ATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: GID-MT566 Faecal microbiota transplant for recurrent Clostridioides difficile infection

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **EAC assessment report Appendix 1& 2 -** Appendices to the independent report produced by an external assessment centre
3. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
4. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
5. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **Patient Expert Statement –** Patient Expert **s**tatement submitted on the technology.
8. **Patient Organisation Submission -** Patient organisation submission submitted on the technology.

9. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
10. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Assessment report: Faecal microbiota transplant for recurrent *Clostridioides difficile* infection

EAC team:

Project lead(s): Katy Wilson (Systematic reviews), Hayden Holmes (Economic model)

Information specialist: Mick Arber

Clinical evidence reviewer Jacoby Patterson, Lavinia Ferrante di Ruffano

Economic evidence reviewer: Chris Bartlett, Laura Kelly

Cost analysis: Hayden Holmes, Laura Coote, Angel Varghese, Laura Kelly

EAC sign-off: Matthew Taylor

Version number	Brief description of changes	Author/reviewer (e.g. J Smith)	Date (DD/MM/YY)	Date sent to NICE (if applicable)
1.0	Draft MT566 complete report	L Ferrante di Ruffano, J Patterson, C Bartlett, L Kelly, K Bartlett, M Arber, A Varghese, L Coote, H Holmes, K Wilson, M Taylor	07/01/2022	07/01/2022
2.0	Clinical Effects and Safety Review: NICE comments addressed Economic evidence: additional detail cost-effectiveness modelling methods, updated results.	L Ferrante di Ruffano, J Patterson, C Bartlett, L Kelly, K Bartlett, M Arber, A Varghese, L Coote, H Holmes, K Wilson, M Taylor	01/02/2022	01/02/2022
3.0	Report updated to reflect Fact Check responses	L Ferrante di Ruffano, J Patterson, C Bartlett, L Kelly, K Bartlett, M Arber, A Varghese, L Coote,	22/02/2022	22/02/2022

Version number	Brief description of changes	Author/reviewer (e.g. J Smith)	Date (DD/MM/YY)	Date sent to NICE (if applicable)
		H Holmes, K Wilson, M Taylor		
4.0	Additional expert engagement for Section 9.2	L Ferrante di Ruffano, J Patterson, C Bartlett, L Kelly, K Bartlett, M Arber, A Varghese, L Coote, H Holmes, K Wilson, M Taylor	03/03/2022	03/03/2022

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

[MT566 Faecal microbiota transplant for recurrent Clostridioides difficile infection]

External Assessment Centre report

Produced by: York Health Economics Consortium

Authors:

Lavinia Ferrante di Ruffano, Senior Research Consultant, YHEC

Jacoby Patterson, Associate Research Consultant, YHEC

Chris Bartlett, Senior Research Associate, YHEC

Laura Kelly, Research Assistant, YHEC

Karen Bartlett, Research Assistant, YHEC

Mick Arber, Senior Information Specialist, YHEC

Angel Varghese, Research Consultant, YHEC

Laura Coote, Research Consultant, YHEC

Hayden Holmes, Project Director, YHEC

Katy Wilson, Project Director, YHEC

Correspondence to:

Hayden Holmes
York Health Economics Consortium
Enterprise House
University of York
YORK
YO10 5NQ
Tel: [redacted]
Email: [redacted]

Date completed: 03/03/2022

Contains confidential information: no

Number of attached appendices: 7

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to evaluate the case for adoption of the technology in the NHS. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

Acknowledgements

The authors would like to thank the following expert advisers who were appointed by NICE and provided advice about CDI, FMT and the use of FMT in the UK:

- Professor Tariq Iqbal (TI), Consultant Gastroenterologist, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust; and Director of University of Birmingham Microbiome Treatment Centre

- Dr Horace Williams (HW), Consultant Gastroenterologist, St Mary's Hospital, Imperial College Healthcare NHS Trust
- Dr Benjamin Mullish (BM), NIHR Academic Clinical Lecturer, Department of Metabolism, Digestion and Reproduction, Imperial College London; and Specialty Registrar, Gastroenterology and Hepatology, St Mary's Hospital, Imperial College Healthcare NHS Trust
- Professor Yashwant Mahida (YM), Professor of Medicine, Honorary Consultant Physician and Gastroenterologist, Queen's Medical Centre, Nottingham University Hospitals NHS Trust
- Professor Peter Hawkey (PH), Professor Emeritus of clinical and Public Health Microbiology, Institute of Microbiology and Infection, University of Birmingham; and Locum Consultant Microbiologist, NHS Grampian; and Director Modus Medica Ltd
- Dr Simon Goldenberg (SG), Consultant Microbiologist and Infection Control Doctor, Guy's and St Thomas' NHS Foundation Trust
- Dr Tom Lee (TL), Consultant Gastroenterologist, Northumbria Healthcare NHS Foundation Trust; and Associate Clinical Lecturer, Population Health Sciences Institute, Newcastle University.

TI, BM, YM, SG and PH declared the following interests:

TI declared non-financial professional interests as FMT lead for UK Gut Microbiome for the Health Expert Panel, and as Director of the Birmingham Microbiome Treatment Centre (both from 2016); and direct financial interests as member of an advisory board for Ferring Pharmaceuticals who have an FMT product to prevent (not treat) CDI, which is not licensed in the UK or Europe (2019 only).

BM declared direct financial interests for receiving consultancy fees from Finish Therapeutics (from 2020) and Ferring Pharmaceuticals (2021 only).

YM declared non-financial professional interests from undertaking a feasibility study to investigate bile acid supplement in the prevention of CDI recurrence (continuing); and indirect interest from obtaining approval from the Nottingham University Hospitals NHS Trust for carrying out FMT (product to be obtained from Birmingham Microbiome Treatment Centre).

SG declared direct financial interests for advisory board membership of Enterobiotix (from 2015) and Tillotts (from 2021), and for receiving research funding from Shionogi (2019 to 2020).

PH declared non-financial professional interests as Director of the Birmingham Microbiome Treatment Centre (2016 to 2020).

Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
AE	Adverse event
AEEC	Attaching and Efficacing *E. coli*
Anti-HBc	Hepatitis B core antigen test
Anti-HCV	Hepatitis C virus antibody test
BID	Bis in die (“twice a day”)
BMI	Body Mass Index
BSG	British Society of Gastroenterology
CD	*Clostridioides difficile*
CDI	*Clostridioides difficile* Infection
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CJD	Creutzfeldt-Jakob disease
CMV	Cytomegalovirus
CPCI-S	Conference Proceedings Citation Index-Science
CPO	Carbapenemase-producing organisms
CRD	Centre for Reviews and Dissemination
CRE	Carbapenem-resistant Enterobacteriaceae
CRP	C-reactive protein
DHSC	Department of Health and Social Care
DSA	Deterministic Sensitivity Analysis
EAC	External Assessment Centre
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr Virus
E. coli	*Escherichia coli*
EED	Economic Evaluation Database
EIA	Enzyme Immunoassay
EIEC	Enteroinvasive *E. coli*
EPB	Enteropathogenic bacteria
EPEC	Enteropathogenic *E. coli*
ESBL	Extended-spectrum beta-lactamase
ETEC	Enterotoxigenic *E. coli*
EUCTR	European Union Clinical Trials Register
F-CDI	Fulminant *Clostridioides difficile* Infection
FC	Fulminant Colitis
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FMT	Faecal Microbiota Transplantation
GI	Gastrointestinal
HAV	Hepatitis A Virus

Term	Definition
HBsAg	Hepatitis B surface antigen test
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIS	Healthcare Infection Society
HIV	Human immunodeficiency virus
HIV ab	Human immunodeficiency virus antibodies
HTLV	Human T-cell lymphotropic virus
IBD	Inflammatory bowel disease
ICER	Incremental Cost Effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IQR	Interquartile range
ITT	Intention to treat
MDRGN	Multidrug resistant Gram-negative (bacteria)
MDRO	Multidrug resistant organism
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention to treat
MTAC	Medical Technologies Advisory Committee
MTEP	Medical Technologies Evaluation Programme
MRSA	Methicillin-resistant *Staphylococcus aureus*
NCT	National Clinical Trial
ND	Nasoduodenal
NDT	Nasoduodenal Tube
NG	Nasogastric
NGT	Nasogastric Tube
NI	No information
NJ	Nasojejunal
NJT	Nasojejunal Tube
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
PCR	Polymerase chain reaction
PICO	Population intervention comparator outcome
pit-hGH	Human-derived pituitary growth factor
PMC	Pseudomembranous colitis
PP	Per protocol

Term	Definition
PPI	Proton pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-adjusted life years
QD	Quaque die (“once a day”)
QID	Quarter in die (“four times each day”)
QOL	Quality of life
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
S-CDI	Severe *Clostridioides difficile* Infection
SC-CDI	Severe-complicated *Clostridioides difficile* Infection
SAE	Serious adverse event
SD	Standard deviation
SF-36	Short Form Survey 36 item
SOT	Solid organ transplant
STI	Sexually transmitted infections
STEC	Shigatoxin-producing *E. coli*
TID	Ter in die (“three times a day”)
VAS	Visual analogue scale
VCA	Viral capsid antigen
VDRL	Venereal disease reaction level
VRE	Vancomycin-resistant *Enterococci*
VTP	Vancomycin taper pulse
Vs	Versus
WHO	World Health Organization
WTP	Willingness to pay

Executive summary

Faecal microbiota transplant (FMT) is a procedure that transfers a sample of gut microorganisms from a healthy donor into the gastrointestinal (GI) tract of a person with *Clostridioides difficile* infection (CDI). Its aim is to re-establish a normal balance of healthy gut bacteria, and so resolve the overgrowth of *Clostridioides difficile* (CD) bacteria causing symptomatic infection (National Institute for Health and Care Excellence 2015). FMT is a variable technology, which can be delivered via several routes of administration and can be preceded by various treatments including short courses of antibiotics and bowel lavage. Preparation of FMT product is also not yet standardised, with faecal concentration and sample management differing according to institutional preference. FMT is innovative in its potential to treat and resolve CDI using gut bacteria rather than antibiotics, posing key benefits to patients and the healthcare system.

The External Assessment Centre (EAC) performed systematic searches to identify both clinical and economic evidence for the impact of using FMT to treat patients presenting with refractory CDI or a second or further CDI recurrence, compared with antibiotics currently recommended by NICE.

Only RCTs were considered eligible for clinical evidence. We identified 5 small RCTs (reported in 13 papers) in patients with recurrent CDI and treated with FMT delivered by nasoduodenal tube (NDT), enema, colonoscopy, or a mixture of colonoscopy and nasojejunal tube (NJT). No eligible RCTs evaluating FMT in patients with refractory CDI were identified. The EAC considered all 5 trials to align fully to the decision problem with the exception of the study populations which, in 3 trials, included a minority of patients with a first CDI recurrence and, so, were considered to partially meet the scope. Meta-analysis was not performed due to small patient numbers and considerable between-study variation across study populations, healthcare settings, FMT treatment methods (including the number of infusions administered), comparator antibiotic doses and regimens, and differences in outcome measurements and time points.

FMT was found to be superior to vancomycin (4 trials) and fidaxomicin (1 trial) for resolving CDI. FMT may lead to more immediate GI side effects than antibiotics. However, these are mild and transient in nature, and differences do not appear to persist beyond the end of treatments. The EAC noted no significant differences in serious adverse events (SAEs) and found no reports of procedural complications, such as perforation or aspiration. FMT did not impact on patient mortality. However, none of the trials were powered to detect a difference in mortality and short follow up does not allow inference beyond 3 months after treatment. Evidence was insufficient for all other outcomes specified in the decision problem.

Reliability of the RCT evidence is limited by small sample sizes, short follow up, risk of measurement bias and early study termination. The EAC considers the key weakness to be the limited generalisability of evidence to the UK NHS setting, with

trial populations appearing to be less frail, with fewer comorbidities, and less likely to be hospitalised. 3 trials also included patients presenting at their first CDI recurrence, and so overall the evidence is more likely to reflect patients who could be more responsive to treatment than patients commonly considered for FMT in the UK.

The EAC conducted an economic evaluation of FMT compared with standard treatments (vancomycin, fidaxomicin, and vancomycin taper pulse (VTP)) for people with a third CDI episode. Four routes of FMT administration were included: FMT via colonoscopy, enema, oral capsule and nasoduodenal tube.

A hypothetical cohort-based Markov model was developed comprising four health states. The cohort begins in the second recurrent CDI health state from which they are divided into the recovered, persistent CDI (if not resolved), or dead states. In subsequent cycles, people who have recovered can transition to the persistent and dead states, whilst people with persistent CDI can either recover or die. A 6-month time horizon was considered with 2-monthly cycles. Utility scores were also applied in addition to health state specific mortality.

All forms of FMT considered was found to be cost saving and cost-effective against all three comparators. FMT colonoscopy was associated with the least cost savings of all four FMT routes, with cost savings of £5,223 per person compared with VTP, whilst FMT oral capsules was estimated to be the most saving (savings of £13,134 against vancomycin).

There is substantial uncertainty in the data used to inform the model. All populations in the trials identified were less frail than those commonly observed in the English health system. Therefore, the effectiveness data for all parameters may be an overestimation, though this may have marginal impact on the incremental results.

Uncertainty was characterised through deterministic and probabilistic sensitivity analyses (DSA and PSA), and various scenario analysis. The cost of FMT colonoscopy and recurrence hospital costs are key drivers of the results. It is difficult to ascertain the true incremental costs and QALYs of all the treatments within this population due to variability in trial populations, protocols and outcomes. However, based on the various sensitivity analyses, all 4 routes of FMT has a high likelihood of being cost saving to the system. The base case results were robust against various scenarios which were conducted on adjusted treatment provision, such as with pre-antibiotic treatment and treatment with VTP if initial FMT failed. Whilst FMT is likely to be clinically superior to antibiotics alone, it is difficult to ascertain the extent it improves health outcomes. However, based on the PSA conducted which captured uncertainty in clinical parameters, all 4 routes of FMT are estimated to incur additional health benefits. Additionally, provided the NGT efficacy found from non-RCT literature and its comparability to cost of FMT enema, FMT via NGT is also likely to be cost saving against all three comparators.

Based on the evidence available and the economic evaluation conducted all 4 routes of FMT administration has the potential to be cost saving to the system, even with the uncertainty in FMT costs and extent of clinical impact.

1 Decision problem

NICE commissioned the EAC to perform a systematic review of the clinical and economic evidence, alongside a cost-consequence analysis, for the use of FMT in people with recurrent or refractory CDI. Since FMT is a medical procedure without a specific manufacturer there is no company submission, and the case for adopting FMT in the NHS has been reviewed solely by the EAC.

The EAC has not proposed any variation to the decision problem specified in the scope. However, we acknowledge that we cannot provide evidence on 2 outcomes because of lack of evidence.

Table 1 Decision Problem from Final Scope

Decision problem	Scope	Proposed variation (if any)	EAC comment
Population	For adults with a refractory CDI or a recurrent episode of CDI who have had 2 or more previous episodes	None	The EAC defined recurrent CDI population as 2 or more episodes at trial baseline.
Intervention	Faecal microbiota transfer (with or without prior treatment with bowel lavage or a short course of antibiotics or both) via different administration routes including: • lower gastrointestinal route (rectal enema, colonoscopy or flexible sigmoidoscopy) • upper gastrointestinal route (endoscopy or using a nasogastric tube, nasoduodenal tube or nasojejunal tube) • via oral capsules containing frozen FMT or freeze-dried (lyophilised) faecal material.	None	
Comparator(s)	Appropriate dosage and duration of oral antibiotics. NICE's guideline on CDI: antimicrobial prescribing recommends Vancomycin (up to 500 mg orally QID for 10 days) with or without Metronidazole (500 mg intravenously TID for 10 days) if first- and second-line antibiotics are ineffective or Vancomycin (125 mg orally QID for 10 days) or Fidaxomicin (200 mg orally BID for 10 days) for a further episode of CDI more than 12 weeks after symptom resolution (recurrence). VTP (125 mg Vancomycin every 6 hours for 10 days, then 125 mg once every 2 to 3 days for 3 weeks) could also be	None	

Decision problem	Scope	Proposed variation (if any)	EAC comment
	considered as a third-line treatment option for CDI.		
Outcomes	The outcome measures to consider include: • Measures of treatment effectiveness (outcomes from each administration route may be considered separately, if appropriate), for example: o Resolution of diarrhoea or other symptoms. o Negative stool test for CD toxin during follow up period (experts state that this measure may be unreliable for up to 3 months post procedure). o Recurrence of CDI leading to retreatment with antimicrobials and/or repeat FMT procedures. o Lack of resolution of CDI leading further gastrointestinal complications and/or surgical interventions (such as colectomy rates) and/or mortality. • Patient-reported outcomes, for example: o Patient acceptability of the treatment modalities. o Health related quality of life (preferably EQ-5D). • Measures of resource use, for example: o Length of hospital stay. o Follow-up GP, hospital visits or telephone consultations. o Follow up tests such as stool test for CD toxin o Pre, intra and post treatment usage of medicines or procedures including antimicrobials, anti-motility drugs, proton pump inhibitors, bowel lavage. o Resources associated with collection, preparation, and administration of FMT treatment. o NHS resource usage such as isolation rooms, barrier nursing, ward closures, theatre or procedure room times, follow up appointments.	Outcomes included: • Resolution of CDI (symptomatic or diagnostic or both). • Recurrence of CDI. • Treatment failure leading to downstream interventions (such as retreatment with antimicrobials, repeat FMT procedures, colectomy). • Procedural AEs (harmful impact of undergoing intervention procedures). • Overall treatment related AEs (harmful effects of treatment interventions) • Mortality. • Effectiveness outcomes (such as QALYs). • Total costs (currency) (intervention, comparator). • Incremental outcomes (ICERs (per QALY gained)). • Budget impact analyses. Patient reported and resource use outcomes for identification by the clinical effects and safety review to help inform cost consequence analysis: Patient reported outcomes: • Patient acceptability of treatment modalities. • Health related quality of life (EQ-5D). Resource use outcomes: • Length of hospital stay. • Follow up GP, hospital visits or telephone consultations. • Follow up tests such as stool testing for CD toxin. • Pre, intra and post treatment usage of medicines or	All outcomes included, some with greater resolution than specified in the scope. No evidence found for: patient acceptability or health related quality of life, resource use such as NHS resource usage and length of hospital stay.

Decision problem	Scope	Proposed variation (if any)	EAC comment
		procedures including antimicrobials, anti-motility drugs, proton pump inhibitors, bowel lavage. • Resources associated with the collection, preparation, and administration of FMT. • NHS resource usage such as isolation rooms, barrier nursing, ward closures, theatre or procedure room times, follow up appointments.	
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	None	No change
Subgroups	None identified	None identified	No change

Abbreviations: AE, adverse events; BID, Bis in die ("twice a day"); CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* infection; EAC, External Assessment Centre; EQ-5D, EuroQol-5 Dimension; FMT, Faecal Microbiota Transplantation; ICER, Incremental cost-effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, Quality-adjusted life year; QID, Quater in die ("four times each day"); TID, Ter in die (3 times daily); VTP, vancomycin taper pulse.

2 Overview of the technology

FMT is a procedure that transfers a sample of gut microorganisms, and the surrounding environment in which they are found, from a healthy donor into the GI tract of a person with CDI. The procedure's aim is to re-establish a normal balance of healthy gut bacteria, and so resolve the overgrowth of CD (National Institute for Health and Care Excellence 2015). FMT is not yet standardised beyond individual institutions, with variation in the quantification, preparation, and storage of donor material, as well as the mode of delivery into the intestine. The British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) have published recommendations for each of these procedures (Mullish 2018). Broadly, a fluid sample is obtained by diluting donor faecal matter with saline or water, homogenised, and filtered to remove large particles (Czepiel 2019). Samples can be used immediately or emulsified with a cryoprotectant and frozen for up to 6 months in aliquots of filtered suspension at -80°C (Mullish 2018). Donors, who may be related or unrelated to the recipient, should be screened for suitability to ensure the absence of transmissible disease and factors influencing the gut microbiota, including screening of blood and stool samples (Mullish 2018). The BSG and HIS also recommend repeat screening of donors and their samples at the time of each stool donation (Mullish 2018).

