTR 2019-003816-29

Study name	Fecal microbiota transplantation in Crohn's disease as relay after anti-TNF withdrawal
Methods	RCT conducted in France
Participants	**Inclusion criteria** • Age 18 years < 75 years • CD (according to the Lennard-Jones criteria) for ≥ 6 months • In steroid-free clinical remission for ≥ 6 months under anti-TNF agent (no clinical evidence of flare or change in CD-specific treatment and CDAI < 150 the week before inclusion [see Addendum 2 in publication]) with willingness to withdraw anti-TNF treatment • For females of child-bearing age: active birth control during at least the period of treatment (week 52) • With health insurance (AME except) • Informed written consent **Exclusion criteria** • CD complication requiring surgical treatment • Contraindication to colonoscopy or anesthesia • Pregnancy or lactation during the study (see Addendum 4 of paper) • Diagnosis of CD restricted to upper gastrointestinal tract (esophagus, stomach, duodenum, jejunum) • History of bowel resection • Current stoma (ileostomy or colostomy) or stoma in last 6 months or any other intra-abdominal surgery within 3 months prior to inclusion • Participation in any other interventional study • People under legal protection
Interventions	**Experimental arm** • FMT in rectal solution or capsule **Control arm** • Sham FMT
Outcomes	**Primary outcome** • Clinical remission (defined by CDAI < 150) at week 52 (V8) without any flare between week 0 (colonoscopy [V2]) and week 52 (V8) **Secondary outcomes** • Relapse-free survival rate from week 0 (V2) to week 52 (V8) • Proportion of endoscopic remission (SES-CD = 2) at week 52 (V8) and change (in %) in endoscopic score (SES-CD) between week 0 (V2) and 52 (V8)

EUCTR 2019-003816-29 *(Continued)*

	• Clinical remission (defined by CDAI < 150) at week 52; endoscopic remission (defined by SES-CD = 2) • Measures of inflammation: blood cell count, CRP level, fecal calprotectin at week 6 (V3), 12 (V4), 24 (V5), 36 (V6), 48 (V7), and 52 (V8) • Microbiota composition and diversity using 16s sequencing technology at week 6 (V3), 12 (V4), 24 (V5), 36 (V6), 48 (V7) and 52 (V8)
Starting date	16 December 2019
Contact information	DRCI Hôpital Saint Louis 1 avenue Claude Vellefaux, 75010 Paris, France Telephone: 0140 27 57 27; email: carla.vandenabele@aphp.fr
Notes	Phase 3 trial

NCT01961492

Study name	
Methods	RCT conducted in Finland
Participants	**Inclusion criteria** • Ages 1–75 years • Active UC (PUCAI 10–64) • Ability to receive FMT via colonoscopy **Exclusion criteria** • Severe UC (PUCAI > 65)
Interventions	**Experimental arm** • Single FMT via colonoscopy as adjunct therapy to standard medical treatment **Control arm** • Standard medical treatment as recommended by ECCO guidelines for UC
Outcomes	**Primary outcome** • UC activity as change from baseline in PUCAI at months 1, 3, 6, and 12 **Secondary outcomes** • Colonic inflammation as change from baseline in fecal calprotectin levels at months 1, 3, 6, and 12 • Colonic inflammation as Endoscopic Mayo score at months 3 and 12 • Adverse events within 1 year
Starting date	
Contact information	
Notes	

NCT02335281

Study name	Standardized Fecal Microbiota Transplantation for Inflammatory Bowel Disease (SFMT-IBD)
Methods	RCT conducted in China
Participants	**Inclusion criteria** • Severe IBD defined as HBI score ≥ 9 • Moderate IBD defined as 7 < HBI < 9 • Montreal classification: age > 14 years, Location L1–3, Behavior B1–3 • Ages 16–70 years **Exclusion criteria** • Diarrhea activity scores < 3 • Severely active disease with perianal diseases • Severely active disease with indication for surgery • Diagnosis of IBD for the first time or in first year • No history of 5-ASA, biologic (antibody), immunomodulatory, or corticosteroid therapy
Interventions	**Experimental arm** • Standardized FMT administered once to the midgut by nasojejunal tube **Control arm** • Traditional mesalazine treatment
Outcomes	**Primary outcome** • Clinical remission (defined as HBI score ≤ 4) at up to 1 year (endpoint of follow-up is the time of clinical recurrence) **Secondary outcomes** • Hospitalization days from administration to discharge when at clinical remission for up to 1 year
Starting date	January 2015
Contact information	Yanling Wei Department of Gastroenterology, Research Institute of Surgery, Da Ping Hospital, The Third Military Medical University, Third Military Medical University
Notes	Estimated enrollment: 40

NCT02998112

Study name	Fecal microbiota transplantation for ulcerative colitis through colonic transendoscopic enteral tubing
Methods	RCT conducted in China
Participants	**Inclusion criteria** • Active, moderate-to-severe UC (Mayo score > 6)

NCT02998112 *(Continued)*

	• History of safety using 5-ASA • Ability to undergo endoscopy examination • Ages 18–65 years **Exclusion criteria** • Use of immunosuppressive drugs and glucocorticoids within 4 weeks • Use of antibiotics within 7 days • High risk of toxic megacolon • Colon cancer or neoplasia • Other severe diseases (e.g. cardiovascular, respiratory, gastrointestinal, and kidney)
Interventions	**Experimental arm** • 5-ASA 4 g/day enema through TET for 1 week; 200 mL FMT suspension infusion through TET for 3 doses every other day for 1 week **Control arm** • 5-ASA 4 g/day enema through TET for 1 week; 200 mL saline infusion through TET for 3 doses every other day for 1 week
Outcomes	**Primary outcomes** • Clinical remission at week 12: Total Mayo score < 2 and no signal item > 1 • Clinical improvement at week 12: Total Mayo score decreased > 3 or > 30% **Secondary outcomes** • Change in intestinal microbiota composition after FMT at week 12: compared with participant's original microbiota and donor microbiota
Starting date	December 2016
Contact information	Faming Zhang Associate professor, Gastroenterology, The Second Hospital of Nanjing Medical University, China
Notes	Estimated enrollment: 188

NCT03078803

Study name	Fecal transplant for Crohn's disease
Methods	Multicenter RCT conducted in Canada
Participants	**Inclusion criteria** • Age ≥ 18 years • Mild-to-moderate ileal, ileo-colonic, or colonic CD • Active ileal or colonic (or both) disease on endoscopy with/without elevated inflammatory markers, i.e. CRP > 8 mg/L, fecal calprotectin > 250 µg/g • If applicable, medications on stable dose: 5-ASA for 4 weeks, prednisone ≤ 20 mg once daily for 4 weeks, budesonide ≤ 6 mg once daily for 4 weeks, azathioprine, 6-mercaptopurine and methotrexate for 12 weeks **Exclusion criteria**

NCT03078803 *(Continued)*

	• Antibiotic exposure within 30 days, probiotic exposure within 14 days, topical IBD therapy within 2 weeks, concurrent antibiotic therapy • SES-CD score < 5, severe CD HBI > 25, or need for hospitalization • Active perianal disease, abdominal abscess, extensive colonic resection, subtotal or total colectomy, ileostomy, colostomy, known fixed symptomatic stenosis or complex fistulae, upper CD • Any need for surgical intervention (e.g. bowel resection within 3 months of enrollment) • Presence of or treatment for *Clostridioides difficile* or other gastrointestinal pathogen including CMV within 28 days; chronic hepatitis B or C, or HIV infection • History or evidence of adenomatous colonic polyps, colonic dysplasia, adhesions preventing colonoscopy to cecum • Active substance abuse or psychiatric problems that may interfere with participation • Pregnancy
Interventions	**Experimental arm** • First FMT at week 0 by colonoscopy + weekly FMT by oral capsules until week 7 **Control arm** • First placebo (water) at week 0 by colonoscopy + weekly placebo by oral capsules until week 7
Outcomes	**Primary outcomes** • Clinical and endoscopic remission at week 8 (HBI < 5 and simple endoscopic score < 5) **Secondary outcomes** • Clinical response at week 8 (HBI reduction by 3 points) • Clinical remission at week 8 (HBI < 5) • Endoscopic response at week 8 (SES-CD score reduction by 50%) • Endoscopic remission at week 8 (SES-CD score < 5) • Quality of life 1 at week 8 (mean changes in Short IBDQ) • Quality of life 2 at week 8 (mean changes in EQ-5D) • Quality of life 3 at week 8 (mean changes in Work Productivity and Activity Impairment: Crohn's Disease Questionnaire)
Starting date	
Contact information	
Notes	

NCT03110289

Study name	Restoration of the microbiome through superdonor selection (RESTORE-UC)
Methods	Multicenter RCT conducted in Belgium and the Netherlands
Participants	**Inclusion criteria** • Age > 18 years • Current mild-to-moderate active UC (Endoscopic Mayo subscore 2–3, Total Mayo score 4–10) • Concomitant UC therapy restricted to current treatment and at stable dose (not in induction phase) • Use of methylprednisolone at maximum dose of 15 mg

NCT03110289 *(Continued)*

	• Negative stool culture (*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Entamoeba histolytica*, *Clostridioides difficile* toxins, and enteropathogenic *Escherichia coli*) **Exclusion criteria** • Significant immunosuppression (e.g. HIV and other infectious diseases, bone marrow malignancies, liver cirrhosis) • Use of topical therapy and trial medications, systemic chemotherapy, antibiotics in the prior 4 weeks • History of surgery (total colectomy, presence of stoma or ileo-anal pouch) • Presence of intra-abdominal fistula, colon carcinoma, diverticulitis • Steroid dependence requiring > 15 mg of methylprednisolone 2 weeks before participation • Diagnosis of CD or indeterminate colitis • Pregnancy
Interventions	**Experimental arm** • "Super-donor" FMT via sigmoidoscopy at baseline, then "rectal instillation" at weeks 1–3 **Control arm** • Autologous FMT via sigmoidoscopy at baseline, then "rectal instillation" at weeks 1–3
Outcomes	**Primary outcomes** • Steroid-free clinical remission at week 8 (total Mayo score ≤ 2, with all Mayo subscores ≤ 1) • Steroid-free endoscopic remission or response at week 8 (≥ 1-point reduction from baseline in endoscopy subscore) **Secondary outcomes** • Changes in calprotectin and CRP before and after FMT at week 8 • Steroid-free clinical remission at week 8 (combined Mayo subscores of ≤ 1 for Rectal Bleeding + Stool Frequency) • Steroid-free clinical response at week 8 (Mayo score decrease ≥ 3 points, ≥ 50% reduction from baseline in combined Rectal Bleeding + Stool Frequency Mayo subscores, or both) • Steroid-free endoscopic response at week 8 (Mayo Endoscopic subscore ≤ 1, with reduction ≥ 1 point from baseline) • Steroid-free endoscopic remission at week 8 (Mayo Endoscopic subscore 0 or 1)
Starting date	
Contact information	
Notes	

NCT03273465

Study name	Fecal microbiota transplantation in ulcerative colitis
Methods	RCT conducted in Israel
Participants	**Inclusion criteria** • Adequate birth control (hormonal or barrier method; abstinence) prior to study entry and for duration of participation: participants of childbearing potential must show negative urine pregnan-

NCT03273465 *(Continued)*

	cy test on study day 1 before FMT; men must also use adequate birth control prior to study and for 3 months after FMT • Ability to understand and willingness to sign written informed consent document, including willingness to accept risk of unrelated donor stool • Ability to swallow oral medications **Exclusion criteria** • Severe, uncontrolled UC • Active or uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy • Delayed gastric emptying syndrome • Known chronic aspiration • History of significant allergy to foods not excluded from the donor diet (excluded foods are tree nuts, peanuts, shellfish, eggs) • Pregnancy and lactation • Inability to swallow pills
Interventions	**Experimental arm** • FMT capsules **Control arm** • Placebo capsules
Outcomes	**Primary outcome** • UC remission (SCCAI < 3) at week 12 **Secondary outcomes** • Improvement in UC symptoms (based on SCCAI) at week 12 • Improvement in UC endoscopic score at week 12, and months 6 and 12 • Markers of inflammation (CRP, WBC, ANC, stool calprotectin) at week 12, and months 6 and month 12 • Change in gut microbiome (diversity and variability) at week 12, and months 6 and month 12 • Use of treatments for UC (e.g. glucocorticoids, immunosuppressive therapy (e.g. azathioprine), or TNF antagonists) at months 6 and 12 • Extra-intestinal disease manifestations at months 6 and 12
Starting date	27 March 2017
Contact information	Assaf-Harofeh Medical Center, Zerifin, Israel, 70300
Notes	Phase 2 trial

NCT03483246

Study name	Impact of fecal microbiota transplantation in ulcerative colitis (REBALANCE-UC)
Methods	RCT conducted in France
Participants	**Inclusion criteria** • Age ≥ 18 to < 75 years • UC (according to the Lennard Jones criteria) diagnosed for ≥ 3 months and:

NCT03483246 *(Continued)*

- Currently active (PMC > 1) and planned to be treated by systemic corticosteroids (minimum prednisone equivalent 40 mg daily) OR
- Currently treated by systemic corticosteroid (minimum prednisone equivalent 40 mg daily) within maximum 3 weeks OR
- Steroid-dependency (≥ 1 unsuccessful attempt to discontinue steroid within the last 6 months before inclusion)
- Health insurance (AME excepted)
- Informed written consent
- For females of childbearing age: active birth control during at least period of treatment until the end of active follow-up period (week 24)

Exclusion criteria

- UC complication requiring surgical treatment
- Treatment with high-dose corticosteroid > 3 weeks before inclusion (prednisone equivalent ≥ 40 mg daily) except in case of steroid-dependence
- Contraindication to colonoscopy or anesthesia
- Pregnancy or breastfeeding during study
- Treatment preceding the colonoscopy with:
  - infliximab or vedolizumab or ustekinumab (< 6 weeks before planned date of colonoscopy) or adalimumab (< 2 weeks before planned date of colonoscopy) or golimumab or tofacitinib (< 4 weeks before planned date of colonoscopy), or a combination of these
  - immunosuppressant (thiopurine, methotrexate, tacrolimus, or other classical immunosuppressant) started or stopped < 3 months before planned date of colonoscopy
  - antibiotic, antifungic, or probiotic treatment < 4 weeks before planned date of colonoscopy
- Participation in any other interventional study
- People under legal protection

Interventions

Experimental arm

- FMT 3 times after inclusion and randomization

Control arm

- Sham transplantation 3 times after inclusion and randomization

Outcomes

Primary outcome

- Steroid-free clinical and endoscopic remission (defined as Total Mayo score ≤ 2 and no subscore > 1; mucosal healing defined as endoscopic subscore 0 or 1 via sigmoidoscopy) at week 12 after FMT or sham

Secondary outcomes

- Steroid-free clinical remission (Partial Mayo Clinic score 0 or 1) at weeks 12 and 24 after FMT or sham
- Steroid-free endoscopic response (Mayo Endoscopy subscore ≤ 1, with reduction of ≥ 1 point from baseline) at week 12 after FMT or sham
- Steroid-free endoscopic remission (Endoscopic Mayo Clinic score of 0) at week 12 after FMT or sham
- Microbiota composition and diversity (assessed by 16s sequencing compared to baseline and donor microbiota) at weeks 12 and 24 after FMT or sham
- Proportion of adverse events (abdominal pain, nausea, vomiting, fever, modified intestinal transit, episode of infection) in each group through study completion, up to 25 months and 1 week
- Inflammatory biologic parameters (CRP, fecal calprotectin, platelet count) up to week 24
- Endoscopic lesions at colonoscopy and sigmoidoscopy by Endoscopic Mayo score at week 12 after FMT or sham

NCT03483246 *(Continued)*

	• Endoscopic lesions at colonoscopy (baseline) and sigmoidoscopy by UCEIS score at week 12 after FMT or sham
Starting date	17 September 2018
Contact information	Service de Gastroentérologie et Nutrition Hôpital Saint Antoine, Paris, 75012, France
Notes	

NCT03561532

Study name	Fecal transplantation in ulcerative colitis (FMT-CU)
Methods	RCT conducted in Finland
Participants	**Inclusion criteria** • Ages 18–75 years with diagnosis of UC based on clinical, endoscopic, and histologic findings • Remission based on Mayo score 0–1 and fecal calprotectin < 100 µg/g • Availability of consecutive fecal samples for 1 year after UC diagnosis • Availability of blood samples to study IBD-associated genetic background • Compliance to attend ileocolonoscopy and FMT within 3–6 months after UC diagnosis and at week 52 **Exclusion criteria** • Need for antibiotic therapy within 3 months • Use of corticosteroids, immunosuppressives, or biologics at baseline • Use of probiotics • Pregnancy
Interventions	**Experimental arm** • Fecal suspension of healthy donor feces; administered into cecum via colonoscopy **Control arm** • Fecal suspension of autologous feces; administered into cecum via colonoscopy
Outcomes	**Primary outcome** • Maintenance of remission of UC at 52 weeks (endoscopic remission and Mayo score < 2)
Starting date	
Contact information	
Notes	

NCT03582969

Study name	Capsulized fecal microbiota transplantation in pediatric ulcerative colitis patients (FMT UC)
Methods	RCT conducted in Israel

NCT03582969 *(Continued)*

Participants	**Inclusion criteria** • People ages 12–18 years with newly diagnosed (> 9 months) mild-to-moderate UC based on colonic biopsy and clinical disease activity (SCCAI 5–12) **Exclusion criteria** • Severe, uncontrolled UC • Use of immunosuppressive or anti-inflammatory medications (except mesalamine) at enrollment • Active or uncontrolled bacterial, viral, or fungal infection requiring systemic therapy • Delayed gastric emptying syndrome • Known chronic aspiration • History of significant allergy to foods not excluded from donor diet (excluded foods are tree nuts, peanuts, shellfish, eggs) • Pregnancy or nursing • Inability to swallow oral medications (pills)
Interventions	**Experimental arm** • Oral capsules of healthy donor feces **Control arm** • Oral placebo capsules
Outcomes	**Primary outcome** • UC remission at 12 weeks (SCCAI < 3) **Secondary outcomes** • Improvement in UC symptoms at 12 weeks (improvement in SCCAI) • Laboratory markers of inflammation (CRP, WBC, ANC, stool calprotectin) at 12 weeks, and 6 and 12 months • Improvement in UC endoscopic score based on Mayo score at 12 weeks, and 6 and 12 months • Change in diversity and variability of gut microbiome at 12 weeks, and 6 and 12 months • Use of UC treatments (glucocorticoids, immunosuppressives (e.g. azathioprine), or TNF antagonists) at 6 and 12 months • Extraintestinal disease manifestations at 6 and 12 months
Starting date	
Contact information	
Notes	

NCT03716388

Study name	Fecal microbiota therapy vs 5-aminosalicylates for induction of remission in newly diagnosed mild-moderately active UC
Methods	RCT conducted in India
Participants	**Inclusion criteria** • Active UC