Other variations in preparation and treatment procedures include whether samples are processed aerobically or anaerobically, bowel cleansing prior to infusion (Cold 2021, Mullish 2018), other concomitant or preparatory treatments (such as prokinetics prior to upper GI administration, or loperamide following lower GI delivery), and dose of delivery.

The prepared faecal sample must be delivered to the intestine, which can be achieved in one of 3 ways:

- upper GI procedure (using either endoscopy, a nasogastric tube (NGT), nasoduodenal tube (NDT), or nasojejunal tube (NJT))
- lower GI procedure (using either colonoscopy, flexible sigmoidoscopy or rectal enema)
- oral capsules containing frozen or freeze-dried (lyophilised) faecal samples.

Each transplant of a faecal sample is referred to as an infusion, with repeated treatment episodes requiring further infusions. All 3 methods of delivery involve the insertion of healthy FMT product direct into the gut of the recipient, which is thought to treat CDI by restoring a healthy microbial community.

However, the precise mechanism by which CD bacteria are inhibited is an active subject of research, and so this similarity in underlying mechanism of action cannot be claimed definitively (Khoruts 2016, Mullish 2018). Existing reviews suggest there may be differences in efficacy and safety between the different modes of delivery (Baunwell 2020, Cold 2021, Pomares Bascunana 2021). Consequently, and in addition to the variability in multiple aspects of sample preparation and storage, evidence for the effectiveness of a single delivery method may not be generalisable to all 3 methods.

FMT is considered a medicinal product in the UK, and samples must be manufactured in accordance with Medicines and Healthcare products Regulatory Agency (MHRA) guidance for human medicines regulation. Pharmacy exemptions are permitted when FMT is administered to named patients within a single institution. However, distributors wishing to set up an external service are first legally required to contact the MHRA to obtain the relevant licenses (Mullish 2018).

The key innovation in FMT is its potential to treat and resolve CDI using gut bacteria, rather than antibiotics, posing key benefits to both patients, the healthcare system, and assisting antimicrobial stewardship more broadly.

3 Clinical context

NHS Trusts in England reported a total of 12,503 cases of CDI during 2020/2021. While the overall incidence (22.2 per 100,000 population) has steadily decreased since the start of mandatory surveillance in 2008 (108 per 100,000) (Public Health England 2021a), the rate of hospital-onset CDI cases has increased each year from 2018 (12.2 per 100,000) to March 2021 (15.4 per 100,000) (Public Health England 2021b).

Approximately 21% of people with CDI in the UK develop recurrent infection (Finn 2021), which is associated with higher mortality (Olsen 2015), greater morbidity, longer hospital stays, and consequently higher resource use and costs (Wilcox 2017). UK experts estimate that every year approximately 450 to 500 patients are treated using FMT for multiple recurrence CDI or refractory CDI (EAC correspondance log).

NICE Guideline on CDI

NICE has produced guidance for the management of people with suspected or confirmed CDI (National Institute for Health and Care Excellence 2021a). Treatment depends on a first assessment of whether the infection is a first or recurring episode, its severity, and individual characteristics (such as age,

frailty and comorbidities) that can affect the risk of complications or recurrence (National Institute for Health and Care Excellence 2021a). Existing treatment is also reviewed, with a preference to discontinue those that may worsen the infection (such as antibiotics and proton pump inhibitors), cause GI activity or worsen CDI symptoms (for example laxatives), or that are problematic in people who are dehydrated (including non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin 2 receptor antagonists and diuretics).

First-line treatment is rehydration and antibiotics, which for adults with a recurrent infection consists of 200 mg fidaxomicin taken orally twice daily ('bis in die', BIS) for 10 days, with an alternative option of vancomycin (125 mg taken orally 4 times a day ('quater in die', QID) for 10 days) for those re-presenting more than 12 weeks after symptom resolution. Life-threatening infections are managed seeking urgent specialist advice and may include an initial course of antibiotics comprising vancomycin (500 mg orally QID for 10 days) with metronidazole (500 mg intravenously 3 times a day ('ter in die', TID) for 10 days).

NICE recommends that FMT is considered for adults with recurrent CDI who have had 2 or more previous episodes. In the NHS FMT is currently carried out in specialist secondary care centres, most commonly as an inpatient procedure (National Institute for Health and Care Excellence 2021b). Delivery by NGT or nasoenteric tube is given by healthcare professionals in either day case units or on hospital wards, while trained endoscopists deliver endoscopic FMT in an endoscopy unit. In their evidence-based guidelines, the BSG and HIS recommend that FMT services should be delivered by multidisciplinary teams, including as a minimum a clinical gastroenterologist, microbiologist or infectious disease specialist, state-registered experienced healthcare scientist and pharmacist (Mullish 2018).

Special considerations, including issues related to equality

The NICE scope notes several specific considerations may apply to groups of recipients with protected characteristics. For example, the need to provide samples from donors with specific dietary properties to people from religious or ethnic communities who may observe strict dietary restrictions (such as meat and alcohol consumption). The EAC also notes that certain elements of the FMT sample preparation process may include ingredients which could be considered unsuitable for consumption by certain religious or ethnic groups, in particular the use of animal-derived gelatin for oral capsule preparation. The EAC also notes that glycerol has been used for the production of frozen FMT samples in a clinical trial context (Hvas 2019). Since both of these components can be manufactured with or without animal product, the

inclusion of these ingredients in the production process may need consultation with affected groups. Experts were unable to confirm whether animal products are used in the FMT production process in the UK (EAC correspondance log). However, these were not considered to constitute a particularly disadvantageous or disproportionate impact of FMT.
Other special considerations to be made when developing an FMT service are the need for appropriate facilities and centralised stool banks.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

We undertook searches to identify studies of FMT in people with CDI. A single set of searches was carried out to identify both clinical and economic evidence. The searches were conducted in a range of resources containing details of research published in the journal literature, conference abstracts and ongoing research. The searches were conducted between 08 October 2021 and 12 October 2021. The searches identified 6,239 records. Following deduplication, 3,893 records were assessed for relevance.

Full details of the EAC's search methods are provided in Appendix A. The study eligibility criteria were designed to address the decision problem and are summarised in Table 2. We aimed to identify RCTs evaluating the efficacy and safety of FMT by any route of delivery, against current NICE recommended comparator care, to treat patients with recurrent CDI who we defined as having at least 2 episodes of CDI at trial inclusion. No other study designs were eligible. Criteria used to select studies for the economic reviews are reported in Appendix D.

Table 2 Summary of the review eligibility criteria

	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years old) with refractory CDI or a recurrent episode of symptomatic CDI who have had two or more CDI episodes at baseline measurement. Refractory CDI: all author definitions.	Children or young people (<18 years old) Recurrent CDI: patients with first episode CDI. CDI unconfirmed by diagnostic test (unless data can be disaggregated).

	Inclusion Criteria	Exclusion Criteria
Intervention	FMT with or without prior treatment with bowel lavage and/or a short course of antibiotics, with routes of delivery: • lower GI route (rectal enema, colonoscopy, or flexible sigmoidoscopy) • upper GI route (endoscopy, NGT, NDT or NJT) • oral capsules containing frozen FMT or freeze-dried (lyophilised) faecal material.	
Comparators	Current treatment for refractory or recurrent CDI recommended by NICE, with or without bowel lavage: ▪ fidaxomicin (any author-defined dose and regimen) ▪ vancomycin with or without metronidazole (any author-defined dose and regimen) ▪ VTP (any author-defined dose and regimen for taper and pulse).	Placebo procedures or treatments
Outcomes	Reporting any of: ▪ Resolution of CDI (symptomatic and/or or diagnostic). ▪ Recurrence of CDI. ▪ Treatment failure leading to downstream interventions (such as retreatment with antimicrobials, repeat FMT procedures, colectomy). ▪ Procedural AEs (harmful impact of undergoing intervention procedures). ▪ Overall treatment related AEs (harmful effects of treatment interventions). ▪ Mortality.	
Study design	RCTs only Cross-over RCTs if data presented at time of cross-over Systematic reviews for the purpose of checking their included studies lists published from 2016 to present.	Non-randomised trials Cohort studies Case-control studies Case series Case reports Non-systematic reviews
Limits	English language studies Conference abstracts providing adequate information for assessment	Non-English language studies Editorials and news articles

Abbreviations: AE, Adverse events; CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; NDT, Nasoduodenal tube; NGT, Nasogastric tube; NICE, National Institute for Health and Care Excellence; NJT, Nasojejunal Tube; VTP, Vancomycin taper pulse,

4.2 *Included and excluded studies*

A total of 6,239 papers were identified by the search. 2,346 duplicate records were removed. 1,077 obviously irrelevant records were excluded at first pass.

At title and abstract screening, 2,670 papers were excluded as irrelevant. 146 reports were sought for retrieval, 1 report was unretrievable (Appendix F Table F2).

A total of 145 full texts were screened, of which 132 were excluded as summarised in the PRISMA diagram (Appendix A, Figure A2) and excluded list of records (Appendix F Table F1).

Five RCTs (reported in 13 papers) were included that were relevant to the decision problem. The 5 main publications were: Cammarota 2015; Hota 2017; Hvas 2019; Rode 2021 and van Nood 2013. The associated papers included trial protocols, clinical trial records and conference abstracts linked to the main publications. The reference lists of these documents were scanned for any eligible studies not identified in the search. No further primary studies were identified. The details of included trials are summarised below in Tables 3 to 14.

Table 3 Cammarota 2015 study details

Cammarota 2015	
How are the findings relevant to the decision problem?	The population partly meets the decision problem. The trial recruited patients presenting with recurrent CDI and at least 1 prior failed course of antibiotics, with no requirement for at least 1 prior recurrence. This therefore constitutes a mixed population, including some patients presenting with their first recurrence. The authors do not specify whether the number of recurrences recorded at baseline includes the trial episode but the median (range) number of recurrences reported at baseline shows the proportion of patients presenting with first recurrence is low and limited to the vancomycin arm: FMT patients had median 3 (range 2 to 5) CDI recurrences at baseline; vancomycin patients had median 3 (range 1 to 4) CDI recurrences at baseline. The intervention, comparator and outcomes fully meet the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 15 to 17 and Appendix B tables B2 to B7. This study confirmed that faecal microbiota transplantation delivered by colonoscopy was significantly more effective than vancomycin regimen for the treatment of recurrent CDI. **Resolution of CDI (Table B2)**

Cammarota 2015	
	A single infusion of FMT cured 13 of 20 patients (65%) compared with 5 of 19 patients (26%) cured with vancomycin (statistical difference not reported) by the end of trial follow-up (10 weeks after end of treatment). After administration of multiple infusions in 6 additional patients (4 patients received 2 infusions; 1 patient received 3 infusions; and 1 underwent 4 infusions), FMT achieved resolution of CDI in a total of 18/20 (90%) patients by 10 weeks after the final infusion ($p<0.0001$ compared with vancomycin 5/19, 26%). The odds ratio for the overall cure rates was 25.2 (99.9% CI: 1.26 to 502.30). After 1 or more FMT infusions, CDI stool toxins were negative in 18/20 (90%) patients at 5 weeks and 10 weeks after the final infusion, compared with 3/19 (16%) patients receiving vancomycin at 5 weeks and 5/19 (26%) patients at 10 weeks after the end of antibiotic treatment (statistical differences not reported). **Recurrence of CDI (Tables B3, B4)** Recurrence of diarrhoea (≥3 loose or watery stools per day for ≥2 consecutive days) 10 weeks after the end of treatment and unexplainable by other causes, with or without a positive CD stool toxin test, occurred in 2 (10%) FMT patients (1 or more infusions) and 12 (63%) vancomycin patients (statistical difference not reported). The time to CDI recurrence from end of treatment (Table B4) was 5 to 7 days in the FMT group vs. 4 to 21 days in the vancomycin group (statistical difference not reported). **Treatment failure leading to downstream interventions (Table B6)** CDI recurrence requiring 1 to 3 further courses of antibiotics was assessed 5 to 14 months after the end of treatments (assessed at the time of writing the manuscript, October 2014) in a sub-group of vancomycin patients who had relapsed during the trial. By this time, 2 FMT patients (number assessed not reported) had required antibiotics following failure of initial FMT, compared with 7 of 9 (78%) vancomycin patients (statistical difference not reported). **Mortality (Table B5)** Mortality due to any cause occurred in 2 (10%) FMT patients (1 or more infusions) vs. 2 (11%) vancomycin patients by 10 weeks after the end of treatments (statistical difference not reported). Longer term all-cause mortality occurring between 5 and 14 months after the end of treatments (assessed at the time of writing the manuscript, October 2014) was reported in 3/20 (15%) FMT patients compared with 6/16 (38%) vancomycin patients (3 comparator patients not analysed as lost to follow-up) (statistical difference not reported). **Procedural AEs (Table 15)** The total number of patients experiencing AEs immediately after FMT was not reported. No patients in the vancomycin arm experienced any AEs. This compared with at least 19 (94%) FMT patients experiencing AEs, consisting of diarrhoea (19, 94%) or bloating and abdominal cramping (12, 60%), all resolving within 12 hours.

Cammarota 2015	
	Overall AEs (Table 16) No patients in either arm experienced AEs during the remainder of the trial. **Unreported outcomes** CDI-associated diarrhoea and SAEs were not reported.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	The study was terminated early by an independent committee after a planned 1-year interim analysis showed a significantly higher efficacy for FMT over vancomycin. The small sample size of this trial (n=39) is a limitation, with the *a priori* power calculation estimating 82 patients (41 per group) would be needed to demonstrate a significant difference in the primary outcome (resolution of CDI). Two concerns regarding the generalisability of this trial to the UK NHS setting: 1) the trial was done in Italy where patient care may not be generalisable to the UK; 2) patients may have fewer comorbidities than common for UK patients (median Charlson Comorbidity Index score of 2 for FMT and vancomycin arms (range 0 to 5 and 1 to 5 respectively), although most included patients were hospitalised at inclusion (15/20 (75%) FMT patients; 16/19 (84%) vancomycin patients) and the mean age suggests a predominantly elderly population (mean age reported as 73 years for the whole population, 71 years (range 29 to 89) for FMT patients and 75 years (range 49 to 93) for vancomycin patients).
How was the study funded?	The study was in part funded by the Catholic University of Rome, Line D-1 research funding.

Abbreviations*:* AE, Adverse events; CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* infection; CI, Confidence interval; FMT, Faecal Microbiota Transplantation; NHS, National Health Service; SAE, Serious adverse events; UK, United Kingdom.

Table 4 Hota 2017 study details

Hota 2017	
How are the findings relevant to the decision problem?	The population partly meets the decision problem. The trial recruited patients presenting with recurrent CDI and at least 1 prior failed course of antibiotics, defined as patients with ≥2 CDI episodes (University Health Network Toronto 2010). This may therefore constitute a mixed population, including some patients presenting with their first recurrence. Reporting between text and baseline table is inconsistent. However, both suggest if patients presenting with a first recurrence were included, the number is small: the text describes most randomised patients as having a history of 4 to 5 prior CDI episodes (range 2 to 9). Baseline table reports the number of 'previous recurrences' as a mean (SD) of 4.4 (1.7)

Hota 2017	
	prior CDI recurrences at baseline for each of the FMT and vancomycin arm patients. The intervention, comparator and outcomes fully meet the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 15 to 17 and Appendix B tables B2 to B7. This study found that in patients experiencing an acute episode of recurrent CDI, a single FMT by enema was not significantly different from oral VTP in reducing recurrent CDI. **Resolution of CDI (Table B2)** Symptom resolution by 120 days following initiation of treatments occurred in 7/16 (43.8%) FMT patients and 7/12 (58.3%) VTP patients (statistical difference not reported). **Recurrence of CDI (Tables B3, B4)** Recurrence of symptomatic CDI with laboratory confirmation (primary outcome) by 120 days following initiation of treatments occurred in 9 of 16 (56.2%) patients who received FMT and 5 of 12 (41.7%) patients receiving VTP. The Bayesian 95% CI for the risk difference was not significant: -2.8% to +47.3%. No patients in either arm experienced recurrence of symptomatic CDI without laboratory confirmation at 14 days or 120 days. Recurrence occurred a median of 9 days after FMT treatment and 35 days after initiating vancomycin tapering (7 days after completing the VTP)(statistical difference not reported). **CDI-associated diarrhoea (Table B5)** Patients in the FMT group experienced a mean (SD) of 0.8 (0.8) days of diarrhoea during 120 days follow-up, compared with 1.7 (0.4) days in the VTP group (statistical difference not reported). **Treatment failure leading to downstream interventions (Table B6)** No patients developed CDI requiring hospital admission. **Mortality (Table B7)** No patients died in either treatment arm by the end of study follow-up (120 days after initiation of treatments). **Procedural AEs and SAEs (Table 15)** The total number of patients experiencing AEs immediately after FMT or during antibiotic use was not reported. Early AEs (occurring between 0 and 7 days after treatment) numbered 55 separate events in FMT patients, compared with 36 events in patients receiving VTP. Late AEs (occurring between 7 and 14 days after treatment) numbered 33 events and 59 events respectively (statistical differences not reported). **Overall treatment-related SAEs (Table 17)**

Hota 2017	
	By 120 days after the initiation of FMT or VTP, 2 (12.5%) FMT patients and 1 (8.3%) VTP patient had experienced a SAE. However, none of these cases was judged to be related to the treatments received (statistical difference not reported). **Unreported outcomes** Overall treatment-related AEs were not reported.
Will any information from this study be used in the economic model?	Used to inform transition probabilities and resource use associated with FMT administration.
What are the limitations of this evidence?	The study was terminated at the interim analysis after randomising 30 patients. A futility interim analysis did not support continuing the study on the grounds that finding a difference between the two treatments was unlikely. The small sample size of this trial (n=30) is a limitation, with the *a priori* power calculation estimating 114 patients (57 per group) would be needed to demonstrate a significant difference in the primary outcome (recurrence of CDI). Three concerns regarding the generalisability of this trial to the UK NHS setting: 1) the trial was done in Canada where patient care may not be generalisable to the UK; 2) the trial did not report the proportion of patients hospitalised at inclusion. However, patients on average may have been comparable in terms of age and comorbidities (mean (SD) age 75.7 (14.5) years for FMT patients and 69.6 (14.2) years for VTP patients). 3) patients receiving FMT were first given a lengthy treatment of vancomycin at 125 mg QID for 14 days. This is longer than clinical experts advise in common practice in the UK.
How was the study funded?	This work was supported by the Physicians Services Incorporated Foundation (grant number PSI 10-2021); Public Health Ontario; University of Toronto Department of Medicine Integrating Challenge Grant; University Health Network; and Sinai Health System (in kind).

Abbreviations*:* AE, Adverse event; CDI, *Clostridioides difficile*; CI, Confidence interval; FMT, Faecal Microbiota Transplantation; NHS, National Health Service; QID, 'quarter in die' (4 times daily); SAE, Serious adverse event; SD, Standard deviation; UK, United Kingdom; VTP, Vancomycin taper pulse.

Table 5 Hvas 2019 study details

Hvas 2019	
How are the findings relevant to the decision problem?	Population, intervention, comparator and outcomes fully meet the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 15 to 17 and Appendix B tables B2 to B7. This study confirmed that FMT by colonoscopy (n=19) or NJT (n=5) preceded by vancomycin was superior to fidaxomicin and

Hvas 2019	
	vancomycin, based on end points of clinical and microbiological resolution or clinical resolution alone. **Resolution of CDI** The primary outcome was combined clinical resolution (absence of abdominal pain using a numerical scale, and <3 bowel movements per day at Bristol ≤5) and microbiological resolution (negative CD PCR toxin test) without need for rescue FMT or colectomy at 8 weeks 'after initial treatment'. After 1 FMT infusion this was achieved in 17 of 24 (71%, 95% CI 49 to 87) patients receiving FMT, 8 of 24 (33%, 95% CI 16 to 55) patients receiving fidaxomicin, and 3 of 16 (19%, 95% CI 5 to 46) patients receiving vancomycin (p=0.009 for FMT vs fidaxomicin; p=0.001 for FMT vs vancomycin). After 1 to 2 infusions, combined clinical and microbiological resolution at 8 weeks was achieved in 18 of 24 (75%) FMT patients compared with 8 (33%) fidaxomicin patients and 3 (19%) vancomycin patients (statistical difference not reported). The same outcome measured 1 week after initial treatment occurred in 13 of 24 (54%) patients after 1 FMT infusion compared with 9 of 24 (38%) fidaxomicin patients (p=0.25), and 2 of 16 (13%) vancomycin patients (p=0.01). Clinical resolution without the need for rescue FMT or colectomy by 1 week follow-up was significantly more common in FMT patients (21/24, 88% FMT) than either fidaxomicin (14/24, 58%; p=0.02) or vancomycin comparator groups (6/16, 38%; p=0.002). At 8 weeks follow-up the difference was also significant (22/24, 92% [95% CI 73 to 99] FMT vs. 10/24, 42% [42%, 95% CI 22 to 63] fidaxomicin [p=0.0002] and vs. 3/16, 19% [95% CI 4 to 46] vancomycin [p<0.0001]). At 8 weeks significantly more FMT patients displayed microbiological resolution without the need for rescue FMT or colectomy (17/24, 71%) than fidaxomicin (11/24, 46%; p=0.08) or vancomycin patients (5/16, 31%; p=0.01). This difference was not statistically significant at 1 week (16/24, 67% FMT vs. 14/24, 58% fidaxomicin [p=0.55] and vs. 7/16 (44%) vancomycin [p=0.21]). **Recurrence of CDI (Table B3)** Clinical recurrence and a positive PCR for CDI at 8 weeks occurred in 2 (8%) FMT patients after a single infusion, compared with 11 (46%) fidaxomicin patients and 11 (69%) vancomycin patients (statistical difference not reported). **CDI-associated diarrhoea (Table B5)** This post-hoc outcome measured resolution of CDI-associated diarrhoea (clinical resolution or persistent diarrhoea or a negative PCR for CDI) was achieved in significantly more FMT patients at both 1-week follow-up (24/24, 100%, vs fidaxomicin 19/24, 79% [p=0.02]; vs vancomycin 11/16, 69% [p=0.003]) and 8 weeks follow-up (22/24, 92% vs. fidaxomicin 13/24, 54% [p=0.003]; vs vancomycin 5/16, 31% [p<0.0001]). **Mortality (Table B7)** No deaths occurred in any patient during study follow-up.

Hvas 2019	
	Procedural AEs and SAEs (Table 15) Immediate AEs (within 24 hours of procedure) were reported in 42% of FMT patients (10/24) and as being transient in nature. AEs occurring during the antibiotic comparator treatment were not reported separately from all events by the end of follow-up. One patient developed a SAE within 24 hours of receiving FMT by colonoscopy, and considered possibly related to the intervention. The event resolved within 24 hours without hospitalisation. **Overall treatment-related AEs (Table 16)** There was no statistical difference in the number of patients experiencing at least 1 AE or SAE between 2 days and 8 weeks after intervention (FMT 12/24, 50%; fidaxomicin 9/24, 38%; vancomycin 8/16, 50%; p=0.62). Similarly, no statistical differences were found in the number of patients experiencing GI symptoms requiring treatment (FMT 2/24, 8%, fidaxomicin 3/24, 13%, vancomycin 0/16, 0%; p=0.35), or GI symptoms not requiring treatment (FMT 4/24, 17%; fidaxomicin 3/24, 13%; vancomycin 2/16, 13%; p=0.89), both considered as probably related to the interventions; or in other AEs considered possibly related to the interventions (FMT 3/24, 13%; fidaxomicin 2/24, 8%; vancomycin 1/16, 6%; p=0.78). **Overall treatment-related SAEs (Table 17)** No difference was found in SAEs requiring hospitalisation and occurring between 2 days and 8 weeks after treatment (FMT 5/24, 21%; fidaxomicin 6/24, 25%; vancomycin 4/16, 25%; p=0.93). All were considered unrelated to the interventions. **Unreported outcomes** Time to recurrence and treatment failure leading to downstream interventions were not reported.
Will any information from this study be used in the economic model?	Data from this trial was used to inform recurrence and resolution transition probabilities, pre-antibiotic treatment regimen, comparator antibiotic treatment regimen.
What are the limitations of this evidence?	The small sample size of this 3-arm trial (n=64) is a limitation as it increases the chances of prognostic imbalances at randomisation, and reduces the power for detecting statistically significant differences. The EAC notes the power calculation estimated 24 patients were needed for the fidaxomicin group and FMT group in order to detect a 40% difference in primary outcome (combined clinical cure and negative stool CD toxin without need for colectomy or repeat FMT infusion) by end of follow-up, with 80% power. This was sufficient for detecting significant differences in the primary outcome. Two concerns regarding the generalisability of this trial to the UK NHS setting: 1) the trial was done in Denmark where patient care may not be generalisable to the UK; 2) patients are likely to have fewer comorbidities than common for UK patients (median Charlson Comorbidity Index score of 1 for all randomised patients), and most included patients were not

Hvas 2019	
	hospitalised at inclusion (6/64 (9%) randomised patients), indicating the population may not be fully generalisable to the UK.
How was the study funded?	Funding This study was financed by the Danish Regions (grant 14/217).

Abbreviations*:* AE, Adverse event; CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* infection; CI, Confidence interval; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; NHS, National Health Service; NJT, Nasojejunal tube; PCR, Polymerase chain reaction; SAE, Serious adverse event; UK, United Kingdom.

Table 6 Rode 2021 study details

Rode 2021	
How are the findings relevant to the decision problem?	Population: this study randomised patients with any number of CDI recurrences, including a majority randomised at their first recurrence. Investigators stratified randomisation according to number of recurrences at presentation (1 vs ≥2 CDI recurrences), allowing the extraction of this randomised subgroup only. The intervention, antibiotic comparator arm and outcomes meet the scope of decision problem. A third arm evaluating the use of faecal bacteriotherapy (12 selected bacterial strains suspended in saline) does not qualify as intervention or comparator for this decision problem, and was not extracted.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 15 to 17 and Appendix B tables B2 to B7. This study confirmed that 1 to 3 infusions of FMT delivered by enema is more effective at achieving clinical cure of CDI than a 7-week VTP. Only 1 outcome was analysed by the subgroup for multiple (≥2) CDI recurrences, as planned *a priori* by study investigators. Additional outcomes reported for the full trial population (presenting for any CDI recurrence) include: clinical cure for 1 FMT infusion, clinical cure for 1 to 2 FMT infusions, recurrence of CDI, treatment failure leading to downstream outcomes, all-cause mortality, possibly CDI-related mortality, and adverse events. These have not been reported here as this population is ineligible for this systematic review. **Resolution of CDI (Table B2)** Clinical cure was defined as the absence of patient-reported diarrhoea or diarrhoea with a negative stool test for CDI, occurring within 90 days of treatment. Cure was observed in 8/14 (57%) patients receiving 1 to 3 infusions of FMT and 6/13

Rode 2021	
	(46%) of patients receiving VTP (intention-to-treat). FMT was more effective than vancomycin (p=0.01). **Mortality (Table B7)** No deaths possibly attributable to CDI occurred in FMT patients. This outcome was not reported for the subgroup of vancomycin patients with multiple (≥2) CDI recurrences. **Unreported outcomes** CDI recurrence and time to recurrence, CDI-associated diarrhoea, treatment failure leading to downstream intervention, procedural AEs and SAEs, overall treatment-related AEs and overall treatment-related SAEs were not reported.
Will any information from this study be used in the economic model?	This trial was used to inform transition probabilities, and resource use for FMT administration.
What are the limitations of this evidence?	The study was terminated due to futility of the third treatment arm (rectal bacteriotherapy) – the main intervention of interest to the authors – and ethical concerns. The small subgroup of patients with ≥2 recurrences eligible for this systematic review (n=27) is a limitation in terms of the number of patients. Three concerns regarding the generalisability of this trial to the UK NHS setting: 1) the trial was done in Denmark where patient care may not be generalisable to the UK 2) patient characteristics were not reported for the multiple recurrence subgroup, precluding definitive conclusions on the generalisability of this evidence to the UK population. Observations for the full trial population include a lower proportion of hospitalised cases at inclusion than might be expected in the NHS (FMT arm: 6/34, 17%; vancomycin arm: 7/31, 23%), and possibly a low Charlson Comorbidity Index (FMT arm: median 2 (range 0 to 7); vancomycin arm: median 2 (range 0 to 6). However, the age distribution of the full trial group appears generalisable to the UK population. 3) patients receiving FMT were first given a lengthy treatment of vancomycin at 125 mg QID for 7 to 14 days. This may be longer than clinical experts advise is common practice in the UK.
How was the study funded?	Hvidovre Hospital; The Research fund of the Department of Infectious Disease, Hvidovre Hospital; Region Sjælland; The Christenson-Cesons Family Foundation; Ministeriet Sundhed Forebyggelse; The Research Council for Naestved/Ringsted/ Slagelse Hospital.

Abbreviations*:* AE, Adverse event; CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; NHS, National Health Service; quarter in die' (4 times daily); SAE, Serious adverse event; UK, United Kingdom; VTP, Vancomycin taper pulse.

Table 7 van Nood 2013 study details

van Nood 2013	
How are the findings relevant to the decision problem?	The population partly meets the decision problem. The trial recruited patients presenting with recurrent CDI and at least 1 prior failed course of antibiotics, with no requirement for at least 1 prior recurrence. This therefore constitutes a mixed population, including some patients presenting with their first recurrence. The authors specify that 8 of 43 (19%) patients were included after a first recurrence and appear distributed across all 3 trial arms, with the following median (range) number of recurrences reported at baseline: FMT patients had median 3 (range 1 to 5) CDI recurrences at baseline; vancomycin-only patients had median 3 (range 1 to 4) CDI recurrences at baseline; vancomycin with bowel lavage had median 2 (range 1 to 9) recurrences at baseline. The intervention, comparator and outcomes fully meet the scope of decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 15 to 17 and Appendix B tables B2 to B7. This trial compared FMT by NDT to 2 antibiotic comparator arms: vancomycin-only and vancomycin followed by bowel lavage. The trial confirmed that a single infusion of FMT was significantly more effective for the treatment of recurrent CDI than both vancomycin or vancomycin with bowel lavage. **Resolution of CDI (Table B2)** Cure of CDI was defined as the absence of diarrhoea or persistent diarrhoea with 3 consecutive negative stool tests, in the absence of relapse. By 10 weeks after the initiation of treatments, a single infusion of FMT cured 13/16 (81%) patients compared with 4/13 (31%) patients receiving vancomycin-only and 3/13 (23%) patients receiving vancomycin with bowel lavage (mITT analysis excluding an FMT patient with protocol violation). After 1 to 2 infusions (overall cure rate), FMT cured 15/16 (94%) patients. FMT infusion was statistically superior to both vancomycin regimens ($p<0.01$ for both comparisons after the first infusion and $p<0.001$ for 1 to 2 infusions). The rate ratio for overall cure was reported as 3.05 for FMT compared with vancomycin-only (99.9% CI, 1.08 to 290.05) and 4.05 as compared with vancomycin with bowel lavage (99.9% CI, 1.21 to 290.12). **Recurrence of CDI (Tables B3, B4)** Five weeks after the initiation of therapy, there was a recurrence of CDI (diarrhoea with a positive stool test) in 1/16 (6%) FMT patients, 8/13 (62%) vancomycin-only patients, and 7/13 (54%) patients receiving vancomycin with bowel lavage (statistical difference not reported). The median time to CDI recurrence was 23 days (range, 13 to 43) after the initiation of vancomycin-only and 25 days (range, 18 to 70) after the initiation of vancomycin with bowel lavage; this outcome was not reported for the FMT group.

van Nood 2013	
	Treatment failure leading to downstream interventions (Table B6) Patients in the FMT group in whom recurrent CDI developed after the first infusion were given a second FMT infusion with faeces from a different donor. This occurred in 3 (19%) of 16 patients. 18/26 patients who had initial antibiotic treatment (69%) had a relapse within 10 weeks of beginning treatment and received off-protocol FMT infusions. **Mortality (Table B7)** The death of one patient in the vancomycin-only group (8%) from severe heart failure and chronic obstructive pulmonary disease was considered to be unrelated to the study drug. No deaths were reported in the other 2 groups (statistical difference not reported). **procedural AEs and SAEs (Table 15)** The total number of patients experiencing AEs immediately after FMT was not reported. The number of events was reported, with at least 15 (94%) FMT patients experiencing an AE which resolved within 3 hours of the procedure. **Overall treatment-related AEs (Table 16)** By 10 weeks after the initiation of treatments, 3 (19%) FMT patients experienced an AE. The total number of patients experiencing AEs during follow-up was not reported for patients in either vancomycin arm. **Overall treatment-related SAEs (Table 17)** One patient experienced a SAE within 10 weeks of receiving FMT, and was considered unrelated to the intervention. No patients in either vancomycin arm experienced SAEs (statistical difference not reported). **Unreported outcomes** CDI-associated diarrhoea was not reported.
Will any information from this study be used in the economic model?	This trial was used to inform transition probabilities.
What are the limitations of this evidence?	The trial was terminated following an unplanned interim analysis done by an independent data and safety monitoring board, to investigate an unexpected and extremely low treatment response rate in the vancomycin control arm. The trial was stopped (using the Haybittle-Peto stopping boundary, p>0.001) after recruitment of 43 participants. The small sample size of this trial is a limitation, with the *a priori* power calculation estimating 114 patients (38 per group) would be needed to demonstrate a significant difference in the primary outcome (resolution of CDI). Three concerns regarding the generalisability of this trial to the UK NHS setting: 1) the trial was done in the Netherlands where patient care may not be generalisable to the UK

van Nood 2013	
	2) patient characteristics include a lower proportion of hospitalised cases at inclusion than might be expected in the NHS (13/42 (31%) analysed patients), and possibly a low Charlson Comorbidity Index (FMT arm: median 3 (range 0 to 4); vancomycin-only arm: median 1 (range 0 to 8); vancomycin with bowel lavage arm: median 1 (range 0 to 6). However, the age distribution appears generalisable to the UK population. 3) patients receiving vancomycin (2 arms) were given a high-dose treatment of vancomycin at 500 mg QID for 14 days. This dose is higher than clinical experts advise is common practice in the UK.
How was the study funded?	Supported by grants from the Netherlands Organization for Health Research and Development (ZonMW, 170881001; VENI grant, MN: 016096044) and a Spinoza Award (to Dr. de Vos) from the Netherlands Organization for Scientific Research.

Abbreviations*:* AE, Adverse event; CDI, *Clostridioides difficile* infection; CI, Confidence interval; FMT, Faecal Microbiota Transplantation; mITT, modified intention-to-treat; NDT, Nasoduodenal tube; NHS, National Health Service; QID, quarter in die ("four times each day"); SAE, Serious adverse event; UK, United Kingdom.

Table 8 Studies selected by the EAC as the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Cammarota 2015 Italy Supplementary papers: NCT02148601 (Catholic University of the Sacred Heart 2013)	2-arm RCT comparing FMT delivered by colonoscopy (preceding short regimen vancomycin and bowel cleaning) vs. vancomycin oral taper regimen (125 mg QID 10 days, with pulse: 125 to 500 mg a day every 2 to 3 days, for at least 3 weeks). Intervention 🟢 Comparator 🟢	39 patients aged ≥18 years presenting with laboratory confirmed recurrent CDI occurring within 10 weeks of stopping previous antibiotics, and ≥1 prior failed course of antibiotics (≥10 days of vancomycin at a dosage of at least 125 mg QID or at least 10 days of metronidazole at a dosage of 500 mg TID). 🟡 University Hospital in Rome. 20 randomised to FMT and 19 to vancomycin. All completed the study.	Primary: resolution of CDI diarrhoea associated with CDI 10 weeks after the end of the treatments. Secondary: toxin negative without recurrent CDI 5 and 10 weeks after the end of the treatments;. immediate AEs; overall AEs, treatment failure leading to downstream interventions, mortality. 🟢	At the planned 1-year interim analysis, FMT showed a significantly higher efficacy than vancomycin. Therefore, after consulting an independent committee (including two internists and one gastroenterologist), the study was stopped when a total of 39 patients were recruited. Variation from decision problem patient population: authors do not specify whether the number of recurrences recorded at baseline include the study episode, or are prior recurrences. The median number of recurrences is 3 in both arms. However an unreported (likely small) number of patients in the vancomycin arm had only 1 recurrence at baseline. Generalisability concerns: not done in a UK setting (Europe); patients may have fewer comorbidities than common for UK patients.
Hota 2017 Canada Supplementary papers: NCT01226992 (University Health Network Toronto 2010)	2-arm RCT comparing FMT delivered by enema (preceded by long course antibiotics) vs. vancomycin oral taper regimen (125 mg QID 14 days, with	30 patients aged ≥18 years; presenting with laboratory confirmed recurrent CDI and a history of ≥2 episodes of CDI, and had received ≥1	Primary: recurrence of symptomatic toxin-confirmed CDI within 120 days of starting the intervention.	The trial was stopped after randomisation of 30 patients, on the basis of futility. Variation from decision problem patient population: patients with 1st