NCT03716388 *(Continued)*

- UC diagnosis based on history of chronic (> 4 weeks), inflammatory (with blood and mucus) diarrhea
- Total Mayo score 4–10, Mayo Endoscopic subscore > 1
- Histopathology suggestive of UC

Exclusion criteria

- Severe UC (Total Mayo score 11–12, Endoscopic Mayo score 3)
- Uncertainty about diagnosis of UC: infective colitis/indeterminate colitis/Crohn's colitis
- Associated IBS
- History of surgery or colorectal surgery
- Exposure to antibiotics or probiotics in last 4 weeks
- Evidence of infections (e.g. *Clostridioides difficile*, CMV, HIV, parasitic infections or extra-intestinal infections requiring antibiotics)
- Significant cardiopulmonary comorbidities (high risk for repeated colonoscopy)
- Pregnancy
- Refusal to consent for repeated colonoscopies

Interventions	**Experimental arm** • FMT fresh sample, administered via colonoscopy at weeks 0, 2, 6, 10, and 14 **Control arm** • Mesalamine
Outcomes	**Primary outcome** • Clinical remission (Mayo score ≤ 2, each subscore ≤ 1) at week 14 **Secondary outcomes** • Clinical response (reduction of Mayo score ≥ 30% and ≥ 3 points compared to baseline) at weeks 0, 2, 6, 10, and 14 • Endoscopic remission (Endoscopic Mayo subscore 0) at week 14 • Histologic remission (Nancy grade 0 or 1) at week 14
Starting date	1 December 2018
Contact information	Contact: Ajit Sood, DM Dayanand Medical College and Hospital, Ludhiana, Punjab, India, 141001
Notes	Phase 3 trial

NCT03804931

Study name	Fecal microbiota transplantation for ulcerative colitis
Methods	RCT conducted in China
Participants	**Inclusion criteria** • Adults with active, moderate-to-severe UC (Mayo score > 6) • "Safety using history of 5-ASA" • Ability to undergo endoscopy examination

NCT03804931 *(Continued)*

	Exclusion criteria • Antibiotic use within 7 days • High risk of toxic megacolon • Colon cancer or neoplasia • Other severe diseases (cardiovascular, respiratory, gastrointestinal, kidney)
Interventions	**Experimental arm** • 200 mL prepared fecal suspension from healthy donors, injected into intestine; 2 treatments + mesalazine or prednisone (or both) **Control arm** • Saline infusion + mesalazine or prednisone (or both)
Outcomes	**Primary outcomes** • Clinical remission (Total Mayo score < 2 and no subscore > 1) at week 12 • Clinical improvement (Total Mayo score decreased > 3) at week 12 **Secondary outcomes** • Change in intestinal microbiota composition after FMT vs original microbiota and donor microbiota at week 12
Starting date	
Contact information	
Notes	

NCT03998488

Study name	
Methods	Single-center RCT conducted in the US
Participants	**Inclusion criteria** • People age ≥ 18 years with intact descending colon • Documented prior history of mild-to-moderate UC • Endoscopically confirmed active UC ≥ 15 cm at week 0 screening via colonoscopy (Total Mayo score 4–10 with Endoscopic subscore ≥ 1) • If on steroid or biologic therapy, stable dose for 4 weeks prior to screening, maintained throughout trial • Discontinuation of anti-rCDI antibiotics (e.g. vancomycin, fidaxomicin) 48 hours prior to FMT delivery **Exclusion criteria** • Biopsy-confirmed CD • Severe UC (Total Mayo score > 10) • Clinical complications requiring emergent management, such as stricture, bowel obstruction, perforation, abscess, or a combination of these • History of FMT • PSC

NCT03998488 *(Continued)*

	• Treatment for malignancy within past 5 years • Concurrent *Clostridioides difficile* or other infections • Active or latent tuberculosis • Clinically meaningful laboratory abnormalities, such as hemoglobin < 8 and alanine aminotransferase > 3 × upper limit of normal • History of anaphylactic reactions to food allergens or allergy to psyllium husk • Any other condition that, as deemed by study investigator, would jeopardize the safety or rights of study participant, influence completion of study, or confound the study
Interventions	**Experimental arm** • Investigational FMT once at day 0 via colonoscopy + placebo FMP250 at week 8 via flexible sigmoidoscopy • Investigational FMT once at day 0 via colonoscopy + placebo FMP250 at week 8 via flexible sigmoidoscopy + psyllium (twice daily for 8 weeks) **Control arm** • Placebo FMT once at day 0 via colonoscopy + investigational FMP250 at week 8 via flexible sigmoidoscopy ± psyllium (twice daily for 8 weeks)
Outcomes	**Primary outcomes** • Clinical response at week 8 (post-FMT reduction of Mayo score by > 3 (+30% reduction) with accompanying decrease in Rectal Bleeding subscore ≥ 1) **Secondary outcomes** • Clinical remission at week 8 (post-FMT Mayo score ≤ 2 without any subscore > 1) • Endoscopic response or remission at week 8 (post-FMT Mayo Endoscopic subscore 0–1 with ≥ 1 reduction from baseline or Mayo Endoscopic subscore 0) • Number and type of treatment-related adverse events between week 0 colonoscopy and week 12 post-FMT • Change in number of disease-related complications such as hospitalizations, surgeries; and endoscopies; medical complications; and mortality between week 0 colonoscopy and week 12 post-FMT
Starting date	
Contact information	
Notes	

NCT04034758

Study name	Safety and efficacy of heterologous FMT by SQIMC-md capsule in mild–moderate ulcerative colitis patients (SQIMC-md)
Methods	RCT conducted in China
Participants	**Inclusion criteria** • Age ≥ to < 70 years • UC diagnosis based on clinical symptoms and laboratory and colonoscopic findings, including histopathologic results of intestinal mucosa • UC Total Mayo score 4–10 (mild-to-moderate activity) and Mayo Endoscopic score ≥ 2 as assessed within 4 weeks prior to enrollment and clinical symptoms that are at least stable

NCT04034758 *(Continued)*

	• Failure to acquire clinical remission after full dose and adequate course (4 weeks) of 5-ASA or precursor treatment • Written informed consent (or assent when appropriate, according to institutional guidelines) **Exclusion criteria** • HIV/AIDS or other severe immunodeficiency • Severe prior allergic reaction to food or supplementary material of placebo • Pregnancy or lactation • CMV or EBV colitis suspected by endoscopic findings and confirmed by immunohistochemistry and biopsy PCR • Decompensated life-threatening disease including but not restricted to liver cirrhosis (bleeding varices, ascites, encephalopathy, or icterus), myocardial infarction, and malignancy
Interventions	**Experimental arm** • Oral administration of 30 SQIMC-md capsules containing 2×10^{13} copies of prepared fecal microbiota lyophilized powder from multiple healthy donors' fresh feces + full dose of oral 5-ASA **Control arm** • Oral administration of 30 placebo capsules containing edible pigmented starch + full dose of oral 5-ASA
Outcomes	**Primary outcome** • Clinical response rate after SQIMC-md treatment (Mayo score decrease ≥ 3 points and ≥ 30% from baseline, with decrease of ≥ 1 point in subscore for Rectal Bleeding or absolute subscore ≤ 1 for Rectal Bleeding) at week 8 **Secondary outcomes** • Incidence of treatment-emergent adverse events at week 12 • Clinical response rate at weeks 4 and 12 • Clinical remission rate (Mayo score ≤ 2 points and no single score > 1 point) at week 12 • Mean (or median) decrease of fecal calprotectin at week 12 • Mean (or median) change from baseline in IBDQ Total score and subscore at week 12
Starting date	30 August 2019
Contact information	Department of Gastroenterology, Tongji Hospital, China
Notes	

NCT04202211

Study name	FMT for remission of active ulcerative colitis in adults
Methods	RCT conducted in Canada
Participants	**Inclusion criteria** • Active UC (Mayo score > 3 and Mayo Endoscopic subscore > 1, within 30 days of enrollment or at baseline) **Exclusion criteria** • Severe UC requiring hospitalization at time of enrollment

NCT04202211 *(Continued)*

	• Need for oral/intravenous systemic antibiotic therapy at time of enrollment • Increase in medical therapy for UC within 3 months of enrollment (continued treatment with stable dose of 5-ASA, azathioprine, 6-mecaptopurine, cyclosporine, prednisone, anti-TNF agents, or a combination of these for ≥ 3 months allowed) • Use of another investigational product, probiotic (except yogurt) • Abdominal surgery within past 60 days • Neutropenia (absolute neutrophils < 0.5×10^9/L); evidence of toxic megacolon or gastrointestinal perforation on imaging; peripheral WBC > 35.0×10^9/L, temperature > 38.0 °C; active infectious diarrhea at time of enrollment • Pregnancy or lactation • History of anaphylaxis to any food • Severe underlying disease with life expectancy < 30 days • Any condition that would pose harm to participant or research staff
Interventions	**Experimental arm** • Lyophilized FMT via 10 oral capsules twice-weekly for 8 weeks + placebo enema twice-weekly for 8 weeks • Lyophilized FMT via 10 oral capsules twice-weekly for 8 weeks + lyophilized FMT enema twice-weekly for 8 weeks **Control arm** • Placebo via 10 oral capsules twice-weekly for 8 weeks + placebo enema twice-weekly for 8 weeks

Outcomes	**Primary outcome**
	• Remission of UC following lyophilized FMT (Mayo score ≤ 2 and Mayo Endoscopic score ≤ 1) at week 9
	Secondary outcomes
	• Incidence/absence of adverse events with lyophilized FMT (safety and tolerability) up to 5 years post-FMT
	• UC disease progression (immediately after FMT to up to 5 years post-FMT) based on:
	  ◦ clinical flare requiring hospitalization up to 3 months post-FMT
	  ◦ increase in dosages of current UC medications up to 3 months post-FMT
	  ◦ time to colectomy for UC flare up to 12 months post-FMT
	  ◦ time to death directly attributable to UC up to 5 years post-FMT
	  ◦ improvement in clinical response (decrease in Partial Mayo score by ≥ 3 from pre- to post-lyophilized FMT)
	  ◦ improvement in participant-reported health-related quality of life using Valuation of Lost Productivity and RAND VR12 at pre- and 5, 12, 24 weeks post-lyophilized FMT and annually for 5 years
	  ◦ reduction in biologic inflammatory markers (CRP and fecal calprotectin) from pre- to post-lyophilized FMT

Starting date	
Contact information	
Notes	

NCT04328922

Study name	Fecal microbial transplantation and vedolizumab treatment of Crohn's disease
Methods	RCT conducted in Israel
Participants	**Inclusion criteria** • Mild-to-moderately active disease determined by the HBI of 5 to ≤ 15 • Eligibility to commence treatment with vedolizumab (screened for tuberculosis and hepatitis B, without active infection or abscess) **Exclusion criteria** • CD in remission (HBI < 5) or with severe disease (HBI > 16) • Presence of stoma • Hospitalization • Any ongoing or planned antibiotic therapy • Active intestinal infection – positive stool culture or *Clostridioides difficile* infection • Severe disease (e.g. malignant disease; hepatic failure; renal failure; cardiovascular, metabolic, neurologic disease) • Pregnancy or lactation • Severe food allergies • Inability to sign informed consent or complete study protocol
Interventions	**Experimental arm** • Capsules of fecal matter solution (feces from healthy donor, glycerol, and saline solution) **Control arm** • Placebo capsules of glycerol and saline

Outcomes	**Primary outcomes**
	• Safety of FMT before vedolizumab treatment in participants with CD (measured by disease exacerbations, hospitalizations, and surgery rate in treatment vs placebo group) at weeks 14 and 46
	• Efficacy of FMT before vedolizumab treatment in participants with CD that results in higher remission rate at weeks 14 and 46
	Secondary outcomes
	• Efficacy of FMT before vedolizumab treatment in participants with CD that results in:
	  ◦ clinical response rate at weeks 14, 22, and 46
	  ◦ endoscopic response at week 46
	  ◦ endoscopic remission at week 46
	  ◦ histologic healing at week 46
	  ◦ biologic remission at weeks 14, 22, and 46
	• Safety of FMT before vedolizumab treatment in participants with CD that results in low adverse events rate at week 46

Starting date	3 July 2018
Contact information	Department of Gastroenterology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Notes	

NCT04373473

Study name	Evaluation of the safety and efficacy of lyophilized fecal microbiota transplantation administered orally for prevention of relapse or intestinal inflammation in adults with ulcerative colitis
Methods	RCT conducted in the US
Participants	**Inclusion criteria** • Age ≥ 18 years with history of active UC in the past 12 months based on standard clinical, endoscopic, or histologic criteria • Clinical remission of UC (Partial Mayo score ≤ 2 with each subscore ≤ 1), on stable maintenance therapy • Having an attending physician for non-FMT care **Exclusion criteria** • Inability to take multiple capsules orally • Pregnancy or lactation • Exposure to systemic non-topical antibiotics within 14 days of first treatment • HIV, hepatitis B, or hepatitis C infections • rCDI or FMT in past 6 months • Non-IBD active gastrointestinal conditions (e.g. IBS, microscopic colitis, celiac disease, short gut syndrome, colostomy, colectomy, fistulae, strictures, chronic parasitic infections, diverticulitis) or history of bile acid diarrhea • Immunocompromise (e.g. in setting of primary disorders or due to medication such as oral prednisone > 20 mg/day or prednisone-equivalent) • Active cancer or ongoing chemotherapy (except for superficial non-metastatic cancers and maintenance chemotherapy) (or both) • Use of an investigational drug within 90 days of screening visit • History of significant uncontrolled systemic disease that could interfere with study participation/objectives • Life expectancy < 1 year
Interventions	**Experimental arm** • Oral fecal capsules from 3 healthy donors for 12 weeks **Control arm** • Identical-looking oral capsules for 12 weeks
Outcomes	**Primary outcome** • Remission (Partial Mayo score ≤ 3) after 12 weeks of treatment at 9 months **Secondary outcomes** • Quality of life (health-related quality-of-life score) after 12 weeks of treatment at 9 months • Participant-reported Hospital Anxiety and Depression Scale score after 12 weeks of treatment at 9 months
Starting date	
Contact information	
Notes	

NCT04434872

Study name	Fecal microbiota transplantation as a treatment for ulcerative colitis
Methods	RCT conducted in Israel
Participants	**Inclusion criteria** • Ages 18–70 years • Diagnosis of UC for > 3 months • Active colitis disease with endoscopic score > 0 • Ability to sign an informed consent **Exclusion criteria** • Acute neutrophilia (< 500 neutrophils/μL) • Severe immunodeficiency • *Clostridioides difficile* infection • Exposure to antibiotics in previous 2 weeks • Hospitalization • Proctitis involving < 10 cm of rectum • Malignancy within past 5 years (excluding basal cell carcinoma) • Unstable dose of steroids or 5-ASA within past 2 weeks or immunomodulator and biologic therapy within past 12 weeks
Interventions	**Experimental arm** • Donor-based FMT once via colonoscopy (250 mL), then 3 more times via either nasojejunal tube or enema (100 mL each), depending on extent of disease **Control arm** • Autologous FMT once via colonoscopy (250 mL), then 3 more times via either nasojejunal tube or enema (100 mL each), depending on extent of disease
Outcomes	**Primary outcome** • Clinical improvement at week 8, defined by SCCAI and Mayo score **Secondary outcomes** • Histologic remission at week 8, based on sigmoidoscopy assessment • Long-term remission after 1 year, based on questionnaires
Starting date	
Contact information	
Notes	Study was terminated due to lack of budget

NCT04521205

Study name	A multicenter clinical trial: efficacy, safety of fecal microbiota transplantation for inflammatory bowel disease
Methods	RCT conducted in China
Participants	**Inclusion criteria**

NCT04521205 *(Continued)*

	• People with IBD for whom standard or conventional medical treatment was ineffective, with recurrent symptoms, with drug dependence or recurrence with reduced or discontinued use, or untreated patients who voluntarily received FMT **Exclusion criteria** • Contraindications for gastrointestinal endoscopy • Other serious diseases (e.g. respiratory failure, heart failure, severe immunodeficiency) • Indications for surgery
Interventions	**Experimental arm** • Standardized FMT via capsule, given 3 times a week **Control arm** • FMT via blank capsule
Outcomes	**Primary outcome** • Clinical remission (by modified Mayo score ≤ 2 and endoscopy) at up to 1 year (endpoint of follow-up at time of clinical recurrence)
Starting date	September 2020
Contact information	Contact: Yanyun Fan, Doctor18759212670trudy@163.com Zhongshan Hospital Xiamen University, Xiamen, China
Notes	Phase 1 trial

NCT04637438

Study name	Fecal microbiota transplantation in postoperative Crohn's disease
Methods	RCT conducted in Finland
Participants	**Inclusion criteria** • Age > 18 years • Ability to provide written consent • Stricturing or fistulizing (or both) CD needing ileocecal or ileal resection **Exclusion criteria** • Pregnancy • Active infection, abscess, or fistula at the time of first colonoscopy • Use of antibiotics or probiotics at the time of first colonoscopy • Life expectancy < 1 year • Inability to provide written consent
Interventions	**Experimental arm** • FMT via colonoscopy **Control arm** • Water infusion via colonoscopy

NCT04637438 *(Continued)*

Outcomes	**Primary outcome** • Change in endoscopic Rutgeerts score between first and second colonoscopy at 1 year (Rutgeerts endoscopic score ranges from i0 indicating remission to i4 indicating severe postoperative relapse) **Secondary outcomes** • Safety of FMT (FinFMT-Questionnaire) at 3 and 12 months, and 5 years • Clinical activity of CD (HBI) at 6 and 12 months, and 5 years • Histologic activity of CD (modified Global Histological Activity Score) at 1 and 5 years • Change of microbiota in stool samples and in intestinal biopsies at 6, 12, and 48 weeks, and 5 years • Participant-reported outcome at 12 and 48 weeks, and 5 years • Change in inflammatory marker CRP at 6, 12, 24, and 48 weeks, and 5 years • Need for hospitalization through study completion, at mean of 1 and 5 years • Need for treatment escalation through study completion, at average of 1 and 5 years • Fecal calprotectin at 6, 12, 24, and 48 weeks, and 5 years • Hemoglobin at 6, 12, 24, and 48 weeks, and 5 years
Starting date	November 2020
Contact information	Tampere University Hospital Contact: Elina Jokinen, PhD +3583311611; email: elina.jokinen@pshp.fi
Notes	