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
	pulse: 125 mg BID 1 week, 125 mg Quaque die ("once a day") (QD) 1 week, 125 mg every 2 days 1 week, 125 mg every 3 days 1 week). Intervention Comparator	treatment course with oral vancomycin (minimum 10 days of 500 mg total daily oral vancomycin). Ontario. 16 randomised to FMT and 14 to VTP. 2 patients in the VTP group withdrew - one to seek FMT elsewhere and another due to repeated protocol non-compliance.	Secondary: early recurrence of symptoms within 14 days, relapse within 120 days (same strain of CD), days diarrhoea, mortality, CDI-associated hospitalisation, AEs and SAEs.	recurrence could enter the trial, so the study population is mixed. However, authors report that most randomised patients had a history of 4 to 5 episodes. Generalisability concerns: trial not done in a UK setting (Canada); FMT patients given lengthy antibiotic pre-treatment.
Hvas 2019 Denmark Supplementary papers: NCT02743234 (University of Aarhus 2016) EUCTR record (Aarhus University Hospital 2015)	3-arm RCT comparing FMT delivered by colonoscopy or NJT (preceded by short course antibiotics and bowel lavage (colonoscopy only)) vs. fidaxomicin (200 mg BID 10 days) and vs. vancomycin (125 mg QID 10 days). Intervention Comparator	64 patients aged ≥18 years presenting with recurrent CDI documented within 8 weeks of stopping anti-CDI treatment; ≥3 liquid stools (Bristol 6 to 7) per day, a positive PCR test result for CD toxin A, toxin B, or binary toxin, and at least 1 prior treatment course with vancomycin or fidaxomicin for CDI. A public referral gastroenterology centre.	Primary: combined clinical resolution and a negative PCR result for CD toxin 8 weeks after the allocated treatment. Secondary: clinical resolution at week 8, negative CD test at week 8, combined clinical resolution and negative CD test result at week 1, clinical resolution at week 1, negative CD test result at week 1, CDI-associated diarrhoea, mortality, immediate AEs, overall AEs.	Antibiotic treatment at time of assessment was an exclusion criterion. Generalisability concerns: trial not done in a UK setting (Europe); few patients hospitalised; patients likely to be less frail and have fewer comorbidities than common for UK.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		24 randomised to FMT; 24 to fidaxomicin and 16 to vancomycin. All completed the study.		
Rode 2021 Denmark Supplementary papers: NCT02774382 (Hvidovre University Hospital 2017)	3-arm RCT comparing FMT delivered by enema (preceded by long course antibiotics) vs. vancomycin (standard or extended taper), and vs. rectal bacteriotherapy (a 12-strain defined bacterial mixture, ineligible for extraction). Intervention (FMT) 🟢 Comparator (vancomycin) 🟢	98 patients aged ≥18 years presenting with laboratory-confirmed recurrent CDI within 90 days after a former episode of CDI; and have received at least one course of either vancomycin (at least 125 mg QID for 10 days) or metronidazole (at least 500 mg TID daily for 10 days); possibly have started oral vancomycin ≤7 days recruitment. Patient group extracted: randomisation stratified by number of CDI recurrences (first vs ≥2), extraction of multiple (≥2) recurrence group only. 🟢 2 University hospitals. Patients with ≥2 recurrences: 14 randomised to FMT; 13	Primary: clinical cure of CDI, defined as absence of diarrhoea or diarrhoea with a negative CD test, within 90 days after end of treatment (last FMT of end of VTP). Secondary (not reported for extracted subgroup) included clinical cure within 180 days after ended treatment, safety (occurrence of AEs and SAEs) and 180-day mortality (all-cause and possibly CDI-related mortality). 🟡	Rectal bacteriotherapy is not eligible for this review, no further details are reported. The authors planned to include 150 participants in each group (450 participants in total) and planned an interim analysis on the primary endpoint for the first 90 participants, using the Haybittle-Peto boundary ($p<0.001$) to determine if a potentially inferior treatment (if only one) should be removed from the trial or if the trial should be terminated (if two inferior treatments). When the reported results were apparent, including the mortality data, the study was terminated due to futility regarding the rectal bacteriotherapy intervention (compared to antibiotics) and ethical concerns, even though the Haybittle-Peto boundary was not met. Limitations: data could only be extracted for 1 outcome. Generalisability concerns: trial not done in a UK setting (Europe); low

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		randomised to vancomycin. No losses to follow-up in either arm.		proportion hospitalised, and patients may have fewer comorbidities than common for UK patients (unclear as patient characteristics reported for full population only); FMT patients given lengthy antibiotic pre-treatment.
van Nood 2013 The Netherlands Supplementary papers: NTR1177 (Academic Medical Centre 2008)	3-arm RCT comparing FMT delivered by NDT (preceded by short course antibiotics and bowel lavage) vs. vancomycin (500 mg QID 14 days) and vs. vancomycin with bowel lavage. Intervention (FMT) ● Comparator (vancomycin) ●	43 patients aged ≥18 years presenting with CDI relapse after ≥1 course of adequate antibiotic therapy (≥10 days of vancomycin at a dose of ≥125 mg QID or ≥10 days of metronidazole at a dose of 500 mg TID). 8/43 included after a first recurrence. ● Academic Medical Center in Amsterdam. 17 patients randomised to FMT, 13 to vancomycin-only, and 13 to vancomycin with bowel lavage. 41 (95%) patients completed the study protocol, 42 patients were analysed (mITT).	Primary: cure without relapse within 10 weeks after the initiation of therapy. Secondary: cure without relapse after 5 weeks, CDI recurrence, treatment failure leading to downstream interventions, mortality, immediate AEs, overall AEs. ●	Initially, the inclusion of 40 patients per study group was planned. Because most patients in both control groups had a relapse, the data and safety monitoring board did the interim efficacy analysis and advised termination of the trial. Variation from decision problem patient population: a minority of patients presented with a first CDI recurrence. Generalisability concerns: trial not done in a UK setting (Netherlands); few patients hospitalised; patients likely to be less frail and have fewer comorbidities than common for UK; comparator antibiotic was at a high dose.

Abbreviations: AE, Adverse events; BID, Bis in die ("twice a day"); CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* infection; EAC, External Assessment Centre; EUCTR, European Union Clinical Trials Register; FMT, Faecal Microbiota Transplantation; NHS, National Health Service; mITT, Modified intention to treat; NDT, Nasoduodenal tube; NJT, Nasojejunal Tube; PCR, Polymerase chain reaction; QD, Quaque die ("once a day"); QID, Quater in die ("four times each day"); RCT, Randomised controlled trial; SD, Standard deviation; SAE, Severe adverse events; TID, Ter in die (3 times daily); UK, United Kingdom; VTP, Vancomycin taper pulse.

- Study matches the scope fully for this PICO element
- Study matches the scope partially for this PICO element
- Study does not match the scope for this PICO element

Table 9 Trial characteristics summary

Study	Objective	Trial design Phase (NCT number)	Cross-over	Location of study (n / countries)	Number of trial sites	Date patient recruitment	Patient eligibility criteria	Patient exclusions
Cammarota 2015	To study the effect of FMT via colonoscopy in patients with recurrent CDI compared with the standard vancomycin regimen.	RCT II (NCT02148601) (Catholic University of the Sacred Heart 2013)	Patients in whom the 2 study treatments failed were re-evaluated to establish whether they were able to receive off-protocol treatment with donor faeces.	Italy	1	From July 2013 through June 2014	Patients ≥18 years, had a life expectancy ≥3 months, a symptomatic CDI recurrence after ≥1 courses of specific antibiotic therapy (≥10 days of vancomycin at a dosage of at least 125 mg QID or ≥10 days of metronidazole at a dosage of 500 mg TID), and were	Prolonged immunodeficiency due to recent chemotherapy; HIV; prolonged use of steroids; pregnancy; use of antibiotics other than metronidazole, vancomycin or fidaxomicin at baseline; admission to an ICU; requirement for vasoactive drugs; other infectious

Study	Objective	Trial design Phase (NCT number)	Cross-over	Location of study (n / countries)	Number of trial sites	Date patient recruitment	Patient eligibility criteria	Patient exclusions
							believed able to undergo colonoscopy. Recurrent CDI defined as diarrhoea (≥3 loose or watery stools per day for ≥2 consecutive days, or ≥8 stools in 48 hours) and positive CDI toxin stool test (ELISA) within 10 weeks from end of previous antibiotic treatment.	causes of diarrhoea; unable to undergo colonoscopy; prior colectomy; stools positive for: parasites, *Salmonella spp., Shigella spp., Y. enterocolitica, Campylobacter, S. agalactiae, S.aureus,* EPEC, or other microorganisms except for CD; blood positivity for HAV-IgM, HBsAg, Anti-HCV, Anti-HIV 1/2, VDRL; unable to follow trial protocol procedures (Catholic University of the Sacred Heart 2013).
Hota 2017	To assess the safety and efficacy of FMT by enema with VTP for the	RCT II-III (NCT01226992) (University Health	Participants who recurred with CDI in-study were offered crossover to the alternative study treatment	Canada	1	From January 2011 to July 2014	Adults (≥18 years of age) with a history of at least 2 episodes of laboratory or pathology-	Neutropenia, graft-vs-host disease, or other severe immune-compromised states; CDI requiring

Study	Objective	Trial design Phase (NCT number)	Cross-over	Location of study (n / countries)	Number of trial sites	Date patient recruitment	Patient eligibility criteria	Patient exclusions
	treatment of recurrent CDI.	Network Toronto 2010)	and followed for an additional 120 days.				confirmed CDI and had received at least one course of oral vancomycin (minimum 10 days of 500 mg total daily dose). Symptoms of CDI were self-reported and confirmed by study physicians to meet standard epidemiologic definitions of diarrhoea. for CD toxin or PCR for CD toxin gene was accepted for laboratory confirmation.	ICU admission; evidence of active, severe colitis unresponsive to oral vancomycin; hypersensitivity or intolerance to oral vancomycin; chronic GI diseases that may cause diarrhoea; planned therapy in next 120 days that may cause diarrhoea (such as chemotherapy); planned surgery requiring perioperative antibiotics within 120 days; pregnancy; significant bleeding disorder; or inability to tolerate FMT procedure.
Hvas 2019	To compare the effects of FMT by colonoscopy or NJT, fidaxomicin	RCT III (NCT02743234)	Participants who recurred with CDI after the primary allocated	Denmark	1 (Aarhus)	All patients referred for recurrent CDI from 5 April	Recurrent CDI documented within 8 weeks after stopping anti-CDI	Pregnancy or breastfeeding, inability to speak or understand the

Study	Objective	Trial design Phase (NCT number)	Cross-over	Location of study (n / countries)	Number of trial sites	Date patient recruitment	Patient eligibility criteria	Patient exclusions
	and standard-dose vancomycin for recurrent CDI.	(University of Aarhus 2016)	treatment were offered rescue FMT.			2016 to 10 June 2018.	treatment. Age ≤ 18 years, ≤ 3 more liquid stools (Bristol 6 to 7) /day, a positive PCR test result for CD) toxin A, toxin B, or binary toxin, and at least 1 prior treatment course with vancomycin or fidaxomicin for CDI.	Danish language, any ongoing antibiotic treatment, use of drugs with a known interaction with vancomycin or fidaxomicin, allergy to either study drug, fulminant colitis that contraindicated medical treatment, the treating physician's evaluation that the patient could not tolerate project inclusion, or frail or septic patients were not randomised.
Rode 2021	To compare the efficacy and safety of FMT by enema with vancomycin (standard or taper) or with rectal bacteriotherapy to treat recurrent CDI.	RCT III (NCT02774382) (Hvidovre University Hospital 2017)	No crossover or rescue therapy during the trial	Denmark	2 (Zealand and Hvidovre)	From May 2017 to December 2018 at Zealand University Hospital and from June 2017 to March 2019 at Hvidovre	Age ≥18 years; recurrence of CDI, defined as diarrhoea (≥3 loose or liquid stools per day) and a new positive PCR test for CD (or PMC diagnosed by endoscopy or biopsy) within 90	Life expectancy <3 months; allergy towards vancomycin; other GI diseases, infections and conditions with diarrhoea or disturbed symptom reporting, such as colectomy; planned

Study	Objective	Trial design Phase (NCT number)	Cross-over	Location of study (n / countries)	Number of trial sites	Date patient recruitment	Patient eligibility criteria	Patient exclusions
						University Hospital	days after a former episode of CDI; receipt of ≥ 1course of either vancomycin (at least 125 mg QID for 10 days) or metronidazole (at least 500 mg TID for 10 days); possibly have started oral vancomycin within seven days prior to inclusion.	concomitant antibiotic treatment for >14 days after inclusion; severe immune suppression; pregnancy, breast-feeding women, fertile women with no safe birth control.
van Nood 2013	To compare the efficacy and safety of FMT by NDT with vancomycin treatment, with and without bowel lavage, in patients with recurrent CDI.	RCT Phase not reported (NTR1177) (Academic Medical Center Amsterdam 2008)	Patients in whom recurrent CDI developed after the first FMT infusion were given a second infusion from a different donor. (Patients in whom antibiotic therapy failed were offered FMT off protocol.)	The Netherlands	1	From January 2008 through April 2010	Age ≥18 years; life expectancy of ≥3 months and a proven relapse of CDI-associated diarrhoea after ≥1 course of adequate antibiotic therapy (≥10 days of vancomycin at a dose of ≥125 mg QID or ≥10 days of metronidazole at a dose of 500 mg TID). CDI diarrhoea	Prolonged compromised immunity because of recent chemotherapy, the presence of HIV infection with a CD4 count <240, or prolonged use of prednisolone ≥60 mg per day; pregnancy; use of antibiotics other than for treatment of CDI at baseline;

Study	Objective	Trial design Phase (NCT number)	Cross-over	Location of study (n / countries)	Number of trial sites	Date patient recruitment	Patient eligibility criteria	Patient exclusions
							defined as: (i) ≥3 loose or watery stools per day for ≥2 consecutive days, or ≥8 loose stools in 48 hours and (ii) a positive Clostridium toxin stool test (ELISA).	admission to an ICU; or need for vasopressor medication for maintenance of normal blood pressure.

Abbreviations*:* CD, *Clostridioides difficile*; CD4, Cluster of differentiation 4 cells; CDI, *Clostridioides difficile* infection; EIA, Enzymatic immunoassay; EPEC, enteropathogenic E. coli; ELISA, enzyme-linked immunosorbent assay; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; HAV, Hepatitis A Virus; HBsAg, Hepatitis B surface antigen; HCV, Hepatitis C Virus; HIV, Human immunodeficiency virus; ICU, Intensive Care Unit; NCT, National Clinical Trial; NDT, Nasoduodenal Tube; PCR, Polymerase chain reaction; PMC, Pseudomembranous colitis; QID, Quater in die ("four times each day"); RCT, Randomised controlled trial; TID, Ter in die ("three times a day"); VDRL, Venereal disease reaction level; VTP, Vancomycin taper pulse.

Table 10 Patient Characteristics (CDI at baseline)

Study	Intervention	Age Median years (range)	Gender male n (%)	Ribotype 027 n (%)	Hospital-acquired infection n (%)	Symptom duration (current episode) Median days (range)	Stool frequency per 24 h Median (range)	Prior CDI episodes median number (range)	Time since onset first CDI Median days (range)
Cammarota 2015	FMT by colonoscopy	Mean 71 (29 to 89)	8 (40)	NR	10 (50)	NR	6 (2 to 15)	3 (2 to 5) 'Median recurrences'	NR
	Vancomycin	Mean 75 (49 to 93)	8 (42)	NR	14 (74)	NR	6 (2 to 12)	3 (1 to 4) 'Median recurrences'	NR
Hota 2017	FMT by enema	Mean 75.7 (SD 14.5)	5 (31)	NR	NR	NR	NR	Mean 4.4[a] (SD 1.7)	NR
	VTP	Mean 69.6 (SD 14.2)	4 (33)	NR	NR	NR	NR	Mean 4.4 (SD 1.7)	NR
Hvas 2019	FMT by colonoscopy or NJT	68 (22 to 90)	4 (17)	0 (0)	NR	9 (4 to 112)	7 (3 to 31) liquid stools per 24h	4 (2 to 7)	141 (30 to 963)
	Fidaxomicin	64 (24 to 87)	11 (46)	0 (0)	NR	14 (1 to 152)	6 (3 to 12) liquid stools per 24h	4 (2 to 10)	147 (35 to 883)
	Vancomycin	72 (21 to 92)	5 (31)	0 (0)	NR	12 (2 to 36)	8 (4 to 20) liquid stools per 24h	3 (2 to 9)	88 (25 to 663)
Rode 2021[b]	FMT by enema	75 (47 to 96)	14 (41)	2 (6)	NR	NR	NR	1 (1 to 6)	NR

Study	Intervention	Age Median years (range)	Gender male n (%)	Ribotype 027 n (%)	Hospital-acquired infection n (%)	Symptom duration (current episode) Median days (range)	Stool frequency per 24 h Median (range)	Prior CDI episodes median number (range)	Time since onset first CDI Median days (range)
	VTP	76 (33 to 94)	17 (55)	2 (6)	NR	NR	NR	1 (1 to 5)	NR
van Nood 2013[c]	FMT by NDT	Mean 73 (SD 13)	8 (50)	3/13 (23) 3 missing	10 (62)	NR	5 (3 to 20)	3 (1 to 5) 'median recurrences'	NR
	Vancomycin	Mean 66 (SD 14)	6 (46)	1/9 (11) 4 missing	6 (46)	NR	5 (3 to 12)	3 (1 to 4) 'median recurrences'	NR
	Vancomycin with bowel lavage	Mean 69 (SD 16)	10 (77)	0/11 (0) 2 missing	10 (77)	NR	5 (3 to 10)	2 (1 to 9) 'median recurrences'	NR

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; NDT, Nasoduodenal tube; NJT, Nasojejunal tube; NR, Not reported; SD, Standard deviation; VTP, Vancomycin taper pulse.

[a] Text describes "most randomized patients were women and had a history of 4 to 5 episodes (range, 2 to 9) of CDI prior to entering the trial.". However, Table 1 refers to number of previous recurrences.

[b] Whole population patient characteristics.

[c] Based on 42/43 patients, 1 excluded from analysis.

Table 11 Patient Characteristics (patient care)

Study	Intervention	Hospitalised at inclusion n (%)	Feeding tube present n (%)	Prior hospital admission for CDI median number (range)	Any prior ICU admission within 1 month of trial n (%)	Prior antibiotic use n (%)	PPI use n (%)
Cammarota 2015	FMT Lower GI: colonoscopy	15 (75)	NR	NR	NR	Antibiotic use before CDI: 20 (100) Prior VTP: 19 (95)	11 (55)
	Vancomycin	16 (84)	NR	NR	NR	Antibiotic use before CDI: 19 (100) Prior VTP: 16 (84)	13 (68)
Hota 2017	FMT Lower GI: enema	NR	NR	Mean 1.2 (SD 0.4)	NR	≥1 prior failed VTP: 13 (81)	7 (47)
	VTP	NR	NR	Mean 1.2 (SD 0.7)	NR	≥1 prior failed VTP: 10 (83)	5 (42)
Hvas 2019	FMT Lower GI: colonoscopy or Upper GI: NJT	2 (8)	2 (8)	NR	0 (0)	Prior metronidazole[c]: 19 (79) Prior vancomycin: 24 (100) Prior fidaxomicin: 1 (4)	9 (38)
	Fidaxomicin	2 (8)	2 (8)	NR	0 (0)	Prior metronidazole: 16 (67) Prior vancomycin: 24 (100) Prior fidaxomicin: 2 (8)	11 (46)

Study	Intervention	Hospitalised at inclusion n (%)	Feeding tube present n (%)	Prior hospital admission for CDI median number (range)	Any prior ICU admission within 1 month of trial n (%)	Prior antibiotic use n (%)	PPI use n (%)
	Vancomycin	2 (13)	1 (6)	NR	0 (0)	Prior metronidazole: 13 (81) Prior vancomycin: 16 (100) Prior fidaxomicin: 0 (0)	6 (38)
Rode 2021[a]	FMT Lower GI: enema	6 (17)	NR	NR	NR	Any since last CDI: 16 (47)	Any since last CDI: 19 (56) Ongoing: 18 (53)
	Vancomycin taper	7 (23)	NR	NR	NR	Any since last CDI: 17 (55)	Any since last CDI: 16 (52) Ongoing: 14 (45)
van Nood 2013[b]	FMT Upper GI: NDT	5 (31)	3 (19)	NR	1 (6)	Prior failed vancomycin taper: 10 (62)	13 (81)
	Vancomycin	4 (31)	2 (15)	NR	0 (0)	Prior failed vancomycin taper: 8 (62)	10 (77)
	Vancomycin with bowel lavage	4 (31)	2 (15)	NR	1 (8)	Prior failed vancomycin taper: 6 (46)	11 (85)

Abbreviations*:* CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; ICU, Intensive care unit; NDT; Nasoduodenal tube; NJT, Nasojejunal tube; NR, Not reported; PPI, Proton pump inhibitor; SD, Standard deviation, VTP; Vancomycin taper pulse.

[a] Whole population patient characteristics.
[b] Based on 42/43 patients, 1 excluded from analysis.
[c] Antibiotics for CDI.

Table 12 Patient Characteristics (comorbidities at baseline)

Study	Intervention	Charlson co-morbidity index score median (range)	IBD n (%) [active IBD n (%)]	Kidney Disease n (%)	Cancer n (%)	Creatinine median mg/dl (range)	Immuno-suppressed n (%)
Cammarota 2015	FMT Lower GI: colonoscopy	2 (0 to 5)	NR	NR	NR	1.2 (0.7 to 2.5)	0 (0)
	Vancomycin	2 (1 to 5)	NR	NR	NR	1.2 (0.8 to 1.7)	0 (0)
Hota 2017	FMT Lower GI: enema	Mean 5.3 (SD 1.9)	NR	NR	NR	NR	0 (0)
	VTP	Mean 4.5 (SD 2.1)	NR	NR	NR	NR	2 (17)
Hvas 2019	FMT Lower GI: colonoscopy or Upper GI: NJT	1 (0 to 5)	5 (21) [1 (4) active]	NR	NR	NR	Immuno-suppressant therapy: 4 (17)
	Fidaxomicin	1 (0 to 3)	6 (25) [1 (4) active]	NR	NR	NR	Immuno-suppressant therapy: 4 (17)
	Vancomycin	2 (0 to 7)	4 (25) [1 (6) active]	NR	NR	NR	Immuno-suppressant therapy: 2 (13)
Rode 2021[a]	FMT Lower GI: enema	2 (0 to 7)	NR	NR	NR	78 (48 to 349) µmol/L	NR
	VTP	2 (0 to 6)	NR	NR	NR	81 (44 to 855) µmol/L	NR

Study	Intervention	Charlson co-morbidity index score median (range)	IBD n (%) [active IBD n (%)]	Kidney Disease n (%)	Cancer n (%)	Creatinine median mg/dl (range)	Immuno-suppressed n (%)
van Nood 2013[b]	FMT Upper GI: NDT	3 (0 to 4)	NR	NR	NR	1.3 (0.6 to 10.3)	NR
	Vancomycin	1 (0 to 8)	NR	NR	NR	1.0 (0.5 to 1.8)	NR
	Vancomycin with bowel lavage	1 (0 to 6)	NR	NR	NR	0.9 (0.6 to 5.2)	NR

Abbreviations*:* CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; IBD, Inflammatory bowel disease; NDT; Nasoduodenal tube; NJT, Nasojejunal tube; NR, Not reported; SD, Standard deviation; VTP, Vancomycin taper pulse.

[a] Whole population patient characteristics.

[b] Based on 42/43 patients, 1 excluded from analysis.

Table 13 Intervention characteristics (FMT)

Study	FMT delivery	First FMT or Repeat FMT	Number FMT doses	Antibiotic pre-treatment	Washout period	Other pre-treatment (*e.g. bowel lavage)*	Infusion rate	Infusion target	FMT Comments
Cammarota 2015	Colonoscopy	First	1 If PMC: repeat FMT infusions every 3 days until resolution of colitis (protocol amendment)	125 mg vancomycin oral QID for 3 days	1 day	Bowel cleaning: 4 L macrogol preparation on last 1 or 2 days of antibiotics (according to the clinical condition of the patients). Patients with repeat infusions: restricted to light diet with preparation of 2L macrogol.	A mean (SD) of 152 (32) g of faeces was infused within 10 minutes	Proximal tract of the colon (cecum/ascending colon)	Patients placed in right lateral recumbency position and asked to maintain this position for ≥1h after the procedure to allow the permanence of material infused into the proximal colon.
Hota 2017	Enema	First	1	125 mg vancomycin oral QID for 14 days	48 hours	None reported	500mL delivered over 10 to 30 minutes	NR	
Hvas 2019	Colonoscopy (n=19, 79%)	First	1 With second infusion if recurrence	125 mg vancomycin orally QID for 4 to 10 days	NR	Standard lavage	NR	1/3 to each of: terminal ileum, cecum, anally to hepatic fixture.	Method considered first choice.

Study	FMT delivery	First FMT or Repeat FMT	Number FMT doses	Antibiotic pre-treatment	Washout period	Other pre-treatment (*e.g. bowel lavage)*	Infusion rate	Infusion target	FMT Comments
			develops after first.						
	NJT (n=5, 21%)	First	1 With second infusion if recurrence develops after first.	125 mg Vancomycin orally QID for 4 to 10 days	NR	Overnight fast	10 minutes	NR	Delivered while patient sitting. Method selected for frail patients who could not tolerate bowel lavage, or with prior technically difficult colonoscopy (adhesions).
Rode 2021	Enema	First	1 to 3 infusions within 14 days based on predefined clinical criteria (ongoing or new-onset diarrhoea (≥3 loose or liquid stools per day), as judged by a trial physician, without new test for CD). Change of donor when repeating FMT.	125 mg Vancomycin orally QID for 7 to 14 days	36 hours	NR	50 g of stool suspended in saline and 20 mL glycerol (final concentration of 10%) to a volume of 170 mL	Catheter inserted rectally approximately 20 to 30 cm up	Enema by a catheter (Ch 12, diam. 4 mm) with participants in left lateral position with bended knees during and for 1 hour after.

Study	FMT delivery	First FMT or Repeat FMT	Number FMT doses	Antibiotic pre-treatment	Washout period	Other pre-treatment (*e.g. bowel lavage)*	Infusion rate	Infusion target	FMT Comments
van Nood 2013	NDT	First	1 to 2 infusions Patients developing recurrent CDI after the first infusion were given a second infusion with faeces from a different donor.	Vancomycin 500 mg orally QID for 4 or 5 days	1 day	Bowel lavage with 4L of macrogol solution on the last day of antibiotic treatment.	2 to 3 mins per 50 mL: first 4 to 5 syringes (50 cc) infused in 10 mins; break of 10 mins; final 5 syringes infused.	Duodenum	Tube placement using an electromagnetic sensing device, or through duodenoscopy, with position confirmed by X-ray. Tube removed 30 minutes after the infusion.

Abbreviations*:* CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota; NDT, Nasoduodenal tube; NJT, Nasojejunal tube; NR, Not reported; PMC, Pseudomembranous colitis; QID, Quater in die (“four times each day”); SD, Standard deviation.

Table 14 Intervention characteristics (Donors and faecal sample preparation)

Study	Donor type *(related, anonymous, mixed)*	Donor characteristics		Screening regularity	Faecal sample *(Fresh or frozen)*	Sample preparation details	Time to infusion (Hours)	Faeces per FMT infusion grams
		Age (Years) **Male n (%)** **BMI median (range)**	**Excluded conditions or other characteristics**					
Cammarota 2015	Mixed Related 16 (80), of which intimate 2 (10); unrelated 2 (10)	Eligible <50 years. Mean age not stated Gender NR BMI NR	<u>History/Symptoms:</u> GI diseases or complaints (abdomen discomfort, alvus disturbances); significant intestinal symptoms of other GI diseases; family history of GI cancer or IBD; systemic diseases (diabetes or neurological disorders). <u>Blood tests:</u> HAV, HBV, HCV, HIV-1/2 ab, EBV, *T. pallidum, S. stercoralis, E. histolytica*; blood cell counts, measurements of transaminase, CRP, albumin and creatinine analysis. <u>Stool tests:</u> CD (culture, toxin), enteric bacteria,	Before donation a further questionnaire used to screen for recent gastrointestinal illnesses, newly contracted infections or other risk factors.	Fresh	Faeces were diluted with 500 mL of sterile saline (0.9%). The deriving solution was blended, and the supernatant strained and poured into a sterile container.	Within 6 h of donation. Mean time from defecation to infusion: 3.8 (SD 0.8)	Mean 152 (SD 32) g

Study	Donor type *(related, anonymous, mixed)*	Donor characteristics		Screening regularity	Faecal sample *(Fresh or frozen)*	Sample preparation details	Time to infusion (Hours)	Faeces per FMT infusion grams
		Age (Years) **Male n (%)** **BMI median (range)**	**Excluded conditions or other characteristics**					
			protozoa, helminths of large and small bowel, VRE, MRSA, MDRGN bacteria <u>Risk factors:</u> Antibiotics (≤6 months), lifestyle factors for contracting infections, recent travel in tropical areas (≤3 months); new sexual relationship (≤6 months); recent needle stick accident; receipt of blood products; body tattoos; use of drugs excretable in faeces with potential risk for recipients.					
Hota 2017	Mixed Related n=11 (69)	Eligible if >18 years. Mean age of included donors: 50 years. Male: 12 (75)	<u>History/symptoms:</u> GI disease (IBD, severe GI motility disorder, severe diverticular disease, other chronic symptoms of undiagnosed diarrhoea, or urine, blood and/or mucous in stool); Malignancy within 5 years; Risk factors for	NR	Fresh	50g faeces diluted with 500mL saline.	Maximum 48 hours	NR

Study	Donor type *(related, anonymous, mixed)*	Donor characteristics		Screening regularity	Faecal sample *(Fresh or frozen)*	Sample preparation details	Time to infusion (Hours)	Faeces per FMT infusion grams
		Age (Years) **Male n (%)** **BMI median (range)**	**Excluded conditions or other characteristics**					
		BMI: Not considered	prion-related disease (family history of CJD, corneal or dural transplant, receipt of pit-hGH); Chronic STIs (such as anogenital herpes, anogenital warts, chancroid or syphilitic lesions); Dementia or degenerative neurological disorders of unknown aetiology. <u>History/physical signs:</u> Immuno-suppression, chronic liver disease, cholestasis. <u>Infectious diseases</u> (HIV-1/2; HAV, HBV, HCV; HTLV-1/2; Syphilis; VRE, MRSA, CRE, CD stool toxin; *Salmonella, Shigella, E.coli 0157-H7, Yersinia, Campylobacter*; ova and parasites on stool					

Study	Donor type *(related, anonymous, mixed)*	Donor characteristics		Screening regularity	Faecal sample *(Fresh or frozen)*	Sample preparation details	Time to infusion (Hours)	Faeces per FMT infusion grams
		Age (Years) **Male n (%)** **BMI median (range)**	**Excluded conditions or other characteristics**					
			examination; *H. pylori* (if recipient is negative). High risk for recent HIV, HBV/HCV. Signs/Symptoms: active encephalitis, meningitis, systemic viral/bacterial/fungal infection. Receipt of: live vaccine (≤30 days); blood transfusion from outside Canada (≤6 months); bite from potentially rabid animal (≤6 months); ≤3 months any of: antibiotics for >2 days, medicinal probiotics, cholestyramine.					
Hvas 2019	Anonymous Voluntary donors identified and recruited	Age NR Gender NR BMI NR	Risk factors (due to gastrointestinal complaints, risk behaviour, and diet)	At the beginning and ending of 2-month donation cycles.	Frozen	Diluted with saline (0.9%). 10% glycerol titre added when	Within 4 hours of thawing	50

Study	Donor type *(related, anonymous, mixed)*	Donor characteristics		Screening regularity	Faecal sample *(Fresh or frozen)*	Sample preparation details	Time to infusion (Hours)	Faeces per FMT infusion grams
		Age (Years) **Male n (%)** **BMI median (range)**	**Excluded conditions or other characteristics**					
	at public blood donation centre.					aliquoted into CryoBags, with storage at -80ºC		
Rode 2021	Anonymous Donor stool bank with extensively tested universal donors recruited from the Danish Blood Donor Corps	Age: Median 41 (range 21 to 63) Male: 4 (40) BMI: NR	<u>Blood tests:</u> Leukocytes, differential count, platelets, haemoglobin; IgA; HbA1c; HAV-IgM, HBV (HBsAg, Anti-HBc), HCV (anti-HCV); HIV-1/2; Syphilis; CMV (CMV-IgM, CMV-IgG); EBV (VCA-IgM, VCA-IgG, EBNA IgG). <u>Stool tests:</u> Enteropathogenic bacteria (CD, *Salmonella, Shigella, C. coli, C. jejuni, Y. enterocolitica, Aeromonas, diarrhoeagenic E. coli* (STEC, EPEC, ETEC, EIEC, AEEC); Enteropathogenic viruses (Adenovirus, Rotavirus,	NR	Frozen	50g of stool suspended in saline and 20mL glycerol (final concentration of 10%) to a volume of 170mL. Stored frozen at −80°C for up to 1 year	NR	50

Study	Donor type *(related, anonymous, mixed)*	Donor characteristics		Screening regularity	Faecal sample *(Fresh or frozen)*	Sample preparation details	Time to infusion (Hours)	Faeces per FMT infusion grams
		Age (Years) **Male n (%)** **BMI median (range)**	**Excluded conditions or other characteristics**					
			Norovirus, Astrovirus, Sapovirus); Enteropathogenic parasites (*E. histolytica, G. lamblia, C. parvum, C. hominis,* worms); Multiresistant bacteria (ESBL. producing *E. coli, K. pneumoniae, P. mirabilis*, VRE and CPO); *H. pylori* antigen.					
van Nood 2013	Mixed	Age: Eligible if <60 years. Mean age 44 years (SD 18.1) Gender: NR BMI: NR	Risk factors: questionnaire for infectious diseases, any GI illness or GI complaints (abdominal discomfort, regular loose stools, constipation), family history of intestinal cancer or inflammatory bowel disease, general illness or use of excretable medication. Stool tests: parasites (including *B. hominis and D. fragilis*), CD, and EPB	Every 4 months	Fresh	Faeces were collected by donor on day of infusion with immediate transport to the hospital. Faeces were diluted with 500mL of sterile saline (0.9%), stirred, and the	Within 6 hours Mean (SD): 3.1 (1.9)	Mean (SD) 141 (71)

Study	Donor type *(related, anonymous, mixed)*	Donor characteristics		Screening regularity	Faecal sample *(Fresh or frozen)*	Sample preparation details	Time to infusion (Hours)	Faeces per FMT infusion grams
		Age (Years) **Male n (%)** **BMI median (range)**	**Excluded conditions or other characteristics**					
			(*Salmonella, Shigella, Y. enterocolitica, Campylobacter* species). <u>Blood tests:</u> HIV ab; HTLV-1/2; HAV, HBV, HCV; CMV; EBV; *T. pallidum; S. stercoralis; E. histolytica.*			supernatant strained and poured in a sterile bottle. Procedure repeated until all saline was dissolved and a 500cc bottle filled.		

Abbreviations*:* AEEC, Attaching and Efficacing E. coli; Anti-HBc, Hepatitis B core antigen test; Anti-HBV, Hepatitis B Virus antibody test; Anti-HCV, Hepatitis C Virus antibody test; BMI, Body Mass Index; CD, *Clostridioides difficile*; CJD, Creutzfeldt-Jakob disease; CMV, Cytomegalovirus; CPO, Carbapenemase-producing organisms; CRE, Carbapenem-resistant Enterobacteriaceae; CRP, C-reactive protein; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr Virus; EIEC, *Enteroinvasive E. coli*; EPB, Enteropathogenic bacteria; EPEC, Enteropathogenic *Escherivhia coli*; ESBL, Extended-spectrum beta-lactamase; ETEC, Enterotoxigenic *E. coli*; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; HAV, Hepatitis A Virus; HbA1c; Hemoglogin A1c test; HBsAg, Hepatitis B surface antigen test; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human immunodeficiency virus; HIV ab, Human immunodeficiency virus antibodies; HTLV, Human T-cell lymphotropic virus; IBD, Inflammatory bowel disease; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; MDRGN, Multidrug resistant Gram-negative bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, Not reported; pit-hGH, human-derived pituitary growth factor; SD, Standard deviation; STEC, Shigatoxin-producing *Escherichia coli*; STI, Sexually transmitted infections; VCA, Viral capsid antigen; VRE, Vancomycin-resistant Enterococci.

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

Characteristics of the included studies are summarised in tables 8 to 13. All included studies were RCTs. Only one trial (Hvas 2019) completed after recruiting the target number of patients. The other 4 trials were terminated early, 2 for greater than expected treatment effect at interim analysis (Cammarota 2015 and van Nood 2013), 1 for futility of FMT compared with the antibiotic comparator (Hota 2017), and 1 for futility of an ineligible intervention (rectal bacteriotherapy) compared with the antibiotic comparator Rode 2021). One trial was multicentre, reporting data from 2 sites in Denmark (Rode 2021), and the remaining trials were single centre done in Italy (Cammarota 2015), Denmark (Hvas 2019), The Netherlands (van Nood 2013) and Canada (Hota 2017).

Three trials assessed FMT delivered by a lower GI route, 2 using enema (Hota 2017, Rode 2021) and 1 using colonoscopy (Cammarota 2015). A fourth trial (Hvas 2019) used mixed routes, administering FMT by colonoscopy as first preference, or by NJT in patients too frail to tolerate bowel lavage or with a prior technically difficult colonoscopy because of adhesions; however, outcomes were not reported separately for the 2 delivery methods. The remaining trial (van Nood 2013) delivered FMT by NDT, an upper GI route. No included trials evaluated FMT delivered by capsule, by NGT, or by flexible sigmoidoscopy.

The number of FMT infusions administered during the trial varied from 1 (Hota 2017), 1 to 2 (van Nood 2013, Hvas 2019), 1 to 3 (Rode 2021) or up to 4 infusions (Cammarota 2015). All trials administered vancomycin prior to FMT, ranging from 3 days (Cammarota 2015) to 14 days (Hota 2017). This was followed by bowel lavage in 3 trials (Cammarota 2015, Hvas 2019, van Nood 2013). FMT samples were derived from fresh product (Cammarota 2015, Hota 2017, van Nood 2013) or frozen product (Hvas 2019, Rode 2021), and in all cases saline was used as the mixing agent.

FMT was compared with vancomycin in 3 trials (Hvas 2019, Rode 2021, van Nood 2013), to VTP in 2 trials (Cammarota 2015, Hota 2017), and to fidaxomicin in 1 trial. Two trials recruited patients to 3 arms; Hvas 2019 randomised patients between FMT, vancomycin and fidaxomicin treatments, while van Nood 2013 randomised patients between FMT, vancomycin (‘vancomycin-only’) and a third group receiving vancomycin with bowel lavage. Rode 2021 was also a 3 arm trial, though the third arm (a 12-strain defined bacterial mixture termed rectal bacteriotherapy) was not an eligible

intervention or comparator and so this trial was extracted as a 2-arm trial comparing FMT with vancomycin. The remaining trials used 2-arm designs (Cammarota 2015, Hota 2017).

Included trials were small, with a median of 39 analysed patients, ranging from 27 (Rode 2021) to 64 (Hvas 2019), which reflects the termination of 4 of the 5 trials at interim analysis.

Patient eligibility criteria were broadly similar to the degree that they included adults with symptomatic CDI recurrence confirmed by positive diagnostic test for CD toxin, and after at least 1 prior failed course of antibiotics. A key difference was that 3 trials (Cammarota 2015, Hota 2017, van Nood 2013) included patients with a mixed number of CDI recurrences not just those with 2 or more recurrences, as stated in the decision problem. Van Nood 2013 report 8 of 43 included patients (19%) presented with a first recurrence. The number of patients included at first recurrence was not specified by Hota 2017 or Cammarota 2015. However, their baseline characteristics suggest these patients were in the minority, Hota 2017 reporting a mean of 4.4 (SD 1.7) prior CDI episodes (Hota 2017), and Cammarota 2015 reporting a median (range) of 3 (1 to 5) CDI recurrences at study inclusion. Rode 2021 also recruited patients with any CDI recurrence but stratified randomization according to the number of prior recurrences (1 vs ≥2), allowing extraction of the multiple recurrence subgroup. The remaining trial (Hvas 2019) recruited patients with 2 or more prior recurrences.