NCT04924270

Study name	Safety and efficacy of faecal microbiota transplantation in treatment-naïve patients with newly diagnosed chronic inflammatory diseases (FRONT)
Methods	RCT conducted in Denmark
Participants	**Inclusion criteria** • New diagnosis of rheumatoid arthritis, reactive arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, gouty arthritis, hidradenitis suppurativa, pulmonary sarcoidosis, CD, or UC • Treatment-naïve (no current or previous disease-modifying antirheumatic drugs or systemic immunosuppressive drugs including glucocorticoids) • Presence of treatment indication (no contraindications) and patient acceptance to start first-line treatment in accordance with Danish national guideline for specific diagnosis following baseline visit **Exclusion criteria** • Celiac disease, food allergy, or severe food intolerance • Malignancy • Hepatitis B and C, HIV, HTLV1/2, active tuberculosis, or other serious chronic infections • Pregnancy or lactation • Not wishing to participate or not suited for FMT intervention or project evaluation
Interventions	**Experimental arm** • 50 g feces diluted in sterile saline (0.9% sodium chloride) and glycerol, blended, centrifuged, and filtered to remove particulate material before transfer to double-layered FMT capsules

NCT04924270 *(Continued)*

	Control arm • Placebo capsules consisting of 0.9% sodium chloride and glycerol, added brown food coloring
Outcomes	**Primary outcome** • Change from baseline in the PCS of the SF-36 at week 8 (± 1 week) **Secondary outcomes** • Change from baseline in the MCS of the SF-36 at week 8 (± 1 week) • Change from baseline in Patient Global Assessment (VAS 0–100 mm) at week 8 (± 1 week) • Change from baseline in participant fatigue (VAS 0–100 mm) at week 8 (± 1 week) • Change from baseline in participant pain (VAS 0–100 mm) at week 8 (± 1 week) • Change from baseline in Physician's Global Assessment (VAS 0–100 mm) at week 8 (± 1 week) • Change from baseline in CRP at week 8 (± 1 week) • Change from baseline in the PCS of the SF-36 at week 52 (± 2 week) • Change from baseline in the MCS of the SF-36 at week 52 (± 2 week) • Change from baseline in Patient Global Assessment (VAS 0–100 mm) at week 52 (± 2 week) • Change from baseline in participant fatigue (VAS 0–100 mm) at week 52 (± 2 week) • Change from baseline in participant pain (VAS 0–100 mm) at week 52 (± 2 week) • Change from baseline in Physician's Global Assessment (VAS 0–100 mm) at week 52 (± 2 week) • Change from baseline in CRP at week 52 (± 2 week)
Starting date	First posted: 11 June 2021
Contact information	Torkell Ellingsen, MD PhD Tel: +45 6611 3333; email: torkell.ellingsen@rsyd.dk
Notes	

NCT04970446

Study name	The MIRO II study: microbial restoration in inflammatory bowel diseases (MIRO II)
Methods	Multicenter RCT conducted in Australia
Participants	**Inclusion criteria** • Active CD • Age 18–70 years **Exclusion criteria** • Active perianal or fistulizing disease, symptomatic stricture likely to require surgical treatment, PSC, enteropathy or colitis other than CD, active gastrointestinal infection • Presence of stoma or ileoanal pouch • Pregnancy • Immunodeficiency (beyond that caused by immunosuppressants used with IBD), e.g. HIV or common variable immune deficiency • Prednisolone dose > 20 mg or budesonide dose > 6 mg • Alcohol consumption of a dependent nature • Recent overseas travel

NCT04970446 *(Continued)*

	• Contact with COVID-19-positive or DHHS-defined close contact with COVID-19-positive individual in 8 weeks prior to study entry
Interventions	**Experimental arm** • FMT after 1 week of antibiotic therapy **Control arm** • Placebo liquid formulation after 1 week of antibiotic therapy
Outcomes	**Primary outcome** • Clinical response (CDAI decrease ≥ 100 or CDAI < 150) at week 8
Starting date	First posted: 21 July 2021
Contact information	Amy Wilson O'Brien Tel: +61430461146; email: amy.wilson-obrien@svha.org.au
Notes	

NCT04997733

Study name	Fecal microbiota transplantation in Crohn's disease as relay after anti-TNF withdrawal (MIRACLE)
Methods	RCT conducted in France
Participants	**Inclusion criteria** • Age ≥ 18 to < 75 years • CD diagnosis (according to Lennard-Jones criteria) for ≥ 6 months • Steroid-free clinical remission for ≥ 6 months with anti-TNF agent (no clinical evidence of flare, no change in CD-specific treatment (anti-TNF, immunosuppressive, etc.) within 6 months before inclusion) and CDAI < 150 the week before inclusion; willingness to withdraw anti-TNF treatment • Women of childbearing age with active birth control during at least the period of treatment (week 52) • With health insurance • Informed written consent **Exclusion criteria** • CD complication requiring surgical treatment • Contraindication to colonoscopy or anesthesia • Pregnancy or lactation (see Addendum 4 in publication) • Diagnosis of CD restricted to the upper gastrointestinal tract (esophagus, stomach, duodenum, jejunum) • Active perineal disease (evidence of perineal abscess or active draining fistula or presence of seton or perineal ulceration) • History of bowel resection • Current stoma (ileostomy or colostomy) or stoma in the last 6 months; any other intra-abdominal surgery within 3 months prior to inclusion • Participation in any other interventional study • People under legal protection

NCT04997733 *(Continued)*

Interventions	**Experimental arm** • Colonoscopy + FMT (frozen preparation of 50 g of stools in 300 mL of saline [0.9% sodium chloride]) in terminal ileum or colon • At weeks 12 and 24 after first colonoscopy: treatment by capsule (15 capsules contain 0.8 g of stools by visit) **Control arm** • Colonoscopy + sham transplantation (frozen preparation of 0.9% sodium chloride with 10% glycerol) in terminal ileum or colon • At weeks 12 and 24 after first colonoscopy: treatment by capsule (15 capsules contain placebo)
Outcomes	**Primary outcome** • Clinical remission (CDAI < 150) at week 52 (V8) without any flare between week 0 (colonoscopy [V2]) and week 52 (V8): flare defined by CDAI (see Addendum 2 in publication) > 250 or 150–250 points with 70-point increase from baseline over 2 consecutive weeks **Secondary outcomes** • Relapse-free survival at week 52 • Mucosal healing at week 52 • Clinical remission at week 52 • Endoscopic remission at week 52 • Changes in complete blood count at weeks 6, 12, 24, 36, 48, and 52 • Changes in CRP at weeks 6, 12, 24, 36, 48, and 52 • Changes in fecal calprotectin at weeks 6, 12, 24, 36, 48, and 52 • Changes in intestinal microbiota composition at weeks 6, 12, 24, 36, 48, and 52
Starting date	First posted: 10 August 2021
Contact information	
Notes	

NCT05030064

Study name	Clinical study on the fecal microbiota transplantation in the treatment of ulcerative colitis with depression
Methods	RCT conducted in China
Participants	**Inclusion criteria** • Course of disease > 6 months, clearly diagnosed as UC with depression (diagnostic criteria: (2020) "JSGE Evidence-based Clinical Practice Guidelines: Inflammatory Bowel Disease" and Chinese Mental Disorders Classification and Diagnostic Standards-3); improved Mayo score ≤ 10 points, PHQ-9 score ≥ 5 points • Ages 18–65 years • BMI 18–30 kg/m^2 • Basic reading comprehension skills • Agreement to participate in study and sign informed consent form **Exclusion criteria**

NCT05030064 *(Continued)*

	• Unspecified UC • Travel abroad in past month • History of alcoholism, drug abuse, or smelting • Use of antibiotics and probiotic preparations within 1 month • Bipolar disorder, persistent mood disorder, and mania • Pregnancy and lactation • Malignant tumors, gastrointestinal infection, IBS, bowel cancer and other gastrointestinal diseases • History of gastrointestinal surgery • Obesity, hypertension, diabetes, heart disease, stroke, and other serious chronic diseases (hereditary, metabolic, endocrine diseases) • Other serious diseases (e.g. of the heart, brain, lung, liver, kidney) • Infectious diseases: hepatitis B or C, HIV, syphilis (rapid recovery of positive plasma), EBV and CMV infection (immunoglobulin M positive) • Abnormal liver function: AST or ALT > 2 × upper limit of normal • Renal insufficiency: serum creatine > 1.5 × upper limit of normal or eGFR < 60 mL/minute • Dyslipidemia: total cholesterol > 4.0 mmol/L, triglycerides > 2.0 mmol/L, low-density lipoprotein cholesterol > 2.5 mmol/L, high-density lipoprotein cholesterol < 1.0 mmol/L • CRP > 8 mg/L • Anticoagulation therapy • Participation in other clinical trials at the time of enrollment • Refusal to join group or other factors affecting compliance and participation
Interventions	**Experimental arm** • 16 FMT capsules (each containing 200 mg of intestinal bacteria), once a week for 4 weeks **Control arm** • 16 placebo capsules, once a week for 4 weeks
Outcomes	**Primary outcome** • PHQ-9 score at week 12 **Secondary outcomes** • Self-Rating Depression Scale score at week 12 • Hamilton Anxiety Scale score at week 12 • Hamilton Depression Scale score at week 12 • Hospital Anxiety and Depression Scale score at week 12 • Gastrointestinal Symptom Rating Scale score at week 12 • Modified Mayo score for UC at week 12 • IBDQ score at week 12 • WBC, CRP, ESR, procalcitonin, interleukin-6, intestinal flora at week 12
Starting date	10 September 2021
Contact information	Yanling Wei, Deputy Chief Physician, Third Military Medical University, Chongqing, China Tel: 86-15310354666; email: lingzi016@126.com
Notes	

NCT05538026

Study name	Effectiveness of fecal microbiota transplantation as add-on therapy in mild-to-moderate ulcerative colitis
Methods	RCT conducted in Ukraine
Participants	**Inclusion criteria** • Ages 18–60 years • Endoscopically and morphologically confirmed UC with Partial Mayo score 4–6, Mayo Endoscopic subscore ≥ 1, fecal calprotectin > 150 µg/g • Treatment with mesalazine 3 g/day for last 4 weeks • Negative stool culture for pathogenic bacteria (*Shigella* spp, *Salmonella* spp, *Campylobacter* spp, *Yersinia* spp) and toxin-producing *Clostridioides difficile* **Exclusion criteria** • Pregnancy, planning pregnancy, or lactation • Postponed operations on abdominal cavity • Severe mental disorders, alcohol or drug abuse • Use of systemic corticosteroids, biologic agents, and probiotics within 8 weeks before study • Any condition or circumstance that would prevent/interfere with either completion of study or analysis of results, in the opinion of investigator
Interventions	**Experimental arm** • FMT via colonoscopy to proximal colon **Control arm** • Mesalazine 3 g (2 g orally + 1 g rectally) once daily
Outcomes	**Primary outcomes** • Change in Partial Mayo score > 2 at 8 weeks • Changes in fecal calprotectin at 8 weeks **Secondary outcomes** • Change in microbiome profile at 4 weeks
Starting date	1 September 2020
Contact information	Nazarii Kobyliak, Associate Professor, Endocrinology Department, Bogomolets National Medical University
Notes	

Pai 2019

Study name	PediCRaFT: Pediatric Crohn's Disease Fecal Transplant Trial (PediCRaFT)
Methods	RCT conducted in Canada
Participants	**Inclusion criteria** • Children and adolescents ages 3–17 years

Pai 2019 *(Continued)*

	• CD or IBD-Unclassified favoring CD (as deemed by the participant's primary pediatric gastroenterologist) • Active symptoms **Exclusion criteria** • Severe comorbid medical illness (at discretion of participant's primary pediatric gastroenterologist) • Concomitant *Clostridioides difficile* infection • Severe CD flare requiring hospitalization • Commenced new or temporary medical therapies (i.e. corticosteroids, antibiotics, prebiotics) within 4 weeks prior to trial; note: weaning doses of corticosteroid will be permitted (≤ 0.25 mg/kg/day) • Current enrollment in another clinical trial • Inability to give informed consent or assent
Interventions	**Experimental arm** • Baseline FMT colonoscopic infusion at week 0, followed by twice-weekly oral microbiota capsule therapy for 6 weeks (including week 0) **Control arm** • Baseline normal saline colonoscopic infusion at week 0, followed by twice-weekly dextrose-containing oral placebo capsule therapy for 6 weeks (including week 0)
Outcomes	**Primary outcomes** • Monthly recruitment rate at week 30: assessment of recruitment rate (based on participants meeting all eligibility criteria who were approached for trial entry) • Dropout rate after enrollment at week 30: rate of participants leaving the trial (participant- or protocol-directed exclusion) after enrollment • Rate of participant protocol adherence at week 30: rate of participants providing all required blood, stool, and urine samples per protocol • Rate of adverse events at week 30: rate of participants requiring hospitalization, or experiencing PCDAI increase ≥ 20 at 2 successive measures **Secondary outcomes** • Clinical: improvement in disease symptoms at baseline, and weeks 6 and 30: PCDAI decrease ≥ 15 from baseline: weeks 6 and 30 • Clinical: remission in disease symptoms at weeks 6 and 30: PCDAI ≤ 10: weeks 6 and 30 • Clinical: improvement in serum inflammatory markers at baseline, and weeks 6 and 30: decrease CRP from baseline: weeks 6 and 30 • Clinical: improvement in mucosal inflammatory markers at baseline, and weeks 6 and 30: decrease fecal calprotectin from baseline: weeks 6 and 30 • Clinical: change in urine metabolomics at baseline, and weeks 6 and 30: change in urine metabolite profile from baseline: weeks 6 and 30 • Clinical: change in fecal microbiome at baseline, and weeks 6 and 30: change in fecal 16s rRNA + metagenomics profile from baseline: weeks 6 and 30
Starting date	1 December 2018
Contact information	Nikhil Pai, BSc, MD Division of Pediatric Gastroenterology & Nutrition, McMaster Children's Hospital
Notes	

Stallmach 2022

Study name	Transfer of FRozen Encapsulated multi-donor Stool filtrate for active ulcerative Colitis (FRESCO): study protocol for a prospective, multicenter, double-blind, randomized, controlled trial
Methods	Multicenter RCT conducted in Germany

Participants	**Inclusion criteria**
	• Ages 18–75 years
	• Prior endoscopically confirmed active UC of ≥ 6 months and disease extent of ≥ 15 cm from anal verge
	• Active disease (Mayo score 4–10 and Mayo Endoscopic subscore > 1) at study entry
	• May be receiving 1 of the following drugs:
	  ○ oral 5-ASA compounds with stable prescribed dose for ≥ 4 weeks prior to randomization and the first 12 weeks after randomization
	  ○ azathioprine, 6-mercaptopurine, or methotrexate with stable prescribed dose for 8 weeks prior to randomization and the first 12 weeks after randomization
	  ○ oral corticosteroid therapy (prednisone at stable dose ≤ 20 mg/day or budesonide at stable dose of ≤ 9 mg/day) if prescribed dose has been stable for 2 weeks prior to randomization
	  ○ topical therapy (foams, enema) with mesalazine or budesonide if prescribed dose has been stable for 2 weeks prior to randomization
	• Complete vaccination against SARS-CoV-2 as recommended by the Standing Committee on Vaccination at the Robert Koch Institute
	• Ability to understand and willingness to sign informed consent document and comply with protocol
	
	Exclusion criteria
	• CD or indeterminate colitis or proctitis alone
	• Clinical emergencies requiring emergent management (e.g. acute abdomen: bowel obstruction, perforation or abscess (or both), previous bowel surgery)
	• Concurrent gastrointestinal infections or other causes of diarrhea
	• Congenital or acquired immunodeficiency, severe comorbidities (e.g. diabetes mellitus, cancer, systemic lupus, decompensated cirrhosis, recent malignancy in last 3 years)
	• Negative EBV/CMV serology
	• Pregnancy
	• Inability or unwillingness to undergo colonoscopy
	• Previous treatment with anti-TNF, integrin, or interleukin-12/interleukin-23 antibodies within last 8 weeks
	• Previous treatment with calcineurin or JAK inhibitors within last 4 weeks
	• Systemic antibiotic use within the last 8 weeks
	• Participation in clinical trial within last 3 months
	• History of FMT or FMFT
	• Probiotic use within 14 days of study start date
	• Not ensuring frozen storage (−15 ± 5 °C) of capsules
	• Medical conditions or circumstances that interfere with appreciation of the nature, significance, scope, and possible consequences of the clinical trial; signs of non-compliance

Interventions	**Experimental arm** n = 58 • Classical FMT 5 capsules orally twice daily, 5 days per week for weeks 1–12 Or n = 58

Stallmach 2022 *(Continued)*

	• Multidonor FMFT 5 capsules orally twice daily, 5 days per week for weeks 1–12 **Control arm** n = 58 • Placebo 5 capsules orally twice daily, 5 days per week for weeks 1–12
Outcomes	**Primary outcome** • Clinical remission (Mayo score ≤ 2, without any subscore > 1; participants unavailable at week 12 follow-up will be considered as non-responders) at week 12 after first FMT or FMFT **Secondary outcomes** • Steroid-free clinical remission at week 12 • Clinical response (decrease in Mayo score by 3 points with decrease in bleeding subscore by 1, or Total Mayo score 0–1) at week 12 • Quality of life (IBDQ) at weeks 0, 4, 8, 12, 24, 36, and 52 • Adverse events • Fecal calprotectin and histologic remission (based on Geboes Histologic Scores and Nancy Histological Index) at week 12 • Microbiome/virome profiling
Starting date	October 2021
Contact information	Professor Andreas Stallmach Tel: +49-3641-9 ext 324401; email: andreas.stallmach@med.uni-jena.de
Notes	

UMIN000033127

Study name	Multicenter randomized controlled trial to study the efficacy of multidonor fecal microbiota transplantation for Crohn's disease
Methods	Multicenter RCT conducted in Japan
Participants	**Inclusion criteria** • People age 12 ≤ to < 80 years • Active CD (CDAI score ≥ 150) **Exclusion criteria** • Past history of allergy to drugs used in study • Possibility of pregnancy • Complications such as fistulas and perforation, except anal fistulas
Interventions	**Experimental arm** • FMT **Control arm** • Normal saline administration

UMIN000033127 *(Continued)*	
Outcomes	**Primary outcome** • Improvement of CDAI score **Secondary outcomes** • IBDQ • Modified SES-CD • Hydrogen level in glucose hydrogen breath test • Urine lactulose–mannitol ratio • Change in fecal microbiome and metabolome
Starting date	
Contact information	
Notes	

5-ASA: 5-aminosalicylic acid; ALT: alanine transaminase; ANC: absolute neutrophil count; AST: aspartate transaminase; BMI: body mass index; CD: Crohn disease; CDAI: Crohn's Disease Activity Index; CMV: cytomegalovirus; CRP: C-reactive protein; EBV: Epstein-Barr virus; ECCO: European Crohn's and Colitis Organisation; eGFR: estimated glomerular filtration rate; EQ-5D: EuroQol Five-Dimensions Questionnaire; ESR: erythrocyte sedimentation rate; FMFT: fecal microbiota filtrate transfer; FMT: fecal microbiota transplantation; HBI: Harvey Bradshaw Index; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; MCS: Mental Component Score; n: number; PCDAI: Pediatric Crohn's Disease Activity Index; PCR: polymerase chain reaction; PCS: Physical Component Score; PHQ-9: Patient Health Questionnaire-9; PSC: primary sclerosing cholangitis; PUCAI: Paediatric Ulcerative Colitis Activity Index; rCDI: recurrent *Clostridioides difficile* infection; RCT: randomized controlled trial; rRNA: ribosomal ribonucleic acid; SCCAI: Simple Clinical Colitis Activity Index; SES-CD: Simple Endoscopic Score for Crohn Disease; SF-36: 36-Item Short Form Health Survey; TET: transendoscopic enteral tubing; TNF: tumor necrosis factor; UC: ulcerative colitis; V7: visit 7 (etc.); UCEIS: Ulcerative Colitis Endoscopic Index of Severity; VAS: visual analog scale; WBC: white blood cell count.

DATA AND ANALYSES

Comparison 1. Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC)

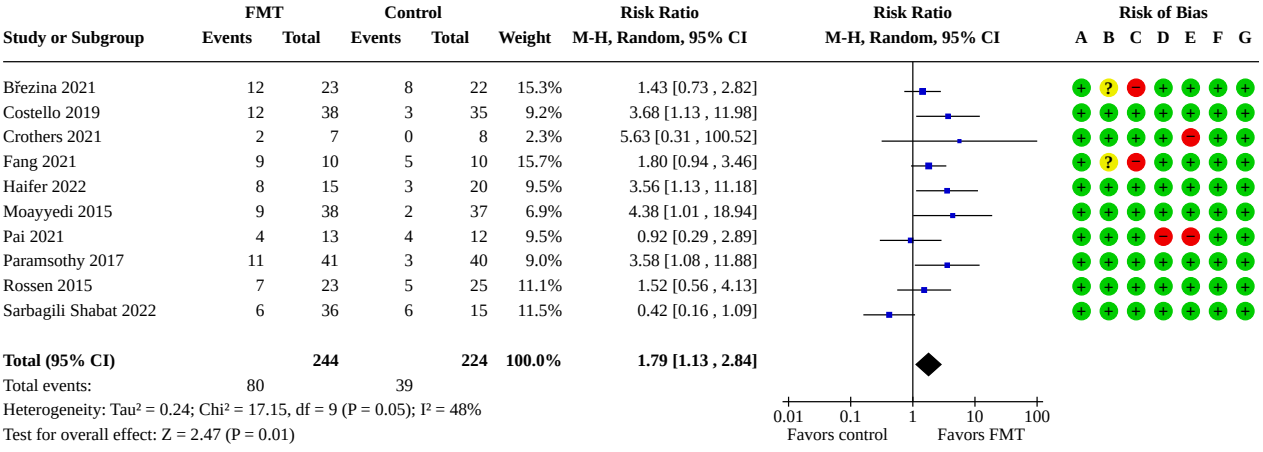
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Induction of clinical remission in UC at longest follow-up	10	468	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.13, 2.84]
1.2 Induction of clinical remission in UC at 8 weeks	8	408	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.93, 3.05]
1.3 Induction of clinical remission in UC at 12 weeks	3	108	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.89, 2.66]
1.4 Induction of clinical remission in UC at longest follow-up: subgroup analysis by route of administration	10	468	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.13, 2.84]
1.4.1 Upper gastrointestinal	2	83	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.97, 5.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.2 Lower gastrointestinal	7	370	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.93, 2.92]
1.4.3 Mixed (upper and lower) route	1	15	Risk Ratio (M-H, Random, 95% CI)	5.62 [0.31, 100.52]
1.5 Induction of clinical remission in UC at longest follow-up: subgroup analysis by type of donor	10	468	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.13, 2.84]
1.5.1 Single donor	6	191	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.76, 2.48]
1.5.2 Multiple donors	4	277	Risk Ratio (M-H, Random, 95% CI)	2.77 [1.54, 4.98]
1.6 Induction of clinical remission in UC at longest follow-up: subgroup analysis by age	10	468	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.13, 2.84]
1.6.1 Children	1	25	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.29, 2.89]
1.6.2 Adults	9	443	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.17, 3.17]
1.7 Induction of clinical remission in UC at longest follow-up: subgroup analysis by frequency of FMT	10	468	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.13, 2.84]
1.7.1 Single infusion	1	20	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.94, 3.46]
1.7.2 Multiple infusions	9	448	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.05, 3.18]
1.8 Induction of clinical remission in UC at longest follow-up: sensitivity analysis using fixed-effect model	10	468	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.37, 2.57]
1.9 Induction of clinical remission in UC at longest follow-up: sensitivity analysis for available cases	10	382	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.07, 2.94]
1.10 Induction of clinical remission in UC at longest follow-up: composite of clinical score and endoscopic score	8	392	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.51, 3.02]
1.11 Serious adverse events for induction of remission in UC	10	468	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.88, 3.55]
1.12 Serious adverse events for induction of remission in UC: subgroup analysis by route of administration	10	468	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.88, 3.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12.1 Upper gastrointestinal	2	83	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.32, 4.49]
1.12.2 Lower gastrointestinal	7	370	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.92, 5.23]
1.12.3 Mixed (upper and lower) route	1	15	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.09, 15.08]
1.13 Serious adverse events for induction of remission in UC: subgroup analysis by type of donor	10	468	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.88, 3.55]
1.13.1 Single donor	6	191	Risk Ratio (M-H, Random, 95% CI)	2.36 [0.83, 6.69]
1.13.2 Multiple donors	4	277	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.55, 3.58]
1.14 Serious adverse events for induction of remission in UC: subgroup analysis by age	10	468	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.88, 3.55]
1.14.1 Children	1	25	Risk Ratio (M-H, Random, 95% CI)	4.62 [0.63, 34.05]
1.14.2 Adults	9	443	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.73, 3.26]
1.15 Serious adverse events for induction of remission in UC: sensitivity analysis using fixed-effect model	10	468	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.95, 3.68]
1.16 Serious adverse events for induction of remission in UC: sensitivity analysis for available cases	10	382	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.88, 3.47]
1.17 Any adverse events for induction of remission in UC	9	417	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.16]
1.18 Induction of endoscopic remission in UC at longest follow-up	5	285	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.64, 3.29]
1.19 Quality of life (Inflammatory Bowel Disease Questionnaire [IBDQ]) scores at longest follow-up for induction of remission in UC	3	131	Mean Difference (IV, Random, 95% CI)	15.34 [-3.84, 34.52]
1.20 Quality of life (IBDQ) scores at longest follow-up for induction of remission in UC: sensitivity analysis without Haifer 2022	2	96	Mean Difference (IV, Random, 95% CI)	22.20 [0.63, 43.78]
1.21 Induction of clinical response in UC at longest follow-up	10	468	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.96, 1.84]
1.22 Induction of endoscopic response in UC at longest follow-up	3	164	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.79, 2.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.23 Withdrawals in studies on induction of remission in UC	10	468	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.62, 1.34]
1.24 Erythrocyte sedimentation rate (ESR) at longest follow-up for induction of remission in UC (mm/hour)	2	113	Mean Difference (IV, Random, 95% CI)	2.98 [-0.38, 6.34]
1.25 ESR at longest follow-up for induction of remission in UC: sensitivity analysis without Moayyedi 2015 (mm/hour)	1	81	Mean Difference (IV, Random, 95% CI)	3.00 [-0.56, 6.56]
1.26 C-reactive protein (CRP) at longest follow-up for induction of remission in UC (mg/L)	3	128	Mean Difference (IV, Random, 95% CI)	1.11 [-1.85, 4.08]
1.27 CRP at longest follow-up for induction of remission in UC: sensitivity analysis without Moayyedi 2015 (mg/L)	2	96	Mean Difference (IV, Random, 95% CI)	-0.44 [-6.52, 5.64]
1.28 Fecal calprotectin at longest follow-up for induction of remission in UC (µg/mg)	3	131	Mean Difference (IV, Random, 95% CI)	-69.49 [-260.62, 121.65]

Analysis 1.1. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 1: Induction of clinical remission in UC at longest follow-up

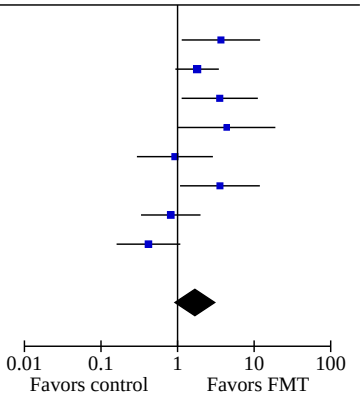


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 2: Induction of clinical remission in UC at 8 weeks

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Costello 2019	12	38	3	35	11.5%	3.68 [1.13 , 11.98]
Fang 2021	9	10	5	10	16.7%	1.80 [0.94 , 3.46]
Haifer 2022	8	15	3	20	11.8%	3.56 [1.13 , 11.18]
Moayyedi 2015 (1)	9	38	2	37	9.2%	4.38 [1.01 , 18.94]
Pai 2021 (2)	4	13	4	12	11.8%	0.92 [0.29 , 2.89]
Paramsothy 2017	11	41	3	40	11.3%	3.58 [1.08 , 11.88]
Rossen 2015 (2)	6	23	8	25	14.2%	0.82 [0.33 , 1.99]
Sarbagili Shabat 2022	6	36	6	15	13.6%	0.42 [0.16 , 1.09]
Total (95% CI)		**214**		**194**	**100.0%**	**1.68 [0.93 , 3.05]**
Total events:	65		34			

Heterogeneity: Tau² = 0.44; Chi² = 18.50, df = 7 (P = 0.010); I² = 62%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable

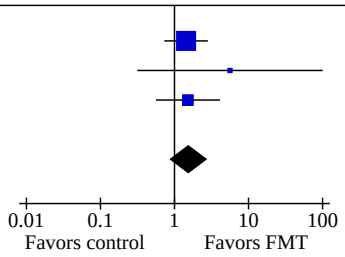


Footnotes
(1) Actual follow-up at week 7.
(2) Actual follow-up at week 6.

Analysis 1.3. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 3: Induction of clinical remission in UC at 12 weeks

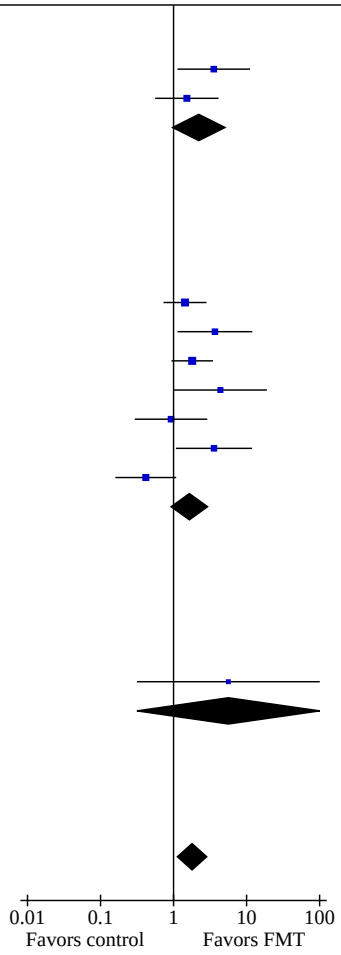
Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	12	23	8	22	66.0%	1.43 [0.73 , 2.82]
Crothers 2021	2	7	0	8	3.6%	5.63 [0.31 , 100.52]
Rossen 2015	7	23	5	25	30.4%	1.52 [0.56 , 4.13]
Total (95% CI)		**53**		**55**	**100.0%**	**1.54 [0.89 , 2.66]**
Total events:	21		13			

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable



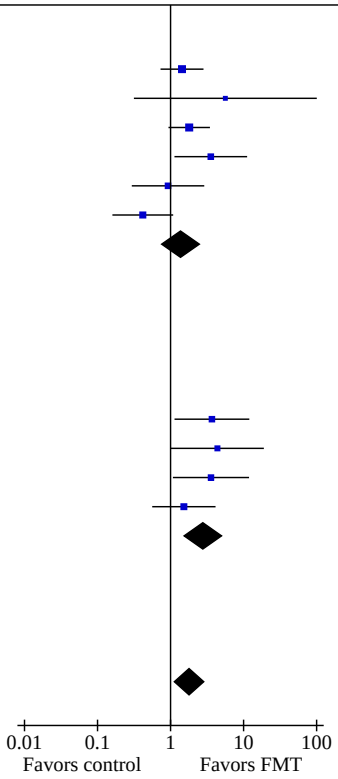
Analysis 1.4. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 4: Induction of clinical remission in UC at longest follow-up: subgroup analysis by route of administration

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Upper gastrointestinal						
Haifer 2022	8	15	3	20	9.5%	3.56 [1.13 , 11.18]
Rossen 2015	7	23	5	25	11.1%	1.52 [0.56 , 4.13]
Subtotal (95% CI)		**38**		**45**	**20.6%**	**2.22 [0.97 , 5.07]**
Total events:	15		8			
Heterogeneity: Tau² = 0.06; Chi² = 1.20, df = 1 (P = 0.27); I² = 17%						
Test for overall effect: Z = 1.89 (P = 0.06)						
1.4.2 Lower gastrointestinal						
Březina 2021	12	23	8	22	15.3%	1.43 [0.73 , 2.82]
Costello 2019	12	38	3	35	9.2%	3.68 [1.13 , 11.98]
Fang 2021	9	10	5	10	15.7%	1.80 [0.94 , 3.46]
Moayyedi 2015	9	38	2	37	6.9%	4.38 [1.01 , 18.94]
Pai 2021	4	13	4	12	9.5%	0.92 [0.29 , 2.89]
Paramsothy 2017	11	41	3	40	9.0%	3.58 [1.08 , 11.88]
Sarbagili Shabat 2022	6	36	6	15	11.5%	0.42 [0.16 , 1.09]
Subtotal (95% CI)		**199**		**171**	**77.1%**	**1.65 [0.93 , 2.92]**
Total events:	63		31			
Heterogeneity: Tau² = 0.33; Chi² = 14.55, df = 6 (P = 0.02); I² = 59%						
Test for overall effect: Z = 1.70 (P = 0.09)						
1.4.3 Mixed (upper and lower) route						
Crothers 2021	2	7	0	8	2.3%	5.63 [0.31 , 100.52]
Subtotal (95% CI)		**7**		**8**	**2.3%**	**5.63 [0.31 , 100.52]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**244**		**224**	**100.0%**	**1.79 [1.13 , 2.84]**
Total events:	80		39			
Heterogeneity: Tau² = 0.24; Chi² = 17.15, df = 9 (P = 0.05); I² = 48%						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: Chi² = 0.91, df = 2 (P = 0.63), I² = 0%						



Analysis 1.5. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 5: Induction of clinical remission in UC at longest follow-up: subgroup analysis by type of donor

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Single donor						
Březina 2021	12	23	8	22	15.3%	1.43 [0.73 , 2.82]
Crothers 2021	2	7	0	8	2.3%	5.63 [0.31 , 100.52]
Fang 2021	9	10	5	10	15.7%	1.80 [0.94 , 3.46]
Haifer 2022	8	15	3	20	9.5%	3.56 [1.13 , 11.18]
Pai 2021 (1)	4	13	4	12	9.5%	0.92 [0.29 , 2.89]
Sarbagili Shabat 2022	6	36	6	15	11.5%	0.42 [0.16 , 1.09]
Subtotal (95% CI)		**104**		**87**	**63.8%**	**1.37 [0.76 , 2.48]**
Total events:	41		26			
Heterogeneity: Tau² = 0.27; Chi² = 10.66, df = 5 (P = 0.06); I² = 53%						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.5.2 Multiple donors						
Costello 2019	12	38	3	35	9.2%	3.68 [1.13 , 11.98]
Moayyedi 2015	9	38	2	37	6.9%	4.38 [1.01 , 18.94]
Paramsothy 2017	11	41	3	40	9.0%	3.58 [1.08 , 11.88]
Rossen 2015	7	23	5	25	11.1%	1.52 [0.56 , 4.13]
Subtotal (95% CI)		**140**		**137**	**36.2%**	**2.77 [1.54 , 4.98]**
Total events:	39		13			
Heterogeneity: Tau² = 0.00; Chi² = 2.22, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
Total (95% CI)		**244**		**224**	**100.0%**	**1.79 [1.13 , 2.84]**
Total events:	80		39			
Heterogeneity: Tau² = 0.24; Chi² = 17.15, df = 9 (P = 0.05); I² = 48%						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: Chi² = 2.72, df = 1 (P = 0.10), I² = 63.3%						

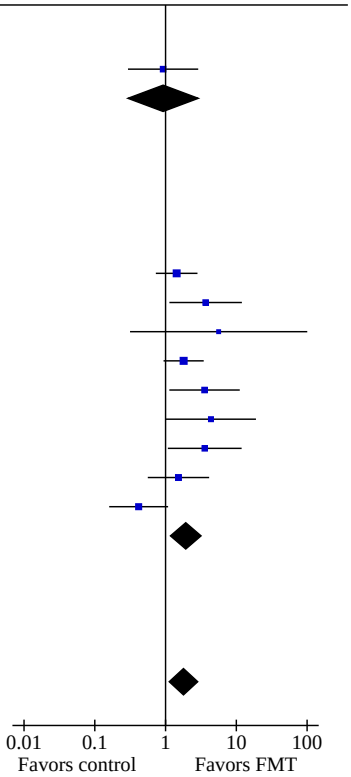


Footnotes

(1) Stool samples from multiple donors not pooled, but a participant received samples from different donors at different times.