There was also some variation in the interval within which recurrence should occur since the previous CDI episode, with trials requiring recurrence to have occurred within 8 weeks (Hvas 2019), 10 weeks (Cammarota 2015) and 12 weeks of treatment cessation (van Nood 2013), or within 90 days of a prior positive CDI test result (Rode 2021). Although Hota 2017 did not include this as an entry criterion, they reported a shorter interval at baseline with a median of 37 days (IQR 16 to 53) since the last recurrence in FMT patients and 21 days (IQR 12 to 27) for VTP patients.

The duration of follow-up varied from 8 weeks (Cammarota 2015, Hvas 2019) to 6 months (Rode 2021). We noted critical differences in how trials defined the start of follow-up, with 2 trials measuring follow-up from the *initiation* of treatments (Cammarota 2015, van Nood 2013), 2 trials from the *end* of treatments (Hota 2017, Rode 2021), while Hvas 2019 was unclear in this respect, reporting outcome timepoints as ‘after initial treatment’.

5.2 *Critical appraisal of studies*

Trials evaluated small numbers of patients which may affect the reliability of the evidence-base, particularly since 4 of the 5 included trials were stopped early. Two of these (Cammarota 2015, van Nood 2013) were terminated due to early benefit, a method that can risk overestimation of effect (Bassler 2010). One other was a 3-arm trial stopped early for futility of rectal bacteriotherapy (an ineligible comparator for this review), causing unclear concerns regarding this trial's reliability for evaluating FMT (Rode 2021). The remaining trial (Hota 2017) was stopped early on grounds that no significant difference in primary outcome (CDI recurrence at end follow-up) was likely based on examination of interim trial data.

Two reviewers independently assessed the risk of bias using the Cochrane RoB 2.0 tool (appraisal summary presented in Appendix B table B8). Four trials were assessed as at high risk of bias (Cammarota 2015, Hota 2017, Hvas 2019, Rode 2021) due to the open label design and measurement of at least one subjective outcome without systematic microbiological confirmation. Cammarota 2015 and Rode 2021 were judged to have an increased risk of bias due to the measurement of outcomes at different timepoints between trial arms, as a consequence of measuring follow-up from the end of treatments. van Nood 2013 was assessed as having some concerns overall due to its open label design. However, all subjective outcomes required objective confirmation by microbiological testing and were adjudicated by an independent committee.

5.3 *Results from the evidence base*

No trials reported on the effectiveness of FMT to treat patients with refractory CDI.

For patients with recurrent CDI, no RCTs reported on the effectiveness of FMT delivered in oral capsules.

Resolution of CDI

All 5 trials assessed resolution of CDI (shows in table B2), although they varied in their definitions, methods and timepoints of measurement. One trial reported at multiple timepoints (Hvas 2019).

Overall 4 trials found FMT to be significantly superior to vancomycin (Cammarota 2015, Hvas 2019, Rode 2021, van Nood 2013) or fidamoxicin (Hvas 2019), with CDI resolution achieved in 57% (Rode 2021) to 94% (van Nood 2013) of patients receiving FMT (any number of infusions) by enema,

colonoscopy, NJT, or NDT. All 4 used a combination of symptomatic resolution with microbiological confirmation. Two trials reported a single FMT infusion to be superior to vancomycin (Hvas 2019, van Nood 2013) and fidaxomicin (Hvas 2019), while a third trial reported a difference without commenting whether it was statistically significant (Cammarota 2015).

The trial evaluating resolution at multiple timepoints (Hvas 2019) found FMT (by colonoscopy or NJT) to be superior to vancomycin at both 1 week (FMT 54% vs. vancomycin 13%, p=0.01) and 8 weeks (FMT 71% vs. vancomycin 19%, p=0.001) after initial treatment, but superior to fidaxomicin only at 8 weeks (FMT 71% vs fidaxomicin 33%, p=0.009).

Hota 2017 reported CDI resolution in fewer FMT patients than those receiving VTP (43.8% vs. 58.3% respectively) but did not report whether the difference was statistically significant.

Relapse/recurrence of CDI

Recurrence of CDI following trial treatments (shown in table B3) was reported by 4 trials, with some variation in outcome definition and measurement. Hota 2017 was the only trial to report comparable CDI recurrence following FMT (by enema, 56.2%) vs. antibiotic (VTP, 41.7%). The remaining trials (Cammarota 2015, Hvas 2019, van Nood 2013) reported lower CDI recurrences in FMT patients (range 6% to 10%) compared with patients receiving antibiotics (vancomycin range 62% to 69%, fidaxomicin 46%). No trials clarified whether observed differences were statistically significant.

Median time to CDI recurrence (shown in table B4) was poorly reported by 3 trials, with no fully comparative results provided.

CDI-associated diarrhoea

Two trials reported data for this outcome, using widely differing definitions (shown in table B5). For FMT by enema, FMT patients experienced a mean (SD) of 0.8 (0.8) days diarrhoea compared with 1.7 (0.4) in patients receiving VTP (Hota 2017) by 120 days following the end of treatments (statistical difference not reported).

For FMT by colonoscopy or NJT (Hvas 2019), FMT was superior to both fidaxomicin and vancomycin for eliminating diarrhoea caused by CDI, achieving an absence of diarrhoea in more patients at both 1-week follow-up (FMT 100% vs fidaxomicin 79%, p=0.02; and vs. vancomycin 69%, p=0.003) and 8 weeks follow-up (FMT 92% vs fidaxomicin 54%, p=0.003; and vs. vancomycin 31%, p<0.0001).

Treatment failure leading to downstream interventions

Three trials provided data for outcomes using widely differing definitions (shown in table B6). Treatment failure leading to an offer of FMT by NDT (van Nood 2013) (second infusion for FMT patients who failed their first treatment, or first infusion for patients failing antibiotic therapy) occurred in 19% FMT patients and 69% patients receiving vancomycin with or without bowel lavage (statistical difference not reported). Hota 2017 reported that no trial patients (FMT by enema or VTP) experienced a CDI recurrence requiring hospitalisation. Cammarota 2015 reported antibiotic use after initial treatment failure (FMT by colonoscopy or VTP), assessed at the time of writing the manuscript (October 2014, occurring between 5 and 14 months after recruitment). Of 12 patients in the vancomycin arm with CDI recurrence, 7/9 (78%, 3 lost to follow-up) required 1 to 3 further courses of antibiotics. 2 FMT patients (both with pseudomembranous colitis (PMC)) relapsed during the trial period for which 1 dose of antibiotics was administered. However, it was unclear whether this outcome had been systematically ascertained for patients in the FMT arm at this later (post-hoc) timepoint. The author's response to an email contact was unclear, and a further contact for clarification did not receive a reply. This has been documented in the correspondence log.

Mortality

Comparative mortality was reported by 4 trials (Cammarota 2015, Hota 2017, Hvas 2019, van Nood 2013) (shown in table B7), none of which reported a statistically significant difference between FMT and comparator antibiotics. Mortality rates during trial follow-up were low, with 2 trials (Hota 2017, Hvas 2019) reporting no deaths in any patient. Similarly, Rode 2021 recorded no deaths in FMT patients. However, mortality for the comparator arm was not reported for the multiple (≥2) recurrences subgroup. Cammarota 2015 was the only trial to report differing all-cause mortality rates after the end of treatment (October 2014, occurring between 5 and 14 months after patient recruitment), finding 15% among FMT patients and 38% (per protocol analysis) among vancomycin patients. However statistical difference was not reported.

6 Adverse events

Data from the MHRA and FDA

FMT is classified as a medicinal product by the MHRA (Medicines and Healthcare products Regulatory Agency 2020), and as a biologic by the FDA. The MHRA website *Alerts, recalls and safety information* (Gov.UK. 2021) and 3 sections of the FDA website (safety recalls (U.S Food and Drug

Administration 2021a), archived safety recalls (U.S. Food and Drug Administration 2021b), and MedWatch (U.S. Food and Drug Administration 2021c)) were searched on 4 January 2022 using the terms ‘FMT’, ‘faecal’, ‘fecal’, ‘microbiota’ or ‘bacteriotherapy’.

We identified 8 safety notices through FDA MedWatch (U.S. Food and Drug Administration 2019a, 2019b, 2019c, 2020a, 2020b, 2020c, 2020d, 2020e). All notified the potential risk of transmitting pathogenic organisms that had not previously been screened for during the preparation of FMT products. Two of these (5 documents) concerned the transmission of multi-drug resistant organisms (MDROs) and of enteropathogenic *Escherichia coli* (EPEC) and Shigatoxin-producing *Escherichia coli* (STEC), arising following patient deaths due to the use of FMT in the US. Three documents reported 2 patients (1 death) who developed invasive infection caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*), with stool testing retrospectively confirming the presence of same-strain ESBL *E. coli* (U.S. Food and Drug Administration 2019a, 2019b, 2019c). The FDA published recommendations to extend donor screening, including initial questions to identify risk factors for colonisation with MDROs and exclusion of donors considered to be at high risk, with definitions provided, as well as donor stool testing for these organisms (U.S. Food and Drug Administration 2019). Specific guidance was provided for MDRO testing procedures with a notification to FMT product producers to place all existing FMT product into quarantine until this extended screening of donors and stools could be completed (U.S. Food and Drug Administration 2019). Two other notices (U.S. Food and Drug Administration 2020a, 2020b) concerned 5 patients contracting EPEC (n=2) and STEC (n=4) from FMT product produced at the same stool bank, of whom 4 were hospitalised and 2 (with STEC infections) died (single donor). Both patients had chronic medical conditions and received FMT for CDI considered not responsive to standard therapies. Stool was not tested for STEC, therefore it remains unknown if STEC infection contributed to these deaths. FDA recommendations for additional patient protection included the introduction of donor screening and a specific stool testing procedure for EPEC and STEC, for both new donors and stored FMT product (U.S. Food and Drug Administration 2020b).

The final 3 notices (U.S. Food and Drug Administration 2020c, 2020d 2020e) recommend enhanced donor screening and stool testing for the possible transmission of SARS-Cov-2 on all FMT product manufactured from stool donated on or after 1 December 2019 (9 Apr 2020) (U.S. Food and Drug Administration 2020d), not associated with any reported patient events. Recommendations include enhanced donor screening with questions to identify risk of exposure, and testing of donors and donor stool, as well as

adding this infection to informed consent procedures for FMT recipients (23 Mar 2020).

No results were found on the MHRA website.

Adverse events (AEs) and serious adverse events (SAEs) reported by included trials

Because FMT infusions commonly need a procedure to administer the product (with the exception of capsules), we sought to summarise AEs and SAEs related to the procedure (data shown in Table 15) separately from those occurring as a result of all patient care received during the trial follow-up period (data shown in Tables 16 to 17).

Procedural AEs were reported by 4 trials (Cammarota 2015, Hota 2017, Hvas 2019, van Nood 2013) inconsistently, with few comparative results, differences in timepoints used, varying symptom definitions, and no reporting of tests for statistical significance, although some differences are evident. One trial (Hvas 2019) reported the total number of patients experiencing an AE (42%) shortly after FMT (by colonoscopy or NJT) but comparator data is not reported.

The most common AEs include:

- diarrhoea (Cammarota 2015, Hvas 2019, van Nood 2013))
    - 3 trials reporting between 13% (Hvas 2019) and 94% (Cammarota 2015, van Nood 2013) of FMT patients,
- bloating with (Cammarota 2015) or without (Hota 2017, Hvas 2019) abdominal cramps
    - 3 trials reporting between 21% (Hvas 2019) and 60% (Cammarota 2015) of FMT patients,
- abdominal pain or cramps (3 trials (Hota 2017, Hvas 2019, van Nood 2013)
    - reporting between 4% (Hvas 2019) and 44% (van Nood 2013) of FMT patients.

These symptoms resolved within between 3 hours (van Nood 2013) and 12 hours (Cammarota 2015), with those in the Hvas 2019 trial described as ‘transient’ (symptom length not reported by Hota 2017).

In the 2 trials reporting comparative data for antibiotic arm patients AEs are not consistently different to those reported for FMT patients. One trial (Cammarota 2015) reported no events (compared with AEs in at least 94% of FMT patients) and another (Hota 2017) reported similar numbers with AEs for patients during the course of antibiotic treatment. For Hota 2017, the authors

reported no difference in prevalence of abdominal pain, tenderness or bloating at 7 days after FMT or initiation of antibiotics. However, we note possible differences in the prevalence of mucoid stools, smelly stools, feeling generally unwell, or anorexia, which the authors did not comment on or provide p-values for; all of which appear to be more frequent in the FMT group. It was also noted that at 7 to 14 days several symptoms (abdominal pain, tenderness, bloating, mucoid stools and smelly stools) occurred more frequently in patients receiving VTP.

For Rode 2021, AEs were not reported separately for the multiple CDI recurrence subgroup and so have not been extracted. However, the authors did report common mild self-limiting gastrointestinal complaints during the 1-hour observation period following FMT by enema.

SAEs occurring shortly after FMT occurred in 1 patient of 1 trial (Hvas 2019), involving sepsis-like symptoms after an uncomplicated FMT by colonoscopy and resolving without hospitalisation within 24 hours.

Treatment-related AEs occurring by the end of trial follow-up were reported by 3 trials with differences in timepoints used. No differences between arms were found. SAEs by the end of follow-up were reported by Hota 2017, Hvas 2019 and van Nood 2013 (Table 17). There were no differences in SAE rates between arms and none of these events was considered to be related to the study treatments by the trials.

Table 15 Procedural AEs and SAEs (harmful impact of undergoing treatment procedures)

Study	Outcome definition and measure	Timepoint of assessment	Intervention	Number patients analysed	Number patients with event (%)
Hota 2017	Early AEs – occurring between 0 and 7 days after treatment	7 days	FMT (enema)	16	NR 55 events[a]
			VTP	12	NR 36 events[b]
	Late AEs – occurring between 7 and 14 days after treatment	14 days	FMT (enema)	11	NR 33 events[c]
			VTP	12	NR 59 events[d]
Hvas 2019	Immediate AEs	24 hours of procedure	FMT (colonoscopy or NJT)	24	10 (42)[e]
			Fidaxomicin	24	NR
			Vancomycin	16	NR
Hvas 2019	Patients with SAEs ('could be related')	24 hours of procedure	FMT (colonoscopy or NJT)	24	1 (4)[f]
			Fidaxomicin	24	NR
			Vancomycin	16	NR
Cammarota 2015	Diarrhoea	Immediately after donor faeces infusion	FMT (colonoscopy)	20	19 (94)
		During 14 days antibiotic treatment	Vancomycin	19	0 (0)
Cammarota 2015	Bloating and abdominal cramping	Immediately after donor faeces infusion	FMT (colonoscopy)	20	12 (60)
		During 14 days antibiotic treatment	Vancomycin	19	0 (0)
van Nood 2013	Gastrointestinal; treatment-related		FMT (NDT)	16	Diarrhoea: 15 (94) Abdominal cramps: 5 (31)

Study	Outcome definition and measure	Timepoint of assessment	Intervention	Number patients analysed	Number patients with event (%)
		On day of infusion of donor faeces			Belching: 3 (19) Nausea: 1 (6) Abdominal pain (associated with cramping): 2 (13) Dizziness with diarrhoea: 1 (6)[g]
			Vancomycin	13	NR
			Vancomycin with bowel lavage	13	NR

Abbreviations: AE, Adverse event; FMT, Faecal Microbiota Transplantation; NDT, nasoduodenal tube, NJT, Nasojejunal tube; NR, Not reported; SAE, Serious adverse event; VTP, Vancomycin taper pulse.

[a] Reported as: Abdominal bloating 6 (37.5%), Abdominal pain/tenderness 6 (37.5%), Abdominal distension 6 (37.5%), Feeling generally unwell 6 (37.5%), Mucoid stools 6 (37.5%), Smelly stools 6 (37.5%), Fatigure 5 (31.2%), Nausea or vomiting 4 (25%), Fecal incontinence 4 (25%), Anorexia 4 (25%), Fever 1 (6.2%), Bloody stools 1 (6.2%), Skin rash 0.

[b] Reported as: Abdominal bloating 6 (50%), Abdominal pain/tenderness 5 (41.7%), Fatigue 5 (41.7%), Abdominal distension 4 (33.3%), Feeling generally unwell 3 (25%), Nausea or vomiting 3 (25%), Fecal incontinence 3 (25%), Mucoid stools 2 (16.7%), Smelly stools 2 (16.7%), Anorexia 2 (16.7%), Skin rash 1 (8.3%), Fever 0, Bloody stools 0.

[c] Reported as: Abdominal bloating 3 (27.3%), Abdominal pain/tenderness 4 (36.4%), Fatigue 4 (36.4%), Abdominal distension 3 (27.3%), Feeling generally unwell 3 (27.3%), Nausea or vomiting 0, Fecal incontinence 3 (27.3%), Mucoid stools 4 (36.4%), Smelly stools 3 (27.3%), Anorexia 2 (18.2%), Skin rash 0, Fever 2 (18.2%), Bloody stools 2 (18.2%).

[d] Reported as: Abdominal bloating 7 (58.3%), Abdominal pain/tenderness 9 (75%), Fatigue 8 (66.7%), Abdominal distension 4 (33.3%), Feeling generally unwell 4 (33.3%), Nausea or vomiting 3 (25%), Fecal incontinence 4 (33.3%), Mucoid stools 6 (50%), Smelly stools 6 (50%), Anorexia 3 (25%), Skin rash 0, Fever 1 (8.3%), Bloody stools 2 (16.7%).

[e] Reported as: transient abdominal pain 1 (10%), bloating 5 (21%), constipation 1 (10%), diarrhoea 3 (13%)

[f] Reviewer calc %. Patient received FMT by colonoscopy and developed a sepsis-like clinical picture. Patient recovered within 24 hours without hospitalisation.

[g] 1 patient with known autonomic dysfunction.

Table 16 Overall treatment-related AEs (harmful effects of treatment interventions)

Study	Outcome definition and measure	Timepoint of assessment	Intervention	Number patients analysed	Number patients with event (%)	Difference between treatments
Cammarota 2015	Patients with AEs	10 weeks (after end of treatment)	FMT (colonoscopy)	20	0 (0)	NR
			Vancomycin	19	0 (0)	
Hvas 2019	At least one AE or SAE, excluding recurrent CDI	Between 2 days and 8 weeks after treatment	FMT (colonoscopy or NJT)	24	12 (50)	p=0.62
			Fidaxomicin	24	9 (38)	
			Vancomycin	16	8 (50)	
Hvas 2019	GI symptoms without treatment (probably related to intervention)	Between 2 days and 8 weeks after treatment	FMT (colonoscopy or NJT)	24	4 (17)	p=0.89
			Fidaxomicin	24	3 (13)	
			Vancomycin	16	2 (13)	
Hvas 2019	GI symptoms with treatment (probably related to intervention)	Between 2 days and 8 weeks after treatment	FMT (colonoscopy or NJT)	24	2 (8)	p=0.35
			Fidaxomicin	24	3 (13)	
			Vancomycin	16	0 (0)	
Hvas 2019	Other AEs (possibly related to intervention)	Between 2 days and 8 weeks after treatment	FMT (colonoscopy or NJT)	24	3 (13)	p=0.78
			Fidaxomicin	24	2 (8)	
			Vancomycin	16	1 (6)	
van Nood 2013	GI symptoms (treatment related)	During follow up	FMT (NDT)	16	Constipation: 3 (19)	NR
			Vancomycin	13	Dyspepsia: 1 (8) Constipation: 1 (8)	
			Vancomycin with bowel lavage	13	Constipation: 2 (15) Excess gas:	

Study	Outcome definition and measure	Timepoint of assessment	Intervention	Number patients analysed	Number patients with event (%)	Difference between treatments
					1 (8) Persistent diarrhoea: 1 (8)	

Abbreviations*:* AE, Adverse event; CDI, *Clostridioides difficile* Infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; NDT, nasoduodenal tube, NJT, Nasojejunal tube; NR, Not reported; SAE, Serious adverse event.