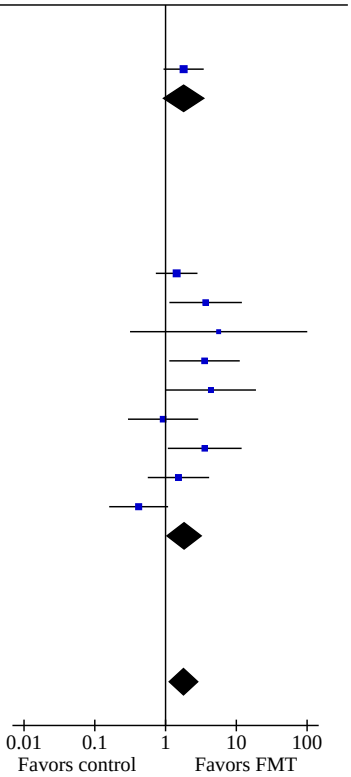
Analysis 1.6. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 6: Induction of clinical remission in UC at longest follow-up: subgroup analysis by age

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Children						
Pai 2021	4	13	4	12	9.5%	0.92 [0.29 , 2.89]
Subtotal (95% CI)		**13**		**12**	**9.5%**	**0.92 [0.29 , 2.89]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.6.2 Adults						
Březina 2021	12	23	8	22	15.3%	1.43 [0.73 , 2.82]
Costello 2019	12	38	3	35	9.2%	3.68 [1.13 , 11.98]
Crothers 2021	2	7	0	8	2.3%	5.63 [0.31 , 100.52]
Fang 2021	9	10	5	10	15.7%	1.80 [0.94 , 3.46]
Haifer 2022	8	15	3	20	9.5%	3.56 [1.13 , 11.18]
Moayyedi 2015	9	38	2	37	6.9%	4.38 [1.01 , 18.94]
Paramsothy 2017	11	41	3	40	9.0%	3.58 [1.08 , 11.88]
Rossen 2015	7	23	5	25	11.1%	1.52 [0.56 , 4.13]
Sarbagili Shabat 2022	6	36	6	15	11.5%	0.42 [0.16 , 1.09]
Subtotal (95% CI)		**231**		**212**	**90.5%**	**1.93 [1.17 , 3.17]**
Total events:	76		35			
Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 16.02$, df = 8 (P = 0.04); $I^2 = 50\%$						
Test for overall effect: Z = 2.59 (P = 0.010)						
Total (95% CI)		**244**		**224**	**100.0%**	**1.79 [1.13 , 2.84]**
Total events:	80		39			
Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 17.15$, df = 9 (P = 0.05); $I^2 = 48\%$						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: $Chi^2 = 1.34$, df = 1 (P = 0.25), $I^2 = 25.6\%$						



Analysis 1.7. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 7: Induction of clinical remission in UC at longest follow-up: subgroup analysis by frequency of FMT

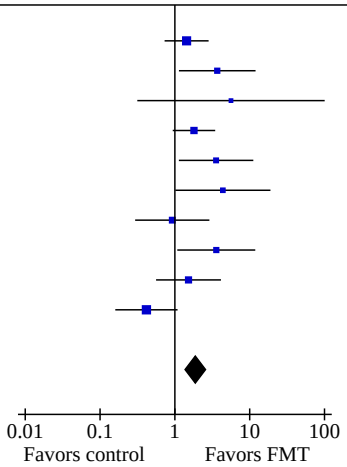
Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Single infusion						
Fang 2021	9	10	5	10	15.7%	1.80 [0.94 , 3.46]
Subtotal (95% CI)		**10**		**10**	**15.7%**	**1.80 [0.94 , 3.46]**
Total events:	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
1.7.2 Multiple infusions						
Březina 2021	12	23	8	22	15.3%	1.43 [0.73 , 2.82]
Costello 2019	12	38	3	35	9.2%	3.68 [1.13 , 11.98]
Crothers 2021	2	7	0	8	2.3%	5.63 [0.31 , 100.52]
Haifer 2022	8	15	3	20	9.5%	3.56 [1.13 , 11.18]
Moayyedi 2015	9	38	2	37	6.9%	4.38 [1.01 , 18.94]
Pai 2021	4	13	4	12	9.5%	0.92 [0.29 , 2.89]
Paramsothy 2017	11	41	3	40	9.0%	3.58 [1.08 , 11.88]
Rossen 2015	7	23	5	25	11.1%	1.52 [0.56 , 4.13]
Sarbagili Shabat 2022	6	36	6	15	11.5%	0.42 [0.16 , 1.09]
Subtotal (95% CI)		**234**		**214**	**84.3%**	**1.83 [1.05 , 3.18]**
Total events:	71		34			
Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 17.18$, df = 8 (P = 0.03); $I^2 = 53\%$						
Test for overall effect: Z = 2.12 (P = 0.03)						
Total (95% CI)		**244**		**224**	**100.0%**	**1.79 [1.13 , 2.84]**
Total events:	80		39			
Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 17.15$, df = 9 (P = 0.05); $I^2 = 48\%$						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$						



Analysis 1.8. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 8: Induction of clinical remission in UC at longest follow-up: sensitivity analysis using fixed-effect model

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Březina 2021	12	23	8	22	19.6%	1.43 [0.73 , 2.82]
Costello 2019	12	38	3	35	7.5%	3.68 [1.13 , 11.98]
Crothers 2021	2	7	0	8	1.1%	5.63 [0.31 , 100.52]
Fang 2021	9	10	5	10	12.0%	1.80 [0.94 , 3.46]
Haifer 2022	8	15	3	20	6.1%	3.56 [1.13 , 11.18]
Moayyedi 2015	9	38	2	37	4.8%	4.38 [1.01 , 18.94]
Pai 2021	4	13	4	12	9.9%	0.92 [0.29 , 2.89]
Paramsothy 2017	11	41	3	40	7.3%	3.58 [1.08 , 11.88]
Rossen 2015	7	23	5	25	11.5%	1.52 [0.56 , 4.13]
Sarbagili Shabat 2022	6	36	6	15	20.3%	0.42 [0.16 , 1.09]
Total (95% CI)		**244**		**224**	**100.0%**	**1.88 [1.37 , 2.57]**
Total events:	80		39			

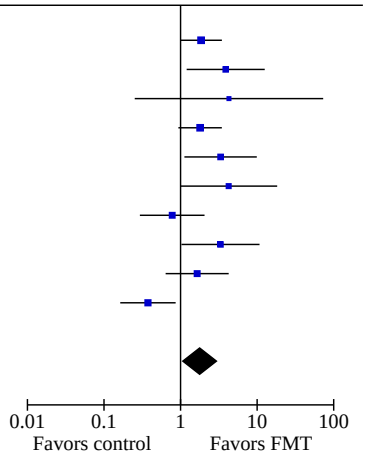
Heterogeneity: Chi² = 17.15, df = 9 (P = 0.05); I² = 48%
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 9: Induction of clinical remission in UC at longest follow-up: sensitivity analysis for available cases

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	12	17	8	21	14.1%	1.85 [0.99 , 3.46]
Costello 2019	12	35	3	34	9.1%	3.89 [1.20 , 12.57]
Crothers 2021	2	6	0	5	2.7%	4.29 [0.25 , 72.90]
Fang 2021	9	10	5	10	13.9%	1.80 [0.94 , 3.46]
Haifer 2022	8	12	3	15	9.8%	3.33 [1.12 , 9.90]
Moayyedi 2015	9	36	2	34	7.2%	4.25 [0.99 , 18.28]
Pai 2021	4	9	4	7	10.8%	0.78 [0.29 , 2.06]
Paramsothy 2017	11	32	3	29	9.1%	3.32 [1.03 , 10.74]
Rossen 2015	7	17	5	20	11.0%	1.65 [0.64 , 4.25]
Sarbagili Shabat 2022	6	24	6	9	12.1%	0.38 [0.16 , 0.86]
Total (95% CI)		**198**		**184**	**100.0%**	**1.77 [1.07 , 2.94]**
Total events:	80		39			

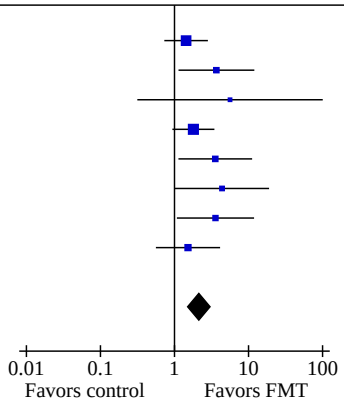
Heterogeneity: Tau² = 0.37; Chi² = 22.77, df = 9 (P = 0.007); I² = 60%
Test for overall effect: Z = 2.23 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 10: Induction of clinical remission in UC at longest follow-up: composite of clinical score and endoscopic score

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	12	23	8	22	26.3%	1.43 [0.73 , 2.82]
Costello 2019	12	38	3	35	8.7%	3.68 [1.13 , 11.98]
Crothers 2021	2	7	0	8	1.5%	5.63 [0.31 , 100.52]
Fang 2021	9	10	5	10	28.3%	1.80 [0.94 , 3.46]
Haifer 2022	8	15	3	20	9.2%	3.56 [1.13 , 11.18]
Moayyedi 2015	9	38	2	37	5.6%	4.38 [1.01 , 18.94]
Paramsothy 2017	11	41	3	40	8.4%	3.58 [1.08 , 11.88]
Rossen 2015	7	23	5	25	12.1%	1.52 [0.56 , 4.13]
Total (95% CI)		**195**		**197**	**100.0%**	**2.13 [1.51 , 3.02]**
Total events:	70		29			

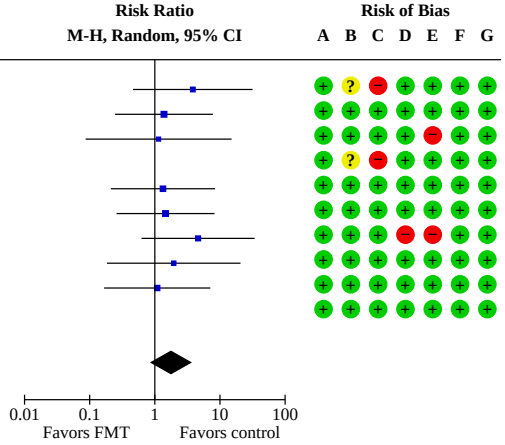
Heterogeneity: Tau² = 0.00; Chi² = 6.24, df = 7 (P = 0.51); I² = 0%
Test for overall effect: Z = 4.27 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 11: Serious adverse events for induction of remission in UC

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	4	23	1	22	10.9%	3.83 [0.46 , 31.62]
Costello 2019	3	38	2	35	16.3%	1.38 [0.25 , 7.79]
Crothers 2021	1	7	1	8	7.3%	1.14 [0.09 , 15.08]
Fang 2021	0	10	0	10		Not estimable
Haifer 2022	2	15	2	20	14.4%	1.33 [0.21 , 8.41]
Moayyedi 2015 (1)	3	38	2	37	16.3%	1.46 [0.26 , 8.25]
Pai 2021	5	13	1	12	12.2%	4.62 [0.63 , 34.05]
Paramsothy 2017	2	41	1	40	8.7%	1.95 [0.18 , 20.68]
Rossen 2015	2	23	2	25	13.8%	1.09 [0.17 , 7.10]
Sarbagili Shabat 2022	0	36	0	15		Not estimable
Total (95% CI)		**244**		**224**	**100.0%**	**1.77 [0.88 , 3.55]**
Total events:	22		12			

Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 7 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable



Footnotes

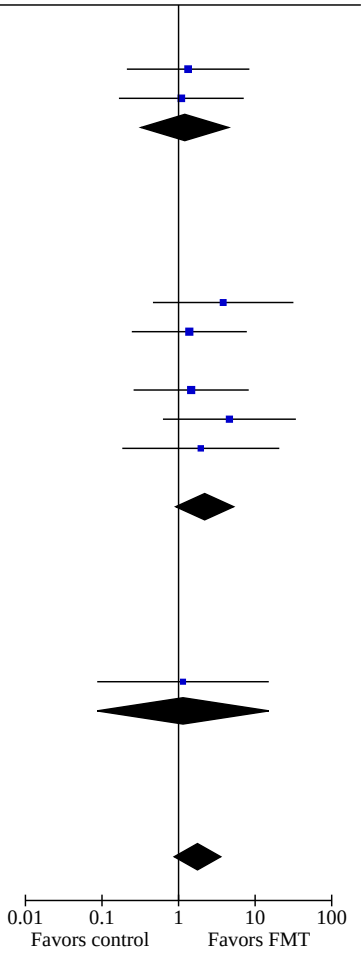
(1) FMT, 2 diagnoses changed to Crohn's colitis and 1 positive for *C difficile* toxin at end of therapy; control, 1 diagnosis changed to Crohn's colitis and 1 hospitalised.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

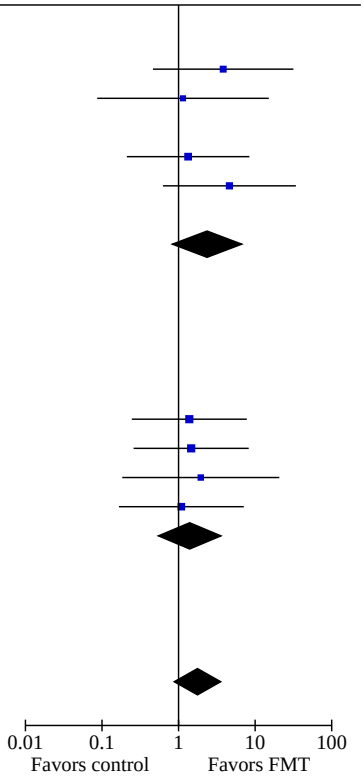
Analysis 1.12. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 12: Serious adverse events for induction of remission in UC: subgroup analysis by route of administration

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Upper gastrointestinal						
Haifer 2022	2	15	2	20	14.4%	1.33 [0.21 , 8.41]
Rossen 2015	2	23	2	25	13.8%	1.09 [0.17 , 7.10]
Subtotal (95% CI)		**38**		**45**	**28.2%**	**1.21 [0.32 , 4.49]**
Total events:	4		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.12.2 Lower gastrointestinal						
Březina 2021	4	23	1	22	10.9%	3.83 [0.46 , 31.62]
Costello 2019	3	38	2	35	16.3%	1.38 [0.25 , 7.79]
Fang 2021	0	10	0	10		Not estimable
Moayyedi 2015	3	38	2	37	16.3%	1.46 [0.26 , 8.25]
Pai 2021	5	13	1	12	12.2%	4.62 [0.63 , 34.05]
Paramsothy 2017	2	41	1	40	8.7%	1.95 [0.18 , 20.68]
Sarbagili Shabat 2022	0	36	0	15		Not estimable
Subtotal (95% CI)		**199**		**171**	**64.5%**	**2.19 [0.92 , 5.23]**
Total events:	17		7			
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.12.3 Mixed (upper and lower) route						
Crothers 2021	1	7	1	8	7.3%	1.14 [0.09 , 15.08]
Subtotal (95% CI)		**7**		**8**	**7.3%**	**1.14 [0.09 , 15.08]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**244**		**224**	**100.0%**	**1.77 [0.88 , 3.55]**
Total events:	22		12			
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 7 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: Chi² = 0.67, df = 2 (P = 0.72), I² = 0%						



Analysis 1.13. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 13: Serious adverse events for induction of remission in UC: subgroup analysis by type of donor

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Single donor						
Březina 2021	4	23	1	22	10.9%	3.83 [0.46 , 31.62]
Crothers 2021	1	7	1	8	7.3%	1.14 [0.09 , 15.08]
Fang 2021	0	10	0	10		Not estimable
Haifer 2022	2	15	2	20	14.4%	1.33 [0.21 , 8.41]
Pai 2021 (1)	5	13	1	12	12.2%	4.62 [0.63 , 34.05]
Sarbagili Shabat 2022	0	36	0	15		Not estimable
Subtotal (95% CI)		**104**		**87**	**44.8%**	**2.36 [0.83 , 6.69]**
Total events:	12		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 3 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.61 (P = 0.11)						
1.13.2 Multiple donors						
Costello 2019	3	38	2	35	16.3%	1.38 [0.25 , 7.79]
Moayyedi 2015	3	38	2	37	16.3%	1.46 [0.26 , 8.25]
Paramsothy 2017	2	41	1	40	8.7%	1.95 [0.18 , 20.68]
Rossen 2015	2	23	2	25	13.8%	1.09 [0.17 , 7.10]
Subtotal (95% CI)		**140**		**137**	**55.2%**	**1.40 [0.55 , 3.58]**
Total events:	10		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 3 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.49)						
Total (95% CI)		**244**		**224**	**100.0%**	**1.77 [0.88 , 3.55]**
Total events:	22		12			
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 7 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.46), I² = 0%						

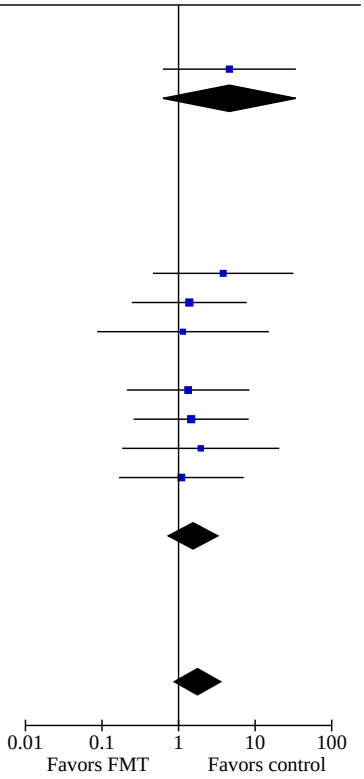


Footnotes

(1) Stool samples from multiple donors not pooled, but participant received samples from different donors at different times.

Analysis 1.14. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 14: Serious adverse events for induction of remission in UC: subgroup analysis by age

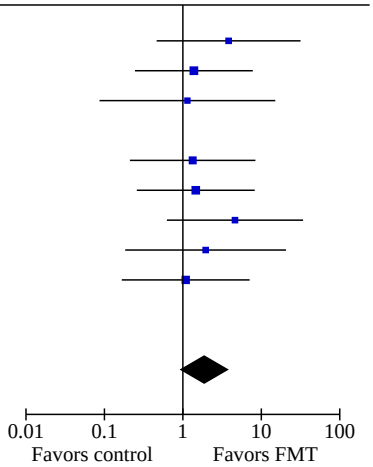
Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Children						
Pai 2021	5	13	1	12	12.2%	4.62 [0.63 , 34.05]
Subtotal (95% CI)		**13**		**12**	**12.2%**	**4.62 [0.63 , 34.05]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
1.14.2 Adults						
Březina 2021	4	23	1	22	10.9%	3.83 [0.46 , 31.62]
Costello 2019	3	38	2	35	16.3%	1.38 [0.25 , 7.79]
Crothers 2021	1	7	1	8	7.3%	1.14 [0.09 , 15.08]
Fang 2021	0	10	0	10		Not estimable
Haifer 2022	2	15	2	20	14.4%	1.33 [0.21 , 8.41]
Moayyedi 2015	3	38	2	37	16.3%	1.46 [0.26 , 8.25]
Paramsothy 2017	2	41	1	40	8.7%	1.95 [0.18 , 20.68]
Rossen 2015	2	23	2	25	13.8%	1.09 [0.17 , 7.10]
Sarbagili Shabat 2022	0	36	0	15		Not estimable
Subtotal (95% CI)		**231**		**212**	**87.8%**	**1.55 [0.73 , 3.26]**
Total events:	17		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 6 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.25)						
Total (95% CI)		**244**		**224**	**100.0%**	**1.77 [0.88 , 3.55]**
Total events:	22		12			
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 7 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: Chi² = 1.01, df = 1 (P = 0.31), I² = 1.1%						



Analysis 1.15. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 15: Serious adverse events for induction of remission in UC: sensitivity analysis using fixed-effect model

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Březina 2021	4	23	1	22	8.7%	3.83 [0.46 , 31.62]
Costello 2019	3	38	2	35	17.7%	1.38 [0.25 , 7.79]
Crothers 2021	1	7	1	8	7.9%	1.14 [0.09 , 15.08]
Fang 2021	0	10	0	10		Not estimable
Haifer 2022	2	15	2	20	14.6%	1.33 [0.21 , 8.41]
Moayyedi 2015	3	38	2	37	17.3%	1.46 [0.26 , 8.25]
Pai 2021	5	13	1	12	8.9%	4.62 [0.63 , 34.05]
Paramsothy 2017	2	41	1	40	8.6%	1.95 [0.18 , 20.68]
Rossen 2015	2	23	2	25	16.3%	1.09 [0.17 , 7.10]
Sarbagili Shabat 2022	0	36	0	15		Not estimable
Total (95% CI)		**244**		**224**	**100.0%**	**1.87 [0.95 , 3.68]**
Total events:	22		12			

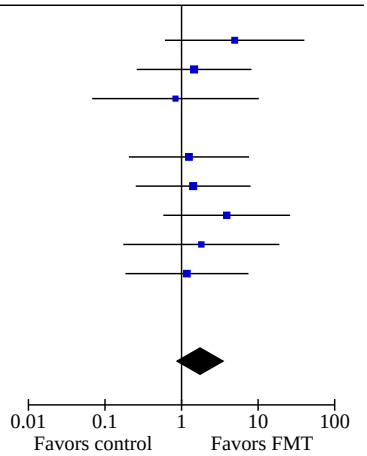
Heterogeneity: Chi² = 2.01, df = 7 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 16: Serious adverse events for induction of remission in UC: sensitivity analysis for available cases

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	4	17	1	21	10.8%	4.94 [0.61 , 40.19]
Costello 2019	3	35	2	34	15.9%	1.46 [0.26 , 8.19]
Crothers 2021	1	6	1	5	7.5%	0.83 [0.07 , 10.20]
Fang 2021	0	10	0	10		Not estimable
Haifer 2022	2	12	2	15	14.5%	1.25 [0.21 , 7.62]
Moayyedi 2015 (1)	3	36	2	34	15.9%	1.42 [0.25 , 7.96]
Pai 2021	5	9	1	7	13.0%	3.89 [0.58 , 26.17]
Paramsothy 2017	2	32	1	29	8.6%	1.81 [0.17 , 18.95]
Rossen 2015	2	17	2	20	13.8%	1.18 [0.18 , 7.48]
Sarbagili Shabat 2022	0	24	0	9		Not estimable
Total (95% CI)		**198**		**184**	**100.0%**	**1.74 [0.88 , 3.47]**
Total events:	22		12			

Heterogeneity: Tau² = 0.00; Chi² = 2.39, df = 7 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Not applicable

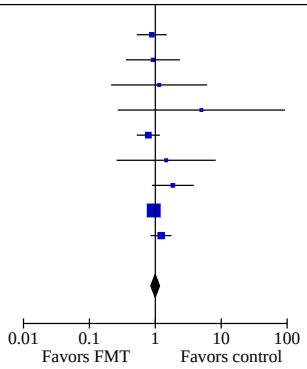


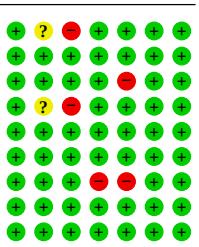
Footnotes

(1) FMT, 2 diagnoses changed to Crohn's colitis and 1 positive for *C difficile* toxin at end of therapy; control, 1 diagnosis changed to Crohn's colitis and 1 h

Analysis 1.17. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 17: Any adverse events for induction of remission in UC

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	12	23	13	22	8.6%	0.88 [0.52 , 1.49]
Costello 2019	7	38	7	35	2.7%	0.92 [0.36 , 2.36]
Crothers 2021 (1)	2	7	2	8	0.8%	1.14 [0.21 , 6.11]
Fang 2021	2	10	0	10	0.3%	5.00 [0.27 , 92.62]
Haifer 2022	10	15	17	20	14.5%	0.78 [0.52 , 1.17]
Moayyedi 2015	3	38	2	37	0.8%	1.46 [0.26 , 8.25]
Pai 2021	10	13	5	12	4.4%	1.85 [0.89 , 3.84]
Paramsothy 2017	32	41	33	40	50.3%	0.95 [0.76 , 1.17]
Rossen 2015 (2)	18	23	16	25	17.7%	1.22 [0.85 , 1.76]
Total (95% CI)		**208**		**209**	**100.0%**	**0.99 [0.85 , 1.16]**
Total events:	96		95			





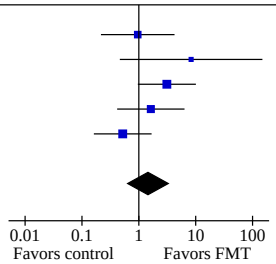
Heterogeneity: Tau² = 0.00; Chi² = 7.48, df = 8 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable

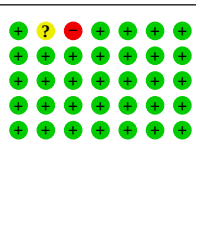
Footnotes
(1) Reported adverse events "possibly or probably related to FMT."
(2) Reported adverse events "related to FMT."

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.18. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 18: Induction of endoscopic remission in UC at longest follow-up

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021 (1)	3	23	3	22	19.5%	0.96 [0.22 , 4.24]
Costello 2019 (2)	4	38	0	35	7.0%	8.31 [0.46 , 148.95]
Haifer 2022	7	15	3	20	25.8%	3.11 [0.96 , 10.08]
Paramsothy 2017	5	41	3	40	21.8%	1.63 [0.42 , 6.36]
Sarbagili Shabat 2022	5	36	4	15	25.9%	0.52 [0.16 , 1.68]
Total (95% CI)		**153**		**132**	**100.0%**	**1.45 [0.64 , 3.29]**
Total events:	24		13			





Heterogeneity: Tau² = 0.32; Chi² = 6.42, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

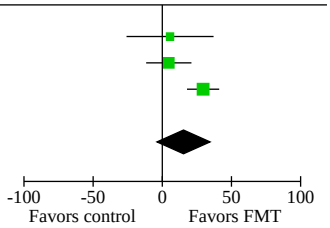
Footnotes
(1) Endoscopic Mayo score 0 at week 12.
(2) Mayo score < 1 at week 8.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.19. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 19: Quality of life (Inflammatory Bowel Disease Questionnaire [IBDQ]) scores at longest follow-up for induction of remission in UC

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Crothers 2021	169	34	7	163.4	27.2	8	21.3%	5.60 [-25.86 , 37.06]
Haifer 2022	183.5	26	15	178.8	22.2	20	36.6%	4.70 [-11.66 , 21.06]
Paramsothy 2017	163	28.125	41	133.5	25.25	40	42.1%	29.50 [17.87 , 41.13]
Total (95% CI)			**63**			**68**	**100.0%**	**15.34 [-3.84 , 34.52]**

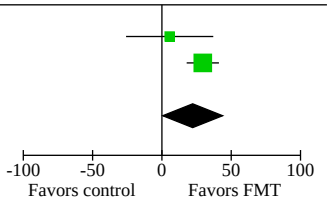
Heterogeneity: Tau² = 192.12; Chi² = 6.72, df = 2 (P = 0.03); I² = 70%
Test for overall effect: Z = 1.57 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 20: Quality of life (IBDQ) scores at longest follow-up for induction of remission in UC: sensitivity analysis without Haifer 2022

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Crothers 2021	169	34	7	163.4	27.2	8	30.5%	5.60 [-25.86 , 37.06]
Paramsothy 2017	163	28.125	41	133.5	25.25	40	69.5%	29.50 [17.87 , 41.13]
Total (95% CI)			**48**			**48**	**100.0%**	**22.20 [0.63 , 43.78]**

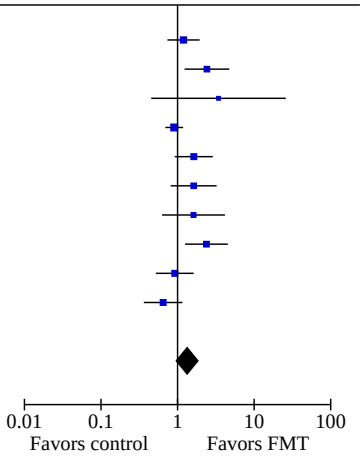
Heterogeneity: Tau² = 139.18; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 21: Induction of clinical response in UC at longest follow-up

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021 (1)	15	23	12	22	12.4%	1.20 [0.74 , 1.94]
Costello 2019 (2)	21	38	8	35	9.9%	2.42 [1.23 , 4.74]
Crothers 2021 (3)	3	7	1	8	2.2%	3.43 [0.45 , 25.93]
Fang 2021 (4)	9	10	10	10	15.3%	0.90 [0.69 , 1.18]
Haifer 2022	11	15	9	20	11.2%	1.63 [0.92 , 2.89]
Moayyedi 2015	15	38	9	37	9.6%	1.62 [0.81 , 3.24]
Pai 2021	7	13	4	12	7.0%	1.62 [0.63 , 4.16]
Paramsothy 2017	22	41	9	40	10.2%	2.38 [1.26 , 4.53]
Rossen 2015	11	23	13	25	11.2%	0.92 [0.52 , 1.63]
Sarbagili Shabat 2022	14	36	9	15	11.0%	0.65 [0.36 , 1.16]
Total (95% CI)		**244**		**224**	**100.0%**	**1.33 [0.96 , 1.84]**
Total events:	128		84			

Heterogeneity: Tau² = 0.16; Chi² = 26.24, df = 9 (P = 0.002); I² = 66%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable



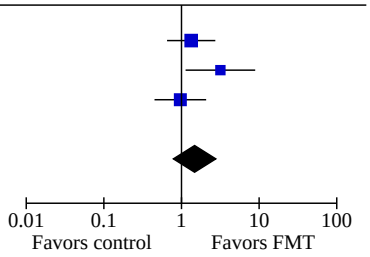
Footnotes

(1) Reduction in Total Mayo score ≥ 2 at week 12.
(2) Reduction in Total Mayo score ≥ 3 at week 8.
(3) 1 FMT participant who demonstrated clinical response but not remission had required steroid therapy during intervention period (week 6).
(4) Proportion of participants who "achieved clinical symptom improvement within 2 weeks after FMT."

Analysis 1.22. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 22: Induction of endoscopic response in UC at longest follow-up

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Haifer 2022	8	15	8	20	38.8%	1.33 [0.65 , 2.73]
Paramsothy 2017	13	41	4	40	25.1%	3.17 [1.13 , 8.90]
Rossen 2015	8	23	9	25	36.1%	0.97 [0.45 , 2.08]
Total (95% CI)		**79**		**85**	**100.0%**	**1.48 [0.79 , 2.76]**
Total events:	29		21			

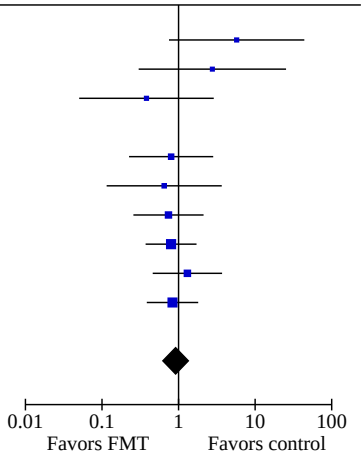
Heterogeneity: Tau² = 0.13; Chi² = 3.48, df = 2 (P = 0.18); I² = 43%
Test for overall effect: Z = 1.21 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 23: Withdrawals in studies on induction of remission in UC

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Březina 2021	6	23	1	22	3.5%	5.74 [0.75 , 43.90]
Costello 2019	3	38	1	35	3.0%	2.76 [0.30 , 25.34]
Crothers 2021	1	7	3	8	3.6%	0.38 [0.05 , 2.88]
Fang 2021	0	10	0	10		Not estimable
Haifer 2022	3	15	5	20	9.1%	0.80 [0.23 , 2.83]
Moayyedi 2015 (1)	2	38	3	37	4.9%	0.65 [0.11 , 3.67]
Pai 2021	4	13	5	12	13.1%	0.74 [0.26 , 2.12]
Paramsothy 2017	9	41	11	40	24.9%	0.80 [0.37 , 1.72]
Rossen 2015	6	23	5	25	13.4%	1.30 [0.46 , 3.70]
Sarbagili Shabat 2022	12	36	6	15	24.4%	0.83 [0.38 , 1.81]
Total (95% CI)		**244**		**224**	**100.0%**	**0.91 [0.62 , 1.34]**
Total events:	46		40			

Heterogeneity: Tau² = 0.00; Chi² = 5.93, df = 8 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable

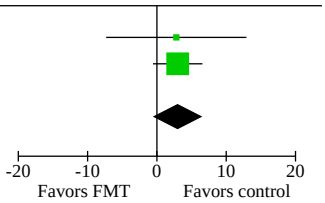


Footnotes
(1) 1 participant needed antibiotics before therapy.

Analysis 1.24. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 24: Erythrocyte sedimentation rate (ESR) at longest follow-up for induction of remission in UC (mm/hour)

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Moayyedi 2015	15.9	17	15	13.1	11.2	17	11.0%	2.80 [-7.32 , 12.92]
Paramsothy 2017	20	7.25	41	17	9	40	89.0%	3.00 [-0.56 , 6.56]
Total (95% CI)			**56**			**57**	**100.0%**	**2.98 [-0.38 , 6.34]**

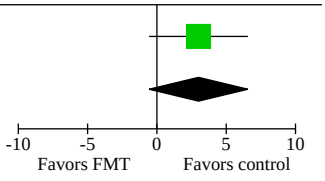
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.25. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 25: ESR at longest follow-up for induction of remission in UC: sensitivity analysis without Moayyedi 2015 (mm/hour)

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Paramsothy 2017	20	7.25	41	17	9	40	100.0%	3.00 [-0.56 , 6.56]
Total (95% CI)			**41**			**40**	**100.0%**	**3.00 [-0.56 , 6.56]**

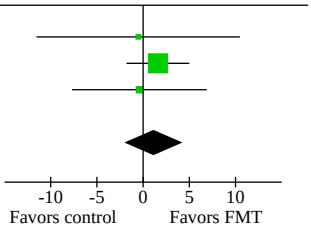
Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 26: C-reactive protein (CRP) at longest follow-up for induction of remission in UC (mg/L)

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Crothers 2021	10.12	10.43	7	10.65	11.31	8	7.3%	-0.53 [-11.54 , 10.48]
Moayyedi 2015	4.9	5.9	15	3.3	3.4	17	76.2%	1.60 [-1.80 , 5.00]
Paramsothy 2017	3.8	11.25	41	4.2	20.73	40	16.5%	-0.40 [-7.69 , 6.89]
Total (95% CI)			**63**			**65**	**100.0%**	**1.11 [-1.85 , 4.08]**

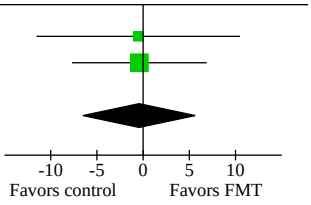
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 27: CRP at longest follow-up for induction of remission in UC: sensitivity analysis without Moayyedi 2015 (mg/L)

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Crothers 2021	10.12	10.43	7	10.65	11.31	8	30.5%	-0.53 [-11.54 , 10.48]
Paramsothy 2017	3.8	11.25	41	4.2	20.73	40	69.5%	-0.40 [-7.69 , 6.89]
Total (95% CI)			**48**			**48**	**100.0%**	**-0.44 [-6.52 , 5.64]**

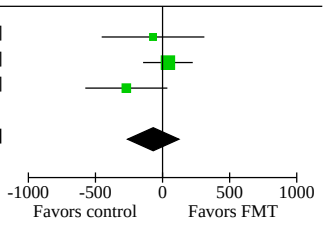
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



Analysis 1.28. Comparison 1: Fecal microbiota transplantation (FMT) versus control for induction of remission in ulcerative colitis (UC), Outcome 28: Fecal calprotectin at longest follow-up for induction of remission in UC (µg/mg)

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Crothers 2021	298	428	7	369	309	8	20.0%	-71.00 [-453.59 , 311.59]
Haifer 2022	465	312	15	425	220	20	51.8%	40.00 [-145.00 , 225.00]
Paramsothy 2017	710	714	41	980	690.19	40	28.2%	-270.00 [-575.80 , 35.80]
Total (95% CI)			**63**			**68**	**100.0%**	**-69.49 [-260.62 , 121.65]**

Heterogeneity: Tau² = 9436.12; Chi² = 2.91, df = 2 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable

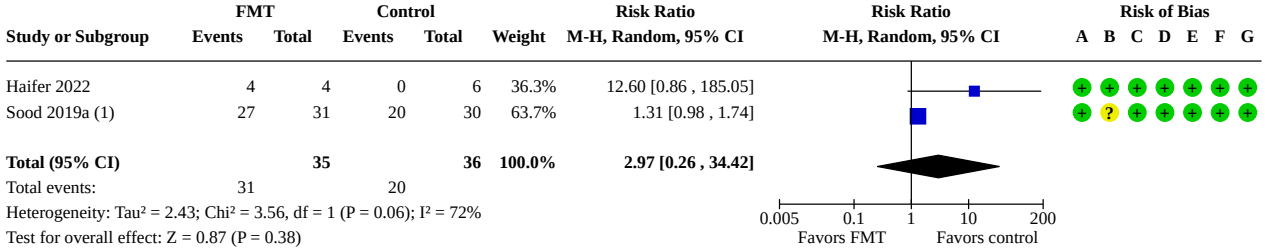


Comparison 2. Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Maintenance of clinical remission in UC	2	71	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.26, 34.42]
2.2 Maintenance of clinical remission in UC: sensitivity analysis using fixed-effect model	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.13, 2.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Maintenance of clinical remission in UC: sensitivity analysis for available cases	2	64	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.47, 5.81]
2.4 Serious adverse events for maintenance of remission in UC	2	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.5 Any adverse events for maintenance of remission in UC	2	71	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.85, 1.59]
2.6 Maintenance of endoscopic remission in UC	2	71	Risk Ratio (M-H, Random, 95% CI)	3.28 [0.73, 14.74]
2.7 Withdrawals in studies on maintenance of remission in UC	2	71	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.05, 1.73]
2.8 Erythrocyte sedimentation rate (ESR) at longest follow-up for maintenance of remission in UC (mm/hour)	1	61	Mean Difference (IV, Random, 95% CI)	-10.40 [-12.54, -8.26]
2.9 C-reactive protein (CRP) at longest follow-up for maintenance of remission in UC (mg/L)	1	61	Mean Difference (IV, Random, 95% CI)	-2.70 [-3.82, -1.58]

Analysis 2.1. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 1: Maintenance of clinical remission in UC



Footnotes

(1) Mayo score ≤ 2 with all subscores ≤ 1 at week 48.