Table 17 Overall SAEs

Study	Outcome definition and measure	Timepoint of assessment	Intervention	Number patients analysed	Number patients with event (%)	Number of patients in whom events were treatment-related	Difference between treatments
Hota 2017	Patients with SAEs	120 days	FMT (enema)	16	2 (12.5*)	0 (0)	NR
			VTP	12	1 (8.3*)	0 (0)	
Hvas 2019	Patients hospitalised due to SAEs (unrelated to intervention)	Between 2 days and 8 weeks after treatment	FMT (colonoscopy or NJT)	24	5 (21)	0 (0)	p=0.93
			Fidaxomicin	24	6 (25)	0 (0)	
			Vancomycin	16	4 (25)	0 (0)	
van Nood 2013	AE requiring hospitalisation	During follow-up	FMT (NDT)	16	1 (6*)	0	NR
			Vancomycin	13	0	0	
			Vancomycin with bowel lavage	13	0	0	

Abbreviations*:* AE, adverse event; FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; NJT, Nasojejunal tube; NR, Not reported; SAE, Serious adverse event; VTP, Vancomycin taper pulse.
*Reviewer calculated

7 Evidence synthesis and meta-analysis

Five small RCTs were identified, comparing eligible antibiotics with FMT delivered by:

- NDT (1 RCT, total 42 analysed patients)
- enema (2 RCTs, total 57 analysed patients)
- colonoscopy (1 RCT, total 39 patients)
- or a mixture of colonoscopy and NJT (1 RCT, total 64 patients).

No trials were identified evaluating FMT delivered by capsule, by nasogastric tube, or by flexible sigmoidoscopy.

No trials were identified evaluating FMT in patients with refractory CDI.

Due to considerable heterogeneity across all PICO aspects, and small patient numbers, quantitative synthesis was not considered to be appropriate. A narrative synthesis is presented in section 8.

8 Interpretation of the clinical evidence

There is no available RCT evidence for the efficacy or safety of FMT in patients with refractory CDI. Clinical experts have highlighted considerable variability in terminology including a likely overlap between the terms ‘recurrence’, ‘relapse’ and ‘refractory’ (EAC communications log). The EAC notes that the patient eligibility criteria for included trials do not explicitly rule out the inclusion of patients with CDI who might have been refractory to antibiotics, with the possible exception of Hota 2017 who explicitly excluded participants “with evidence of active severe colitis unresponsive to vancomycin”. The 4 remaining trials selected patients who had received at least 1 prior course of antibiotics, and experienced relapse or recurrence of symptoms within 2 to 3 months of treatment, or a positive CD toxin test. Therefore while these trials may have included refractory CDI patients without making this explicit, their focus was very much on patients with recurrent disease.

In patients with CDI recurrence, the available evidence suggests that FMT is more effective than comparator antibiotics for resolving CDI. FMT does not impact on patient mortality. However, none of the trials were powered to

detect a difference in mortality. In addition, follow-up times were short and do not allow inference beyond 3 months after treatment.

The data may suggest that FMT, regardless of infusion modality used, leads to more immediate gastrointestinal side effects than antibiotics. However, these are mild and transient in nature, and differences do not appear to persist beyond the end of treatments. We found no evidence of differences in SAEs. There were also no advisories listed on the MHRA, and those on the FDA concern the contraction of infections due to inadequately screened donors. This systematic review did not systematically identify case report evidence, because it is non-comparative and so is a less reliable indicator of the balance of benefits and harms between two interventions. While we are aware of an often-cited case report of an FMT fatality in the UK due to aspiration penaumonia (Baxter 2015), delivered by enteroscope in an elderly patient with serious comorbidities), the current pharmacovigilance records and results from RCTs do not support evidence for any recent serious harm resulting from FMT.

The evidence is insufficient in quantity, consistency and reporting to infer whether FMT reduces further CDI recurrence, CDI-associated diarrhoea, or downstream interventions following treatment failure when compared with treatment with antibiotics.

Results from the evidence base are difficult to interpret due to the small number of patients evaluated and considerable between-study heterogeneity, particularly in methods of FMT delivery, the number of infusions administered and differences in outcome measurements and timepoints. Methods for measuring outcomes are a weakness that may have distorted treatment effects by incorporating detection bias, resulting from the use of subjective outcomes in an unblinded setting, as well as allowing systematic differences in the timepoints of outcomes according to the allocated intervention (trials commencing follow-up at the end of treatments).

Other weaknesses concern the generalisability of the evidence-base to the UK NHS setting. Differences particularly concern the patients being treated in these trials, with 3 trials including patients presenting at their first CDI recurrence and who are therefore likely to be more responsive to treatment than patients with multiple recurrences. In addition, the trial populations appear to be less frail, with fewer comorbidities, and less likely to be hospitalised than those whom experts have advised are commonly considered for FMT in the UK:

- Most trials included predominantly outpatient populations, with hospitalised patients constituting from 9% (Hvas 2019) to 31% (van

Nood 2013) of the total randomised study population. Hota 2017 did not explicitly report this characteristic at baseline, but in their discussion state that all patients received FMT as outpatients. Rode 2021 did not report the hospitalised proportion for patients with multiple CDI recurrences (the extracted subgroup), although 20% of all patients randomised to the FMT and vancomycin comparator arms were hospitalised at baseline. Cammarota 2015 was the only trial to include a high proportion of patients hospitalised at inclusion (79% overall, 75% FMT patients and 84% vancomycin patients).

- The Charlson Comorbidity Index score (range from 0 to 6 for each of 17 indicators, with higher scores indicating greater severity of illness) was low in most trials with medians of 1 to 2 across most arms. Hota 2017 was the only trial to report a higher average score, with a mean (SD) of 4.5 (2.1) and 5.3 (1.9) in antibiotic and FMT arms respectively. Rode 2021 did not report the Charlson Comorbidity Index score for the extracted subgroup.
- Further indications that some trials did not randomise the most frail patients are found in the Hvas 2019 trial, which excluded patients using antibiotics for CDI at the time of assessment (who are therefore likely to have been more frail than those randomised), and reported a low WHO performance score with a median of 1 for each arm (score ranging from 0 to 5, with 0 being fully active). The van Nood 2013 trial reported a mean (SD) Karnofsky performance status of 50 (18), 50 (17) and 56 (21) in the FMT, vancomycin-only, and vancomycin with bowel lavage groups respectively. This scale ranges from 0 to 100, with higher scores indicating improved functional status.

The evidence base comprises 5 trials from non-UK countries (4 done in Europe (Cammarota 2015, Hvas 2019, Rode 2021, van Nood 2013), and 1 in Canada (Hota 2017)). Following discussion with UK clinical experts, the following were noted as variations from typical patient care in the NHS:

- Experts have advised that in patients receiving FMT, pre-treatment with short-course antibiotics is not standard of care, but is common due to the prevalent hospitalised status of these patients. With antibiotic treatment stopped 24 to 48 hours pre-FMT administration. All 5 trials administrated antibiotic pre-treatment to FMT patients, and in 3 trials for a longer period: Rode 2021 and Hota 2017 administered 125 mg oral vancomycin QID for 7 to 14 days prior to FMT, while the Hvas 2019 trial administered this dose for 4 to 10 days prior to FMT.
- For the antibiotic comparator, experts considered standard vancomycin (not a taper pulse dose) to be used in the NHS at doses

of 125 mg or 250 mg QID. One trial (van Nood 2013) administered a high dose of 500 mg QID, for 14 days.

These differences to NHS practice in FMT delivery and dosage and regimen of comparator antibiotics are fairly limited. However, given the important differences in the types of patient for whom evidence of the effectiveness of FMT has been generated, overall we conclude the evidence-base has limited generalisability to the UK context.

8.1 *Integration into the NHS*

No included trials were conducted in the UK.

NICE (National Institute for Health and Care Excellence 2021a) recommends that FMT should be considered for treating recurrent CDI in adults who have had at least one previous recurrence. The technology is already in use in the NHS, though limited to a small number of specialist centres who either process FMT samples in-house (from a stool bank or produced under an investigational medicinal product license). As such, the only significant changes to the patient care pathway concern the scaling up of FMT sample production in such a way that professionals can use FMT to treat patients at short notice. However, the number of potential recipients in the UK is low (450 to 500 patients annually), consisting of patients presenting with a history of multiple CDI recurrences or refractory CDI, and experts from a UK stool bank advised that scaling up production and delivery of FMT product would be feasible (EAC correspondence log).

The more common mode of administration amongst experts was by NGT and colonoscopy, with one expert noting that the use of capsules is increasing. Experts also concurred that the choice of FMT administration method would likely be guided by the patient and their preference, as well the centre's existing expertise (for example colonoscopy) (EAC correspondence log).

8.2 *Ongoing studies*

The Table 18 below summarises key details for the 3 identified ongoing studies.

Table 18 Ongoing studies

Trial number and location	Population	Intervention	Comparator	Outcomes	Estimated completion date
NCT03970200 (University of Pennsylvania 2020) US	Adults (≥18 years) with ≥1 symptomatic CDI episodes and stool test positive for CD (within 7 days prior to enrolment), receiving antibiotic treatment for severe or severe-complicated/fulminant disease within 72 hours of enrolment.	FMT using Penn Microbiome Therapy; either upper GI (capsules or suspension through feeding tube) or lower GI (enema)	Standard of care antibiotics	Resolution of symptoms; AEs	July 2022
NCT03617445 (University of Wisconsin, Madison 2021) US	Adult (≥18 years) SOT recipients with recurrent symptomatic CDI and stool test positive during 180 days following completion of treatment for prior episode, and with clinical response to oral antibiotics for current episode.	FMT oral capsule	Vancomycin	Recurrence; CDI-related QOL; change in gut microbiota; short- and medium-term safety; intestinal colonisation by MDROs.	December 31, 2023
EUCTR2020-004591-17-ES (Mikrobiomik Healthcare Company S.L. 2020) Spain	Adults (≥18 years) with ≥1 CDI recurrences, a current symptomatic and microbiologically confirmed CDI episode, and ≥1 completed course of oral vancomycin in the primary episode, ending at least 48 hours before study enrolment.	FMT oral capsules	Fidaxomicin	Absence of diarrhoea; duration of hospitalisation; complications requiring an admission in an ICU; time to recurrence/relapse; duration of treatment; overall survival; AEs; mortality; ICU admissions; SF-36	Not stated but competent authority decision only in April 2021

Abbreviations: AE, Adverse events; CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* Infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; ICU, Intensive Care Unit; MDRO, Multi-drug resistant organism; QOL, Quality of life; SF-36, Short Form Survey 36 item; SOT, Solid organ transplant.

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

We carried out a single set of searches to identify both clinical and economic evidence in October 2021 (see section 4.1). Search strategies were not restricted by study design or outcome, and the selection of information resources included specialist economics databases. Full details of the EAC's search methods are provided in Appendix A.

A total of 6,239 papers were identified by the search. 2,346 duplicate records were removed. 3,847 records were excluded at first pass.

At title and abstract screening, 5 papers were excluded as irrelevant.

A total of 41 full texts were screened, of which 29 were excluded as summarised in the PRISMA diagram (Appendix C, Figure C1) and excluded list of records (Appendix F Table F3).

Published economic evidence review

Eight economic evaluation studies (reported in 12 papers) were included that were relevant to the decision problem: Abdali (2020), Baro (2017), Konijeti (2013), Lapointe-Shaw (2016), Luo (2020), Merlo (2016), Varier (2015) and You (2020). The methodologies for these are described below. The study limitations and applicability were assessed using the NICE economic evaluations appraisal checklist (National Institute for Health and Care Excellence 2019) and are also summarised. The full appraisal tables are at Appendix B.

Abdali (2020) carried out a cost-utility analysis to compare four treatments for recurrent CDI; FMT via NG, FMT via colonoscopy, oral fidaxomicin, and oral vancomycin. The population was a hypothetical cohort of hospitalised patients over 65 years who had at least one CDI recurrence. The Markov model had four health states: relapsed, recovered, recurrent CDI and dead. The cycle length was two months, to reflect the duration of treatment and time to recurrence. The perspective was the UK NHS. The time horizon was one year, meaning there was no discounting on cost or effects. The data sources used were based on a pragmatic review of published studies and supplemented with expert opinion from within the research team. The study was judged to have minor methodological limitations and be directly applicable to the research question. The minor methodological limitations identified were the short time horizon, meaning that not all intervention effects

are captured in the model, and the cost of pre-FMT antibiotics and AEs were not included. These limitations are minor and not expected to significantly change the study's conclusion on cost effectiveness.

Baro (2017) conducted a cost-utility analysis to compare five different treatments for second recurrence of community-onset recurrent CDI; VTP, fidaxomicin, FMT via colonoscopy, FMT via NDT, and FMT via enema. The population was hypothetical, an adult experiencing their third occurrence of CDI. The possibility of AEs and death from FMT via colonoscopy and FMT via NDT were included in the decision tree. The model considered recurrent CDI to be an episode occurring within eight weeks after the onset of a previous episode that resolved after completion of the initial treatment. The study had a healthcare provider perspective, in France. However, the study authors stated that a societal perspective was taken. It was deemed to be a healthcare perspective as only healthcare costs were included in the model. The time horizon was 78 days, to reflect the duration of AEs, the duration of initial therapy for the relapse, the expected time to relapse, and the duration of treatment for another relapse. There was no discounting on cost or effects. The data sources used were pooled from published sources, which included clinical studies and systematic reviews. The study was judged to have minor methodological limitations and be directly applicable to the research question. The minor methodological limitations identified included not stating if pre-FMT antibiotics were used and taking unit costs from individual hospitals rather than a national resource. These limitations are minor and not expected to significantly change the study's conclusion on cost effectiveness.

Konijeti (2014) conducted a cost-utility analysis to compare six different treatment options for recurrent CDI. The base case analysis compared four different treatment options: FMT via colonoscopy, metronidazole, fidaxomicin, and vancomycin. Sensitivity analysis was conducted on different modes of FMT delivery: FMT via NDT and FMT via enema. The population was a hypothetical cohort of adults with a median age of 65 years who had recurrent CDI. The decision analytic model modelled up to two recurrences following the initial recurrence of CDI. The time horizon was one year, meaning there was no discounting on cost or effects. The perspective was US societal. The data sources were based on a review of published studies. The study was judged to have minor methodological limitations and be directly applicable to the research question. The minor methodological limitations identified included not incorporating additional costs of AEs or anti-microbial resistance. The utilities were not from the best possible sources because utilities data for the mild to moderate and severe CDI health states had to be extrapolated from other comparable causes of diarrhoea. A longer time period could also potentially capture longer term effects of CDI. These limitations are minor and

not expected to significantly change the study's conclusion on cost effectiveness.

Lapointe-Shaw (2016) conducted a cost-utility analysis to compare six different treatments for the first recurrence of CDI: metronidazole followed by vancomycin for subsequent recurrences, vancomycin followed by vancomycin for subsequent recurrences, fidaxomicin followed by vancomycin for subsequent recurrences, vancomycin with FMT via enema, vancomycin with FMT via NG, and vancomycin with FMT via colonoscopy. The hypothetical population modelled was a 70-year-old with their first recurrence of CDI. The decision analytic model had a six-week cycle, with three potential recurrences modelled totalling an 18-week period. This study had a Canadian healthcare provider perspective. The time horizon was lifetime, with a 5% discount rate applied to costs and QALYs. The data sources were taken from published studies. Lapointe-Shaw was judged to have minor methodological limitations and be directly applicable to the research question. The minor methodological limitations identified included not incorporating additional costs of AEs or anti-microbial resistance. These limitations are minor and not expected to significantly change the study's conclusion on cost effectiveness.

Luo (2020) conducted a cost-utility analysis comparing five different interventions for the first recurrence of CDI: vancomycin, fidaxomicin, vancomycin followed by FMT via colonoscopy, vancomycin followed by FMT via capsules, and a one-time infusion of bezlotoxumab during a course of vancomycin. Bezlotuxumab was not an eligible comparator of interest in the review so data related to this intervention will not be reported. The hypothetical population modelled was a 65-year-old adult experiencing a first recurrence of mild-to-moderate CDI. The decision analytic model followed up to three recurrences of CDI, in which patients who experienced a failure could progress to fulminant colitis requiring hospitalisation and potentially colectomy. The time horizon was six months and the study had a third-party payer perspective in the US. The data sources were taken from the literature, including clinical studies and systematic reviews. The study was judged to have minor methodological limitations and be directly applicable to the research question. The minor methodological limitations identified included not incorporating the additional cost of anti-microbial resistance or AEs. A longer time period would also potentially capture longer term effects of CDI. These limitations are minor and not expected to significantly change the study's conclusion on cost effectiveness.

Merlo (2016) conducted a cost-utility analysis comparing three different interventions for recurrent CDI: vancomycin, FMT via ND, and FMT via colonoscopy. The hypothetical population modelled was a cohort of 1,000

men and women, aged 65 years, who had a relapse of CDI after at least one course of antibiotic therapy. The Markov model had a cycle life of 10 days. Subsequent CDI recurrences were modelled. Recurrent CDI patients who do not respond to therapy can receive another round of treatment, require colectomy, die from fulminant colitis, or die from other causes. The time horizon was stated in the paper as 'long term' that was assumed to be lifetime, with a 5% discount rates on costs and health outcomes. The perspective was not clearly stated in the paper but assumed to be healthcare provider in Australia. The data sources were taken from published studies. Merlo was judged to have minor methodological limitations and be directly applicable to the research question. The minor methodological limitations identified included not conducting deterministic sensitivity analysis on the results or including the cost of antimicrobial resistance in the analysis. To better determine the applicability of this study to the research question the study should have directly stated its perspective and time horizon. These limitations are minor and not expected to significantly change the study's conclusion on cost effectiveness.

Varier (2015) conducted a cost-utility analysis comparing FMT via colonoscopy with vancomycin for the third recurrence of CDI. The hypothetical cohort was adults with a third recurrence of CDI. The decision analytic model had a 90-day time horizon and had a US third party payer perspective. The data sources were taken from published studies. The study was judged to be directly applicable to the research question but with very serious methodological limitations. The methodological limitations identified included not including the cost of antimicrobial resistance, AEs or hospitalisation. Sources for baseline outcomes and intervention effects were not taken from the best available sources, proxy data included using utilities from similar disease states as estimates for CDI, and the probability of death was taken from general colonoscopy procedures rather than the FMT procedure. The unit costs of resources were also not taken from the best available sources, the cost of FMT AEs were assumed to be the same as colonoscopy AEs. These limitations are serious and are highly likely to change the study's conclusions about cost effectiveness.

You (2020) conducted a cost-utility analysis of four different interventions for the first recurrence of CDI: vancomycin, vancomycin with an infusion of bezlotoxumab, fidaxomicin, and endoscopic FMT with vancomycin. Bezlotuxumab was not an eligible comparator of interest in the review so data related to this intervention will not be reported. The hypothetical cohort was of adult patients with irritable bowel disease (IBD), aged 49, with a first recurrence of CDI. The time horizon was 12 weeks with the perspective of a public health-care provider in China. One subsequent CDI recurrence was

modelled. The data sources were taken from published studies. The study was judged to have potentially serious methodological limitations and be partially applicable to the research question. The population modelled was patients with IBD, which affects the age of the cohort modelled as well as the AEs included. The methodological limitations identified included not taking unit costs from the best available source, costs were taken from unspecified 'local sources' and online American databases rather than a national source. The mortality rate was taken from a study of 3,000 IBD patients, rather than being FMT procedure specific. The study did not include the costs of antimicrobial resistance or CDI AEs. These limitations are potentially serious and could change the study's conclusions about cost effectiveness.

Results from the economic evidence

The results from the relevant economics studies are shown in Tables 19 to 26.