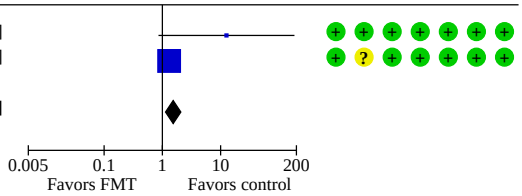
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 2: Maintenance of clinical remission in UC: sensitivity analysis using fixed-effect model

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haifer 2022	4	4	0	6	2.0%	12.60 [0.86 , 185.05]
Sood 2019a (1)	27	31	20	30	98.0%	1.31 [0.98 , 1.74]
Total (95% CI)		**35**		**36**	**100.0%**	**1.53 [1.13 , 2.07]**
Total events:	31		20			

Heterogeneity: Chi² = 3.56, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 2.77 (P = 0.006)
Test for subgroup differences: Not applicable



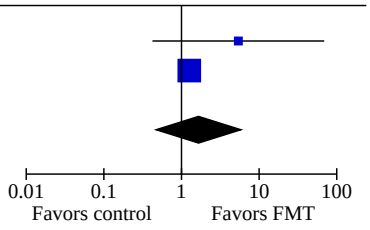
Footnotes
(1) Mayo score ≤ 2 with all subscores ≤ 1 at week 48.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 3: Maintenance of clinical remission in UC: sensitivity analysis for available cases

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Haifer 2022	4	4	0	2	18.8%	5.40 [0.42 , 68.96]
Sood 2019a	27	30	20	28	81.2%	1.26 [0.97 , 1.64]
Total (95% CI)		**34**		**30**	**100.0%**	**1.66 [0.47 , 5.81]**
Total events:	31		20			

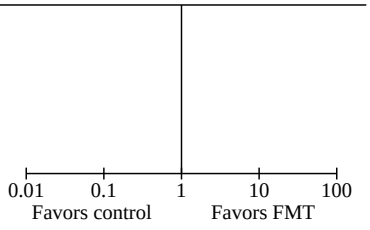
Heterogeneity: Tau² = 0.49; Chi² = 1.57, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 4: Serious adverse events for maintenance of remission in UC

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Haifer 2022	0	4	0	6		Not estimable
Sood 2019a	0	31	0	30		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

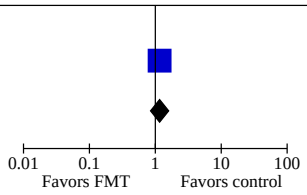
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 5: Any adverse events for maintenance of remission in UC

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Haifer 2022	0	4	0	6		Not estimable
Sood 2019a	24	31	20	30	100.0%	1.16 [0.85 , 1.59]
Total (95% CI)		**35**		**36**	**100.0%**	**1.16 [0.85 , 1.59]**
Total events:	24		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable

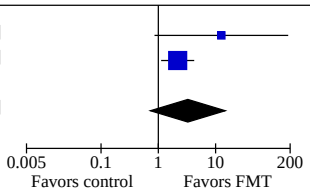


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.6. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 6: Maintenance of endoscopic remission in UC

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Haifer 2022	4	4	0	6	23.3%	12.60 [0.86 , 185.05]
Sood 2019a	18	31	8	30	76.7%	2.18 [1.12 , 4.23]
Total (95% CI)		**35**		**36**	**100.0%**	**3.28 [0.73 , 14.74]**
Total events:	22		8			

Heterogeneity: Tau² = 0.65; Chi² = 1.65, df = 1 (P = 0.20); I² = 40%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable

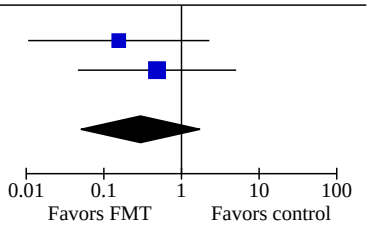


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.7. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 7: Withdrawals in studies on maintenance of remission in UC

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Haifer 2022	0	4	4	6	43.3%	0.16 [0.01 , 2.28]
Sood 2019a	1	31	2	30	56.7%	0.48 [0.05 , 5.06]
Total (95% CI)		**35**		**36**	**100.0%**	**0.30 [0.05 , 1.73]**
Total events:	1		6			

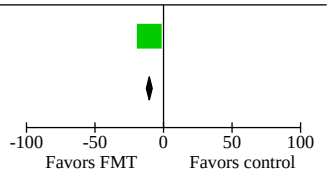
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 8: Erythrocyte sedimentation rate (ESR) at longest follow-up for maintenance of remission in UC (mm/hour)

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Sood 2019a	10.1	2.8	31	20.5	5.3	30	100.0%	-10.40 [-12.54 , -8.26]
Total (95% CI)			**31**			**30**	**100.0%**	**-10.40 [-12.54 , -8.26]**

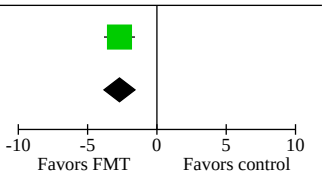
Heterogeneity: Not applicable
Test for overall effect: Z = 9.54 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in ulcerative colitis (UC), Outcome 9: C-reactive protein (CRP) at longest follow-up for maintenance of remission in UC (mg/L)

Study or Subgroup	FMT Mean	FMT SD	FMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Sood 2019a	4.5	1.9	31	7.2	2.5	30	100.0%	-2.70 [-3.82 , -1.58]
Total (95% CI)			**31**			**30**	**100.0%**	**-2.70 [-3.82 , -1.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.74 (P < 0.00001)
Test for subgroup differences: Not applicable



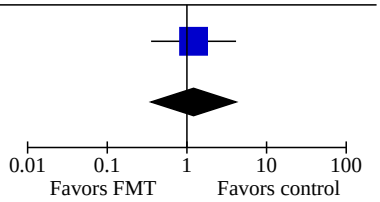
Comparison 4. Fecal microbiota transplantation (FMT) versus control for maintenance of remission in Crohn's disease (CD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Maintenance of clinical remission in CD	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.36, 4.14]
4.2 Withdrawals in studies on maintenance of remission in CD	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.54, 3.46]

Analysis 4.1. Comparison 4: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in Crohn's disease (CD), Outcome 1: Maintenance of clinical remission in CD

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sokol 2020 (1)	4	11	3	10	100.0%	1.21 [0.36 , 4.14]
Total (95% CI)		**11**		**10**	**100.0%**	**1.21 [0.36 , 4.14]**
Total events:	4		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.76)
Test for subgroup differences: Not applicable

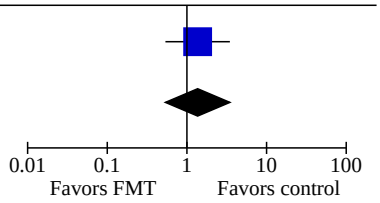


Footnotes
(1) Maintenance identified at week 24.

Analysis 4.2. Comparison 4: Fecal microbiota transplantation (FMT) versus control for maintenance of remission in Crohn's disease (CD), Outcome 2: Withdrawals in studies on maintenance of remission in CD

Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sokol 2020	6	11	4	10	100.0%	1.36 [0.54 , 3.46]
Total (95% CI)		**11**		**10**	**100.0%**	**1.36 [0.54 , 3.46]**
Total events:	6		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Microbiome outcomes

Study	Primary disease addressed	Sequencing platform	Alpha diversity	Beta diversity	Notable bacterial taxonomic profiles	Methods and main findings of microbiome analysis
Moayyedi 2015	UC	MiSeq Illumina	Not reported	"Beta diversity (Bray-Curtis dissimilarity) was calculated using the Phyloseq R package. There was a statistically significant change in microbio-	"Relative abundance and taxonomic profiles were computed using Quantitative Insights Into Microbial Ecology. Taxonomic profiles of the donors highlighted distinct microbial differences between the 2 most com-	"The study authors sequenced the V3 region of the 16S rRNA gene using MiSeq Illumina technology. QIIME and the Phyloseq R package was used for curation of data and in-depth microbiota analyses. This study compared the microbiota of several different donors. Moreover, the authors compared the microbiota of FMT recipients during the time course of the study following FMT. Finally, responders and non-responders microbiota were compared. Microbiota structure analyses utilizing

Table 1. Microbiome outcomes *(Continued)*

			ta composition with more diversity in the treatment group compared with the placebo group at week 6 vs baseline (P= 0.02, Mann-Whitney U test)"	mon donors (A and B) used in this study." • *Lachnospiraceae* • *Blautia* • *Faecalibacterium* • *Ruminococcaceae* • *Clostridiaceae* • *Subdoligranulum* • *Bacteroides* • *Prevotella* • *Lachnospira* • *Clostridiales* • *Erysipelotrichaceae* • *Ruminococcaceae* • *Oscillospira* • *Ruminococcus* • *Eubacterium*	the Bray-Curtis dissimilarity metric demonstrated that patients receiving FMT showed a change in their microbiota following FMT. This shift led to microbiota that was more similar to the donor microbiota over time. Moreover, the authors observed a difference in the microbiota between responders and non-responders**.** Interestingly, two donors were associated with more successful FMTs and these individuals harbored increased *Ruminococcus* and Lachnospiraceae and decreased abundance of *Streptococci* and *Escherichia*."
Paramsothy 2017	UC	MiSeq Illumina	"Increased α diversity was specific to faecal microbiota transplantation; three patients allocated placebo who met criteria for the primary outcome showed no change in diversity. Faecal microbiota transplantation therapy was associated with a significant increase in α diversity, which was durable 8 weeks af-	Not reported	"Several microbial taxa were associated with remission after double-blind faecal microbiota transplantation (*Barnesiella* spp, *Parabacteroides* spp, *Clostridium* cluster IV, and *Ruminococcus* spp) and after open-label faecal microbiota transplantation (*Blautia* spp, *Dorea* spp, *Ruminococcus*, and *Clostridium* cluster XVIII). Both *Fusobacterium* spp and *Sutterella* spp were associated consistently with no remission in patients who had double-blind and open-label fae-	"The study sequenced the V1 through V3 region of 16S rRNA gene using MiSeq Illumina technology. Microbiota analysis and curation were performed utilizing mothur, and altered members of the microbiota were identified using the biomarker discovery algorithm linear discriminant analysis Effect Size (LEfSe). Shotgun metagenomics sequencing was also performed in subsequent follow-up studies. The authors performed RNA extraction to ensure that bacteria detected in their analyses were live and active bacteria. Microbiota analyses were done on 70 patients (314 fecal samples) and 113 donor fecal samples; 55 individual donors were used and 58 batched donor samples. The microbiota of donors was analyzed along with patients receiving individual or batched dFMTs. For recipients, the microbiota composition was analyzed prior to and following FMT, and patients were binned into responders and non-responders. The microbiota of batched donor samples showed higher phylogenetic diversity than individual donors, and overall donor samples had higher diversity than baseline samples from pa-

Table 1. Microbiome outcomes *(Continued)*

			ter therapy completion. patients achieving the primary outcome seemed to have higher baseline microbial diversity before faecal microbiota transplantation and a greater increase in α diversity with faecal microbiota transplantation."		cal microbiota transplantation."	tients with IBD. After four and eight weeks, patients receiving FMT saw an increase in phylogenetic diversity in the microbiota compared to baseline. LEfSe analysis determined that 295 microbial taxa were differentially altered following transplant and 78 of these members showed high linear discriminant analysis scores (>3). Interestingly, regardless of clinical outcome, the authors observed decreased abundance of operational taxonomic units (OTUs) affiliated with the *Bacteroides* genera and increased abundance of OTUs affiliated with the *Prevotella* genera. The authors further describe that FMT was associated with increased diversity in all patients. Importantly, recipients who achieved a successful primary outcome had greater richness in OTUs at baseline, during fecal microbiota transplantation and at 8 weeks. Finally, the authors performed LEfSe analysis comparing patients who responded to non-responders; 87 Taxa were associated with primary outcomes in masked patients and 46 were associated with open-label patients. Remission was associated with taxa with *Barnsiella*, *Parabacteroides*, *Clostridium* cluster IV and *Ruminococcus.* Moreover, Fusobacterium and *Sutterella* were associated with a lack of remission in all patients."
Rossen 2015	UC	Human Intestinal Tract chip (HITchip) phylogenetic microarray	"At 12 weeks after treatment, 16 samples were available from FMT-D patients and 18 FMT-A patients. The diversity index of responders in both groups increased significantly (from S = 5.61 ± 0.29 to S = 5.83 ± 0.15 in responders to FMT-D (P = .06) and	Not reported	"Redundancy analysis showed that the microbiota composition of responders in the FMT-D group shifted from overlap with nonresponders at baseline to healthy donors at week 12. This shift was mainly explained by a regain of *Clostridium* clusters IV, XIVa, and XVIII, and reduction in Bacteroidetes. Notably, changes in *Faecalibacterium prausnitzii* (from 8.00 ±	"The study used the Human Intestinal Tract chip (HITchip) phylogenetic microarray, to perform microbiome diversity analysis. The study compared microbiota profiles of donors and patients with UC. Moreover, this study characterized microbiota profiles prior to and following FMT with donor stool or FMT with autologous stool. Finally, responders and non-responders for each FMT group were compared. Microbiome analysis with HITchip showed that microbiota profiles and diversity indexes of patients with UC was different than healthy donors. This was highlighted by enrichment in taxa belonging to the Bacteroidetes, Proteobacteria, *Bacilli*, and *Clostridium* clusters IX and XI and decreased levels of *Clostridium* IV, IXIVa, and XVIII compared to donors." "Following FMT with both donor stool and autologous stool, diversity increased in responders and

Table 1. Microbiome outcomes *(Continued)*

			from S = 5.81 ± 0.07 to S = 6.03 ± 0.14 in responders to FMT-A (P = .01)). The increase in diversity at week 12 could be attributed to an increase in both richness and evenness in all responders. Diversity in nonresponders did not change over time."		5.72 at baseline to 8.37 ± 5.10 at week 12; P = .68), which belongs to *Clostridium* cluster IV, did not play a role in this increased abundances in our study subjects. Responders to FMT-A shifted away from non-responders, but in a different direction than responders to FMT-D. This shift was mostly associated with an increase in abundance of Bacilli, Proteobacteria, and Bacteriodetes."	did not increase in non-responders. Shifts in the community taxa of responders could be observed in both donor and autologous FMTs. However, the shift between these two responder groups was distinct. Microbiota of FMT responders from donors were highlighted by increases in taxa belonging to the *Clostridium* IV, XIVa, and IVIII groups. Alternatively, the microbiota of responders that received autologous FMT was highlighted by an increase in *Bacilli*, *Proteobacteria*, and *Bacteroidetes*. Correlation analysis further revealed that microbiota of responding recipients showed increased similarity to donor microbiota following FMT. Importantly, no shifts in microbiota were observed in non-responders."
Costello 2019	UC	Not reported	Not reported	Not reported	Association with increased abundance following dFMT: • *Peptococcus niger* • *Faecalicoccus pleomorphus* • *Olsenella sp.* • *Acidaminococcus intestini* • *Senegalimassilia anaerobia* • *Prevotella copri* • *Methanobrevibacter smithii* • *Clostridium methylpentosum* • *Alistipesindistinctus* • *Slackia isoflavoniconvertens* • *Odoribacter splanchnicus*	Studied changes in fecal-associated microbiota following FMT by 16S ribosomal RNA sequencing, stratified by both change in total Mayo score following FMT and randomization. The durability of engraftment of these species acquired following dFMT was assessed by quantifying these species at 12 months. The V4 hypervariable region of the 16S ribosomal RNA gene was amplified and raw sequencing data processed into operational taxonomic units at 97% similarity in stool samples from individual donors, pooled stool batches, and FMT recipients taken at weeks 0, 4, 8, and 52. At baseline, blended donor stool showed the most microbial diversity (measured by operational taxonomic units) followed by individual donor stool then stool of patients with UC. Diversity increased following dFMT compared with aFMT at weeks 4 and 8. There was no significant association between change in total Mayo score following dFMT and baseline diversity (β = 0.6 [95% CI, −4.8 to 5.9]; P = .84) nor change in diversity at week 8 (β = −20.3 [95% CI, −50.7 to 11.2]; P = .23). The 10 bacteria and the archaea *Methanobrevibacter smithii* whose

Table 1. Microbiome outcomes *(Continued)*

					Association with reduced abundance following dFMT: • *Anaerostipescaccae* • *Gordonibacter pamelaeae* • *Clostridium aldenense*	increased abundance were most strongly associated with dFMT at weeks 4 and 8 were all anaerobic. The abundance of these organisms remained relatively stable from weeks 4 to 8; however, by 12 months, there was variability in abundance of many of these organisms. Increased abundance of *Anaerofilum pentosovorans* and *Bacteroides coprophilus* species was strongly associated with disease improvement following dFMT.
Crothers 2021	UC	MoBio Powersoil 96 kit	"Measures of microbial alpha diversity (Shannon index) between subjects and donor samples, and to their own baseline samples, were calculated. No difference in alpha diversity was observed between treatment groups at baseline. FMT did not increase alpha (Shannon) diversity in recipients but did lead to community-level changes in the gut microbiota creating measurable similarity (beta diversity, Jensen-Shannon divergence index) between FMT	"Measures of microbial beta diversity (Jensen-Shannon divergence) between subjects and donor samples, and to their own baseline samples, were calculated. No difference in beta diversity was observed between treatment groups at baseline. FMT did not increase alpha (Shannon) diversity in recipients but did lead to community-level changes in the gut microbiota creating measurable similarity (beta diversity, Jensen-Shannon divergence index) between FMT	"Across all time points, stool samples were dominated at the phylum level by Firmicutes, and Bacteroidetes, which accounted for 88.90% of all sequence reads. Bacteria present at lower proportions included Proteobacteria, and Actinobacteria, accounting for 6.9% and 4.0% of total reads, respectively. At the genus level, samples were dominated by Clostridiales and Bacteroidales, with a lower proportion of Burkholderiales, Bifdobacteriales, Selenomonadlaes, Enterobacteriales, Lactobacillales observed at various time points."	DNA extraction was performed using the MoBio Powersoil 96 kit with minor modifications and 16S rRNA gene libraries targeting the V4 region of the 16S rRNA gene were prepared. Each sample was given a unique reverse barcode and replicates were then pooled, cleaned and normalized prior to sequencing on an Illumina MiSeq 300. Raw sequence reads were then processed and OTU calling performed using the Qiime2—dada pipeline. Measures of microbial alpha diversity (Shannon index) and beta diversity (JensenShannon divergence) between subjects and donor samples, and to their own baseline samples, were calculated. No difference in alpha or beta diversity was observed between treatment groups at baseline. FMT did not increase alpha (Shannon) diversity in recipients but did lead to community-level changes in the gut microbiota creating measurable similarity (beta diversity, JensenShannon divergence index) between FMT subjects and their donor. This convergence, which we termed 'Donor Divergence Index', remained statistically significant through 8 weeks of dosing weeks following cessation of oral cFMT therapy

Table 1. Microbiome outcomes *(Continued)*

			subjects and their donor."	subjects and their donor."		
Fang 2021	UC	Illumina MiSeq	"Alpha diversity index calculation was performed with abundance indexes (Chao1 and ACE) and diversity indexes (Shannon and Simpson). The alpha diversity index of the fecal microbiota in active UC patients, healthy donors and patients after FMT treatment showed no significant difference."	"The beta diversity of the samples was measured using the Bray-Curis distance based on an evenly rarefied OTU abundance table. Statistical differences in measured β-diversity metrics across groups were determined using PERMANOVA with 999 permutations, using adonis in the R package vegan. Shared OTUs were calculated and visualized using the R package Venn diagram. To measure the level of similarity between gut microbial communities, analysis of similarities (ANOSIM) was per-	"The taxonomic profiles showed that the phyla Bacteroidetes, Firmicutes and Proteobacteria were dominant bacteria in the fecal microbiota of healthy donors and active UC patients. The relative abundance of Bacteroidetes was significantly decreased and that of Proteobacteria was significantly increased in active UC patients. Firmicutes showed no significant changes among healthy donors and active UC patients. Compared with healthy donors, patients with active UC showed an increased ratio of Firmicutes and Bacteroidetes. Single fresh FMT could significantly reconstruct the dysbiotic gut microbiota and maintain stability, with an increased proportion of Bacteroidetes and a decreased proportion of Proteobacteria. At the genus level, some specific bacterial biomarkers were identified. The relative abundance of *Es-*	"The gut microbiota was assessed by 16S ribosomal RNA sequencing. The V3–V4 hypervariable region of the 16S rRNA gene was amplified via high-throughput sequencing on the Illumina MiSeq platform, and the raw sequencing data from stool samples from individual donors and FMT recipients pre- and post-FMT treatment were processed into operational taxonomic units at 97% similarity." "The alpha diversity index of the fecal microbiota in active UC patients, healthy donors and patients after FMT treatment showed no significant difference. Principal coordinate analysis (PCoA) was used to indicate the similarity of the microbiota composition among samples. PCoA revealed that the gut microbiota in UC patients significantly deviated from that in healthy donors. Treatment with FMT improved the distance markedly, and the samples clustered tightly together, showing a trend similar to that of their related donors, but did not return to the level of healthy donors. The system clustering tree also indicated that a significant difference existed between UC patients and healthy donors. Linear discriminant analysis effect size (LEfSe) was used to identify differential microorganism communities between groups. The taxonomic profiles showed that the phyla Bacteroidetes, Firmicutes and Proteobacteria were dominant bacteria in the fecal microbiota of healthy donors and active UC patients. The relative abundance of *Bacteroidetes* was significantly decreased and that of *Proteobacteria* was significantly increased in people with active UC patients. Firmicutes showed no significant changes among healthy donors and active UC patients. Compared with healthy donors, patients with active UC showed an increased ratio of Firmicutes and Bacteroidetes. Single fresh FMT could significantly reconstruct the dysbiotic gut microbiota and maintain stability, with an in-

Table 1. Microbiome outcomes *(Continued)*

				formed. The data revealed an apparent separation in the structure of the gut microbiota in each group. Principal coordinate analysis (PCoA) was used to indicate the similarity of the microbiota composition among samples. PCoA revealed that the gut microbiota in people with UC significantly deviated from that in healthy donors. Treatment with FMT improved the distance markedly, and the samples clustered tightly together, showing a trend similar to that of their related donors, but did not return to the level of healthy donors."	*cherichia* was significantly increased in active UC patients and was significantly decreased after FMT. A high abundance of Prevotella was found in the donor gut. FMT-treated patients who achieved remission also tended to have a higher abundance of Prevotella. Taxonomic phylum profiles of the gut microbiota among healthy donors, active UC patients and patients post-FMT treatment: • *Bacteroidetes* • *Firmicute* • *Proteobacteria* *Prevotella* was the dominant genus in the gut microbiota of the healthy donors, and the relative abundance of Prevotella increased after FMT treatment in active UC patients"	creased proportion of *Bacteroidetes* and a decreased proportion of *Proteobacteria*. At the genus level, some specific bacterial biomarker were identified. The relative abundance of *Escherichia* was significantly increased in active UC patients and was significantly decreased after FMT. A high abundance of Prevotella was found in the donor gut. FMT-treated patients who achieved remission also tended to have a higher abundance of *Prevotella*." "The PICRUSt tool was used to predict the functional profiles of gut microbiota with the predicted metagenome, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway functions were categorized using PICRUSt. PICRUSt predicted analyses found that the gut microbiota pathway functions showed that several pathways in gut microbiome among the donor and pre and post FMT treatment changed significantly, especially the pathways of pyruvate metabolism, sulfur metabolism, pantothenate and CoA biosynthesis, glyoxylate and dicarboxylate metabolism, synthesis and degradation of ketone bodies and other transporters were significantly different between the groups."
Pai 2021	UC	Not reported	Not reported	"Beta-Diversity trended higher from	"Several bacterial taxa were associated with achieving the	"Microbial community profiling in fecal samples was performed centrally at McMaster Children's Hospital. We extracted genomic DNA from patient

Table 1. Microbiome outcomes *(Continued)*

				baseline to week 6 in FMT vs placebo arms"	composite clinical outcome after multiple test correction, including *Alistipes* spp and *Escherichia* spp"	and donor stool samples using a protocol previously described" "Beta-Diversity trended higher from baseline to week 6 in FMT vs placebo arms. Several bacterial taxa were associated with achieving the composite clinical outcome after multiple test correction, including Alistipes spp and Escherichia spp"
Březina 2021	UC	Ion Torrent PGM platform with an Ion 316 Chip Kit v2 BC using an Ion PGM Hi-Q View Sequencing Kit (ThermoFisher Scientific)	"The analysis of bacterial diversity was assessed through alpha diversity (Chao1, evenness, Faith's phylogenetic diversity, and Shannon index)." "Alpha diversity, which evaluates the species richness and evenness; Faith's phylogenetic distance; and Shannon diversity showed no significant differences between the FMT and 5-ASA treatment groups, nor between the responder and non-responder subgroups inside each cohort."	"The analysis of bacterial diversity was assessed through beta diversity (Jaccard's distance metric) using the Qiime2 pipeline." "Beta diversity, which evaluates the similarity of bacterial communities among samples, was assessed using Jaccard's non-phylogenetic distance matrix. As early as 2 weeks after the therapy initiation, the authors could differentiate responders from non-responders in both the FMT group (PERMANOVA p = 0.001, PERMDISP p = 0.100) and 5-ASA group (PER-	"In total, 9 phyla, 142 genera, and 184 species were detected in the samples of UC patients. Firmicutes (41–94%) were detected as the dominant phylum in all samples, regardless of treatment, except for one sample (19%) from the FMT group at the baseline, in which Proteobacteria (52%) were flourishing. The second most abundant were Actinobacteria (1–38%), and/or Bacteroidetes (1–37%). Firmicutes were mainly represented by the order *Clostridiales*; *Bacteroidetes* were mainly represented by the order *Bacteroidales*; and in *Actinobacteria*, the order *Bifidobacteriales* predominated. Other phyla including *Fusobacteria*, *Tennericutes*, *Acidobacteria*, *Planctomyceles*, and TM7 were detected with low frequencies (≤0.4%). The	"The amplification of the bacterial variable V4-V5 region of 16S rRNA was performed according to Fliegerova et al using EliZyme HS Robust MIX Red (Elisabeth Pharmacon) and 10 µM of each primer (forward: GGATTAGATACCCTGGTAGT, reverse: CACGACACGAGCTGACG). The thermal cycling conditions included initial denaturation for 10 min at 95 ◦C followed by 30 cycles of 30 s at 95 ◦C, 30 s at 57 ◦C, and 30 s at 72 ◦C. PCR amplicons (≈300 bp [base pairs]) were purified and libraries were prepared using the NEBNext Fast DNA Library Prep Set for Ion Torrent (New England BioLabs) and Ion Xpress Barcode Adapters 1–96 Kit (ThermoFisher Scientific). Libraries were consequently pooled, with their equimolar concentration determined with a KAPA Library Quantification Kit (KAPA Biosystems). The sequencing template was prepared in a One Touch 2 instrument using an Ion PGM OT2 HiQ View Kit (ThermoFisher Scientific). HTS was performed in an Ion Torrent PGM platform with an Ion 316 Chip Kit v2 BC (ThermoFisher Scientific) using an Ion PGM Hi-Q View Sequencing Kit (ThermoFisher Scientific), according to the manufacturer's protocols" "A non-significant increase was detected in Shannon diversity index, for both responders and non-responders, 2 weeks after both therapy types compared to the baseline (Figure S2). A higher Shannon index was still observed when more samples from different sampling points after therapy initiation were included in the calculation, indicating that FMT and 5-ASA can, to a certain extent, influence the microbial alpha diversity of UC patients."

Table 1. Microbiome outcomes *(Continued)*

				MANOVA p = 0.003, PERMDISP p = 0.099)."	donor stool was dominated by Firmicutes, with a prevalence of the families *Lachnospiraceae* (67%) and *Ruminococcaceae* (17%). The relative abundance of *Actinobacteria* (1%) and *Bacteroidetes* (2%) was quite low, represented by the family *Coriobacteriaceae* and the families *Prevotellaceae* and *Bacteroidaceae*, respectively. *F. prausnitzii* was present with a frequency of 3% in the stool of the donor."	
Sarbagili Shabat 2022	UC	Next-generation sequencing libraries were prepared using Nextera DNA library prep [Illumina] and sequenced on a NovaSeq sequencing platform [Illumina]	Did not detect any postdiet microbial shift in alpha diversity in FMT donors.	Not reported	Not reported	The authors performed donor microbiome analysis following and did not report on the recipient's. "Metagenomic DNA was purified using DNeasy PowerMag Soil DNA extraction kit [Qiagen] optimised for Tecan automated platform. Next-generation sequencing [NGS] libraries were prepared using Nextera DNA library prep [Illumina] and sequenced on a NovaSeq sequencing platform [Illumina]. Sequencing was performed with 75-bp single-end reads with the depth of 10 million reads per sample. We filtered metagenomic reads containing Illumina adapters, filtered low quality reads, and trimmed low-quality read edges. We detected host DNA by mapping with Bowtie to the human genome with inclusive parameters, and removed those reads. Bacterial relative abundance [RA] estimation was performed by mapping bacterial reads to species-level genome bins [SGB] representative genomes. We selected all SGB representatives with at least 5 genomes in a group, and for these representatives' genomes kept only unique regions as a reference dataset. Mapping was performed using Bowtie and abundance was estimated by calculating the mean cover-

Table 1. Microbiome outcomes *(Continued)*

						age of unique genomic regions across the 50% most densely covered areas. Bacterial richness declined in 5/7 donors examined. They did not detect any post-diet microbial shift, including in alpha diversity."
Sokol 2020	CD	MiSeq Illumina	"The authors observed a significant increase in alpha diversity following FMT but not sham"	"The similarity of the fecal microbiota samples was assessed using the Sorensen similarity index (Sorensen similarity index = [1 – Bray Curtis dissimilarity index])." "No statistically significant difference was observed between the FMT and sham group at week 6."	"The authors identified several taxa associated with flare, including many taxa belonging to the Gammaproteobacteria class and the Clostridiales order comprising Ruminococcus gnavus. In addition, we also observed taxa associated with maintenance of remission, such as Ruminococcaceae, Coprococcus, and Desulfovibrio genus."	"The similarity of the fecal microbiota samples was assessed using the Sorensen similarity index (Sorensen similarity index = [1 – Bray Curtis dissimilarity index])" "We observed a significant increase in alpha diversity following FMT but not sham" "We then looked at the similarity between donor and recipient microbiota using the Sorensen index. No statistically significant difference was observed between the FMT and sham group at week 6."

aFMT: autologous fecal microbiota transplantation; CD: Crohn disease; CRP: C-reactive protein; dFMT: donor fecal microbiota transplantation; EQ-5D: EuroQol Five-Dimensions Questionnaire; ESR: erythrocyte sedimentation rate; FMT: fecal microbiota transplantation; IBDQ: Inflammatory Bowel Disease Questionnaire; SCCAI: Simple Clinical Colitis Activity Index; UC: ulcerative colitis.

APPENDICES

Appendix 1. Search strategies

MEDLINE Ovid (1946 to 22 December 2022)

1. exp Inflammatory Bowel Diseases/

2.(Inflammatory bowel disease* or IBD).tw,kw.

3.(Crohn* or ileitis or regional enteritis or ileocolitis or granulomatous colitis orgranulomatous enteritis).tw,kw.

4.(colitis or proctocolitis or proctosigmoiditis or proctitis or rectosigmoiditis or rectocolitis orcolorectitis or coloproctitis).tw,kw.

5. or/1-4

6. Fecal Microbiota Transplantation/

7. (bacteriotherap* or colonic restoration or flora reconstitution or RBX2660).tw,kw.

8. FMT.ab.

9. ((Fecal or Faecal or microbiota or microflora or feces or faeces or stool) adj3(transplant* or transfus* or implant* or instillation or donor* or enema or reconstitution orinfusion* or therap* or transfer* or treat*)).tw,kw.

10. ((bacteria or bacterio*) adj2 (transplant* or transfus* or implant* or instillation orinstillment or donor* or enema or reconstitution or infusion* or therap* or transfer* or treat*)).tw,kw.

11. or/6-10 12. 5 and 11

13. limit 12 to dt=202201115-20221222

Embase Elsevier (1974 to 22 December 2022)

#18 #17 AND [15-01-2022]/sd NOT [22-12-2022]/sd

#17 #6 AND #16

#16 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15

#15 'fecal bacteriotherap*':ti,ab,kw

#14 'fecal transfusion*':ti,ab,kw

#13 'fmt':ti,ab,kw

#12 'stool transplant*':ti,ab,kw

#11'faecal microbiome transplant*':ti,ab,kw

#10 'fecal microbiome transplant*':ti,ab,kw

#9 'faecal microbiota transplant*':ti,ab,kw

#8 'fecal microbiota transplant*':ti,ab,kw

#7 'fecal microbiota transplantation'/exp

#6 #1 OR #2 OR #3 OR #4 OR #5

#5 'inflammatory bowel disease*':ti,ab,kw

#4 'ibd':ti,ab,kw

#3 'ulcerative colitis*':ti,ab,kw

#2 crohn*:ti,ab,kw

#1 'inflammatory bowel disease'/exp

Cochrane Central Register of Controlled Trials (CENTRAL; Issue 11, 2022) in the Cochrane Library (searched 22 December 2022)

#1 MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees

#2 Crohn*

#3 Ulcerative NEXT colitis*

#4 IBD

#5 #1 OR #2 OR #3 OR #4

#6 MeSH descriptor: [Fecal Microbiota Transplantation] explode all trees

#7 Fecal NEXT microbiota NEXT transplant*

#8 Faecal NEXT microbiota NEXT transplant*

#9 Fecal NEXT microbiome NEXT transplant*

#10 stool NEXT transplant*

#11 FMT

#12 Fecal NEXT transfusion*

#13 Fecal NEXT bacteriotherap*

#14 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

#15 #5 AND #14

International Standard Registered Clinical/Social Study Number registry (ISRCTN; searched 22 December 2022)

1. Fecal transplantation AND Inflammatory Bowel Disease

2. Fecal transplant AND Inflammatory Bowel Disease

3. Fecal microbiota transplant AND Inflammatory Bowel Disease

WHAT'S NEW

Date	Event	Description
25 April 2023	New search has been performed	Additional studies added in this update
25 April 2023	New citation required and conclusions have changed	We added 7 studies with 222 participants. The certainty of evidence changed.

HISTORY

Protocol first published: Issue 8, 2017
Review first published: Issue 11, 2018

CONTRIBUTIONS OF AUTHORS

Design of the review: AI, MN, SA, OG

Co-ordination of the review: AI

Search and selection of studies for inclusion in the review: AI, NP, MZ, NZM

Collection of data for the review: AI, NP, MZ

Assessment of the risk of bias in the included studies: AI, NP, MZ

Analysis of data: AI, NP, MZ, NZM

Assessment of the certainty of the evidence: AI

Interpretation of data: AI, NZM, ETS, MN, SA, OG

Writing of the review: AI, ETS, NZM, MZ, NP, MN

DECLARATIONS OF INTEREST

AI: none.

NP: none.

MZ: none.

NZM: none.

ETS: none.

OG: none.

SA: none.

MN: none.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other

  No internal support was obtained for this review

External sources

- New Source of support, Other

  No external support was obtained for this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between previous version and current version of the review

The following are differences between the previous version of this review (Imdad 2018) and the current version.

Literature search

In the present update, we performed no additional search for conference proceedings as Embase has covered proceedings from the relevant conferences since 2010.

The search strategies were substantially revised for this update, in that more terms related to FMT were added to increase sensitivity. The updated search strategies are available in Appendix 1.

We had searched the Cochrane IBD Group Specialized Register in the previous version but not in this updated version, as the Register is not available for updated searches.

Types of studies

In the previous version, we aimed to include non-randomized studies with comparator arms, but none of the available studies met these criteria. In this version, we did not consider any non-randomized studies with comparator arms.

Comparators

We updated the comparators in the 'Types of interventions' section from the first version to this version as two of the included studies used autologous FMT as comparators (Costello 2019; Rossen 2015).

Outcomes

The primary outcomes in the previous version were considered at weeks 8 and 12 of follow-up. We kept these same follow-up intervals but also included the data at longest follow-up, as the follow-up intervals were not consistent across all included studies.

We added maintenance of remission in UC or CD at longest follow-up as a primary outcome.

We considered the secondary outcomes of clinical response, endoscopic remission, and endoscopic response at longest follow-up.

One of the secondary outcomes was related to alpha diversity of the microbiome. Studies did not report this outcome consistently, so we reported the microbiome outcomes subjectively in a table.

Summary of findings tables

We created four separate summary of findings tables to address induction and maintenance of remission in UC and CD. This decision was based on the notion that conduct of intervention for induction and maintenance might differ and that the profile of outcomes (e.g. serious adverse events, quality of life) might differ when FMT is used for induction versus maintenance of remission.

We prioritized five outcomes to be included in the summary of findings tables for this review. These included induction of clinical remission, serious adverse events, any adverse events, endoscopic remission, and quality of life. We removed the following outcomes that were included in the summary of findings table in the last version: clinical response and endoscopic response.

Subgroup and sensitivity analyses

In the previous version of this review, we planned for subgroup analyses based on age of participants and frequency of FMT administration; however, there were not enough studies available to perform these subgroup analyses. In this update, we attempted subgroup analyses based on these two variables.

Given that we performed an ITT analysis, which included randomized participants who may not have received the intervention and completed follow-up, we also performed post-hoc available case analyses for the primary outcomes in which only those participants were included who completed follow-up.

We updated the post-hoc analysis conducted in the last version of the review for studies that defined induction of remission using a combination of clinical and endoscopic/histologic criteria.

INDEX TERMS

Medical Subject Headings (MeSH)

*Colitis, Ulcerative [drug therapy]; *Crohn Disease [drug therapy]; Dysbiosis; Fecal Microbiota Transplantation; *Inflammatory Bowel Diseases; Quality of Life; Remission Induction

MeSH check words

Adult; Child; Humans