Table 19 Economic evaluations results: Abdali 2020

Abdali (2020)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Study design: Cost utility analysis (Markov model). Four possible health states: relapsed, recovered, recurrent CDI and dead. Cycle length is two months and reflects the duration of treatment and time to recurrence. **Country:** United Kingdom **Population description:** Hypothetical cohort of hospitalised patients over 65 years who had at least one CDI recurrence. **Interventions:** Four treatment options for recurrent CDI: • FMT via NGT. • FMT via colonoscopy. • Oral fidaxomicin.	**Perspective:** UK NHS **Time horizon:** One year **Discounting:** No discounting **Data sources:** Based on a pragmatic review of published studies and supplemented with expert opinion from within the study research team.	**Interventions:** (per person) FMT via NGT: £8,877 FMT via colonoscopy: £11,716 Fidaxomicin: £14,399 Vancomycin: £17,279 **Currency and cost year:** GBP (£); 2018	**QALYs:** FMT via NGT: 0.645 FMT via colonoscopy: 0.657 Fidaxomicin: 0.577 Vancomycin: 0.513	**ICERs:** The ICER for FMT via colonoscopy compared with FMT via NGT is £242,514 per QALY gained. Fidaxomicin and vancomycin are dominated by FMT via NGT and FMT via colonoscopy. **Uncertainty:** DSA: the model was not sensitive to the cost of different treatments, cost of hospital stay, the response rates for the antibiotics and mortality associated with CDI. However, FMT via NGT was more effective and less costly than colonoscopy if the efficacy of FMT via NGT was similar to FMT via colonoscopy. The length of hospital stay for FMT via NGT and FMT via colonoscopy was tested	**Author identified:** The model inputs were studies with relatively short-term follow-up and so outcomes beyond the time horizon considered by the model are unknown. The potential side effects associated with the different treatment options were not included in the model. The severity of CDI and the number of previous recurrences were not considered. Recurrent episode is assumed to be caused by the same bacterial strain and not reinfection by a different strain. The effectiveness of antibiotics in the

Abdali (2020)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
• Oral vancomycin.				using the same duration for antibiotic treatment, the results suggested that FMT via NGT and FMT via colonoscopy were still less costly than antibiotic treatment. PSA: 34% of the 10,000 simulations showed FMT via NGT would be more effective and less costly than FMT via colonoscopy. The cost-effectiveness acceptability curve showed that FMT via NGT had a 78% probability of being cost-effective compared with FMT via colonoscopy at the NICE threshold of £20,000.	model is constant regardless of the number of previous recurrences or failure to respond. The true cost of using fidaxomicin or vancomycin may be much higher compared with FMT than the study has suggested, as the costing did not include antimicrobial resistance. **Reviewer identified:** Pre-FMT antibiotics are a regular practice, it is not stated if patients receiving FMT received antibiotics. Pre-FMT antibiotics were not included in the costing of the procedure.
Overall applicability: Directly applicable **Overall quality: Minor limitations**					

Abbreviations*:* CDI, *Clostridioides difficile*; DSA, Deterministic Sensitivity Analysis; FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost-Effectiveness Ratio; NGT, Nasogastric Tube; NHS, National Health Service; PSA, Probabilistic Sensitivity Analysis; QALY, Quality Adjusted Life Year.

Table 20 Economic evaluations results: Baro 2017

Baro (2017)					
Study	**Method of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Study design: Cost utility analysis (Decision tree). **Country:** France **Population description:** Hypothetical adult experiencing a second recurrence (third occurrence) of mild-to-moderate CDI diagnosed at an outpatient visit. Recurrent CDI was defined as an episode occurring within eight weeks after the onset of a previous episode that resolved after completion of the initial treatment. **Interventions:** Competing strategies for the management of second recurrence	**Perspective:** Healthcare however the study authors state that a societal perspective was taken. Only healthcare costs were included in the model. **Time horizon:** 78 days **Discounting:** No discounting **Data sources:** Pooled from published sources, which included clinical studies and systematic reviews.	**Interventions (per person):** VTP: €1,235 Fidaxomicin: €2,464 FMT via NDT: €1,834 FMT via enema: €1,610 FMT via colonoscopy: €1,816 **Currency and cost year:** EUR (€); 2016	**QALYs:** VTP: 0.1812 Fidaxomicin: 0.1988 FMT via NDT: 0.2013 FMT via enema: 0.2019 FMT via colonoscopy: 0.2047	**ICER:** FMT via enema was costlier and more effective thanVTP: €18,092 per QALY gained. FMT via colonoscopy was costlier and more effective than FMT via enema: €73,653 per QALY gained. Fidaxomicin and FMT via NDT were dominated by FMT via colonoscopy and FMT via enema. **Uncertainty:** DSA: the probability of cure and of relapse of VTPand probability of cure of FMT via enema, and cost of severe CDI and utility of mild CDI, had an influence on the model. Varying probability of cure lead to FMT via enema (when	**Author identified:** It was assumed that patients entering the model received outpatient treatment and it did not incorporate potential hospitalisations of those with multiple comorbidities. Conclusions were limited by the quality of the studies included. The lack of a standardised protocol for FMT administration led to difficulties in comparison of efficacy across studies. Costs were not currently available at a national level in France, instead they were taken from specific hospitals. It did not account for potential differences in

Baro (2017)					
Study	**Method of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
of community-onset recurrent CDI: • VTP • Fidaxomicin • FMT via colonoscopy • FMT via NDT • FMT via enema				considering versus FMT via colonoscopy) becoming less effective and costlier or more effective and less costly. PSA: 10,000 Monte Carlo simulations showed that FMT via enema was the most cost-effective strategy in 58% of simulations and FMT via colonoscopy was favoured in 19% at a willingness-to-pay threshold of €32,000 per QALY gained.	treatment efficacy between CDI strains. **Reviewer identified:** The patient age was not specified for the adult cohort. Age will affect the mortality rates in the model. A longer time period would incorporate potential long-term effects of recurrent CDI. Pre-FMT antibiotics are a regular practice, it is not stated if patients receiving FMT received antibiotics. Pre-FMT antibiotics were not included in the costing of the procedure. Costing did not include antimicrobial resistance.
Overall applicability: Directly applicable		**Overall quality: Minor limitations**			

Abbreviations: CDI, *Clostridioides difficile*; DSA, Deterministic Sensitivity Analysis; FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NDT, Nasoduodenal tube; NGT, Nasogastric Tube; PSA, Probabilistic Sensitivity Analysis; QALYs, Quality Adjusted Life Years; VTP, Vancomycin taper pulse.

Table 21 Economic evaluations results: Konijeti 2014

Konijeti (2014)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Study design: Cost utility analysis (decision analytic model). **Country:** United States **Population description:** Hypothetical cohort of adults with a median age of 65 years who have recurrent CDI. **Interventions:** Base case analysis was for four different treatment options for recurrent CDI: • FMT via colonoscopy • Metronidazole • Fidaxomicin • Vancomycin Sensitivity analyses were conducted on	**Perspective:** Healthcare however the study authors state that a societal perspective was taken. Only healthcare costs were included in the model. **Time horizon:** One year **Discounting:** No discounting **Data sources:** Based on a review of published studies.	**Interventions:** (per person) FMT via colonoscopy: $3,149 Metronidazole: $3,941 Fidaxomicin: $4,261 Vancomycin: $2,912 FMT via NDT: $4,208 FMT via enema: $4,090 **Currency and cost year:** US Dollars ($); 2012	**QALYs** FMT via colonoscopy: 0.8719 Metronidazole: 0.8292 Fidaxomicin: 0.8653 Vancomycin: 0.8580 FMT via NDT: 0.8553 FMT via enema: 0.8543	**ICERs:** Initial treatment with FMT via colonoscopy was the most cost-effective strategy at the willingness-to-pay threshold of $50,000 per QALY, with an ICER of $17,016 per QALY gained compared with vancomycin. Treatment of recurrent CDI by first-line fidaxomicin or metronidazole was both more expensive and less effective than FMT via colonoscopy. In sensitivity analyses, FMT delivery by less effective strategies (duodenal infusion or enema) was not cost-effective. **Uncertainty:** One way sensitivity analysis showed that	**Author identified:** The study did not account for potential differences in treatment efficacy between CDI strains. The utilities for mild-moderate and severe CDI had to be extrapolated from other comparable causes of diarrhoea. The costs attributed to FMT did not include the infrastructure and personnel costs required in establishing an FMT program. **Reviewer identified:** The potential side effects associated with the different treatment options

Konijeti (2014)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
different modes of FMT delivery, also including: • FMT via NDT • FMT via enema				examining other methods of FMT delivery, FMT via NDT and FMT via enema became more cost-effective than initial vancomycin if their cure rates were >85.2%. The PSA supported findings from the base case analysis, with an ICER of $20,285 for FMT via colonoscopy compared with vancomycin.	were not included in the model. Costing did not include antimicrobial resistance. A longer time period would incorporate potential long-term effects of recurrent CDI. Results of the PSA were not reported in detail.
Overall applicability: Directly applicable **Overall quality: Minor limitations**					

Abbreviations*:* CDI, *Clostridioides difficile*; FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost-Effectiveness Ratio; NDT, Nasoduodenal tube; PSA, Probabilistic Sensitivity Analysis; QALY, Quality Adjusted Life Year.

Table 22 Economic evaluations results: Lapointe-Shaw 2016

Lapointe-Shaw (2016)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Study design: Cost utility analysis (decision analytic model and Markov model).	**Perspective:** Healthcare provider **Time horizon:** Lifetime	**Interventions:** (per person) Metronidazole: $5,386 Vancomycin: $5,929 Fidaxomicin: $7,319 FMT via enema: $5,667	**QALYs** Metronidazole: 9.09 Vancomycin: 9.03 Fidaxomicin: 9.16 FMT via enema: 9.26 FMT via NG: 9.15	**ICERs:** FMT via colonoscopy was dominant in the base case, as it was cost-saving and more	**Author identified:** Conclusions are limited by the quality of parameter estimates.

Lapointe-Shaw (2016)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Country: Canada **Population description:** Hypothetical cohort based on a 70-year-old in the community experiencing their first recurrence of CDI. Up to three CDI recurrences were modelled. **Population size:** 1000-person cohort (when evaluating healthcare outcomes) **Interventions:** • Metronidazole (oral) followed by vancomycin (oral) for subsequent recurrences. • Vancomycin (oral) followed by vancomycin (oral) for subsequent recurrences. • Fidaxomicin (oral) followed by	**Discounting:** 5% discount rates on costs and QALYs (lifetime) **Data sources:** Taken from published sources.	FMT via NG: $5,935 FMT via colonoscopy: $5,246 **Currency and cost year:** Canadian Dollars ($); 2014	FMT via colonoscopy: 9.40 **Health outcomes, per 1000 cohort** Count of recurrences after the first • Metronidazole: 583 • Vancomycin: 636 • Fidaxomicin: 458 • FMT via enema: 340 • FMT via NG: 426 • FMT via colonoscopy: 144 Count of hospitalisations • Metronidazole: 275 • Vancomycin: 284 • Fidaxomicin: 253 • FMT via enema: 233 • FMT via NG: 247 • FMT via colonoscopy: 199 Count of CDI related deaths • Metronidazole: 115 • Vancomycin: 119 • Fidaxomicin: 106 • FMT via enema: 98	effective than all other treatment options. Analyses of cost-effectiveness were made using a willingness-to-pay threshold of $50,000 per QALY. **Uncertainty:** One way sensitivity analysis. Varying all parameters within their stated ranges did not change the preferred treatment strategy, with one exception. FMT via enema became the preferred strategy when the probability of recurrence following this strategy dropped below 8.7%. PSA with 10,000 Monte Carlo trials showed that FMT via colonoscopy was the most beneficial strategy in 87% of trials at a willingness-to-pay	Probability of recurrence remained fixed over time, yet recurrence risk probably declined over time if a first recurrence had not occurred. Conversely, risk of recurrence was thought to rise in relation to the number of recurrences already experienced. The study did not model colectomy as a distinct state. The study did not model adverse drug events because of the mild and transient nature of reported events. **Reviewer identified:** The study did not evaluate how treatment effectiveness would be impacted by

Lapointe-Shaw (2016)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
vancomycin (oral) for subsequent recurrences • Vancomycin with FMT via enema followed by the same using a different donor at each subsequent recurrence • Vancomycin with FMT via NG followed by the same using a different donor at each subsequent recurrence • Vancomycin with FMT via colonoscopy followed by the same using a different donor at each subsequent recurrence			• FMT via NG: 108 • FMT via colonoscopy: 84 Average life years • Metronidazole: 14.78 • Vancomycin: 14.46 • Fidaxomicin: 14.90 • FMT via enema: 15.04 • FMT via NG: 14.87 • FMT via colonoscopy: 15.26	threshold of $50,000 per QALY.	different strains of CDI. The study authors did not include antimicrobial resistance when evaluating the costs.
Overall applicability: Directly applicable **Overall quality: Minor limitations**					

Abbreviations*:* CDI, *Clostridioides difficile*; FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost-Effectiveness Ratio; NG, Nasogastric; PSA, Probabilistic Sensitivity Analysis; QALY, Quality Adjusted Life Year.

Table 23 Economic evaluations results: Luo 2020

Luo (2020)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Study design: Cost utility analysis (decision analytic). **Country:** United States **Population description:** Hypothetical cohort based on a 65-year-old adult experiencing a first recurrence of mild-to-moderate CDI. Up to two subsequent CDI recurrences were modelled. **Interventions:** • Vancomycin. • Fidaxomicin. • Vancomycin followed by FMT via colonoscopy. • Vancomycin followed by FMT via capsules. • Bezlotoxumab (one time infusion) during vancomycin.	**Perspective:** Third-party payer **Time horizon:** 6 months **Discounting:** No discounting **Data sources:** Taken from literature including clinical studies and systematic reviews.	**Interventions (per person):** Vancomycin, 6-week course: $2,542 Fidaxomicin, 10-day course: $4,639 FMT via colonoscopy: $2,671 FMT via capsules: $1,950 **Currency and cost year:** US Dollars ($); 2019	**QALYs** Vancomycin: 0.421 Fidaxomicin: 0.429 FMT via colonoscopy: 0.435 FMT via capsules: 0.429	**ICERs:** FMT via capsules was a cost-effective treatment strategy, with an ICER of $31,205 per QALY gained compared with FMT via colonoscopy. Based on the willingness-to-pay (WTP) threshold of $100,000 per QALY, the strategies of vancomycin, fidaxomicin were dominated by both of the FMT strategies. **Uncertainty:** One way sensitivity analysis. Using an effectiveness of >84.5% or a cost <$3,035, FMT via capsules became the dominant strategy. FMT via capsules dominated when the cost of a colonoscopy exceeded $4,075.	**Author identified:** The study extrapolated data from multiple studies to inform the inputs for costs, effectiveness and utilities. No prospective data on recurrence had been published for FMT oral capsules, so estimates were based on available data from studies which documented lack of clinical resolution as a surrogate. The study did not evaluate how treatment effectiveness would be impacted by different strains of CDI. The study assumed probabilities of cure,

Luo (2020)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
N.B Bezlotuxumab was not an eligible comparator of interest in the systematic review so data related to this intervention are not reported.				PSA showed that FMT via colonoscopy was the most beneficial strategy in 49.5% of trials and FMT via capsules was favoured in 42.3% of trials at a willingness to pay threshold of $100,000 per QALY. At a threshold of $50,000 per QALY, FMT via colonoscopy was the most beneficial strategy in 46.6% of trials and FMT via capsules was favoured in 44.3%. FMT via capsules dominated as the most beneficial strategy at all willingness to pay thresholds less than $28,500 per QALY.	recurrence, and hospitalisation rates would be similar for all recurrences of CDI. The study did not model AEs. **Reviewer identified:** For baseline results a willingness to pay threshold of $100,000 per QALY gained was used. However, $50,000 is a more commonly cited threshold in the US. The study did not include antimicrobial resistance when evaluating the costs of vancomycin or fidaxomicin. The six-month time horizon may not be long enough to capture all of the long-term effects of CDI.
Was used, Overall applicability: Directly applicable Overall quality: Minor limitations					

Abbreviations: AE, Adverse Event; CDI, *Clostridioides difficile*; FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost-Effectiveness Ratio; NG, Nasogastric; PSA, Probabilistic Sensitivity Analysis; QALY, Quality Adjusted Life Year; WTP, willingness-to-pay.

Table 24 Economic evaluations results: Merlo 2016

Merlo (2016)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Study design: Cost utility analysis (Markov model). **Country:** Australia **Population description:** A hypothetical cohort of men and women, aged 65 years, who had a relapse of CDI after at least one course of antibiotic therapy. Subsequent CDI recurrences were modelled. **Population size:** Cohort of 1000 patients **Interventions:** • Vancomycin	**Perspective:** Not stated **Time horizon:** Long term, assumed to be lifetime **Discounting:** 5% discount rates on costs and health outcomes **Data sources:** Taken from published sources.	**Interventions (per person):** FMT via colonoscopy: $2,251 FMT via nasoduodenal infusion: $2,190 Vancomycin • First cycle: $658 • Subsequent cycles: $438 **Currency and cost year:** Australian Dollars (AU$); 2015	**QALYs** CDI: 0.88 Colectomy: 0.536 Ileostomy: 0.7	**ICERs:** Both FMT via nasoduodenal infusion and FMT via colonoscopy resulted in improved quality of life and reduced cost compared with vancomycin. The incremental effectiveness of either FMT delivery compared with vancomycin was 1.2 (95% CI: 0.1, 2.3) QALYs, or 1.4 (95% CI: 0.4, 2.4) life years saved. Treatment with vancomycin resulted in an increased cost of $4,094 (95% CI: $26, $8,161) compared with FMT via nasoduodenal infusion and $4,045 (95% CI: $33, $8,124)	**Author identified:** The model did not incorporate the risks of FMT via nasogastric infusion over FMT via colonoscopy, for example aspiration and vomiting. The efficacy rate of vancomycin after each round of treatment was assumed to be constant. **Reviewer identified:** The study did not account for potential differences in treatment efficacy between CDI strains. The study did not account for antimicrobial

Merlo (2016)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
• FMT via nasoduodenal infusion • FMT via colonoscopy.				compared with FMT via colonoscopy. **Uncertainty:** PSA was undertaken using the Monte Carlo method with 1,000 simulations. The results were not stated.	resistance in the costing.
Overall applicability: Directly applicable **Overall quality: Minor limitations**					

Abbreviations*:* CDI, *Clostridioides difficile*; FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost-Effectiveness Ratio; NG, Nasogastric; PSA, Probabilistic Sensitivity Analysis; QALY, Quality Adjusted Life Year.

Table 25 Economic evaluations results: Varier 2015

Varier (2015)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Study design: Cost utility analysis (decision analytic model). **Country:** United States **Population description:** Hypothetical cohort of adults with the third recurrence of CDI.	**Perspective:** Third party payer **Time horizon:** 90 days **Discounting:** No discounting **Data sources:** Taken from published sources.	**Interventions (per person):** Vancomycin: $3,788 FMT via colonoscopy: $1,669 **Currency and cost year:** US Dollars ($); 2011	**QALYs** Vancomycin: 0.235 FMT via colonoscopy: 0.242	**ICERs:** FMT via colonoscopy was dominant in the base case compared with vancomycin. **Uncertainty:** One-way sensitivity analysis was carried out. FMT via colonoscopy was more effective than vancomycin as long as the cure rate for FMT via colonoscopy was ≥70%	**Author identified:** AEs of vancomycin not included. AEs and probability of death from FMT via colonoscopy were assumed to be equivalent to diagnostic colonoscopy procedures. It was assumed that all patients entering

Varier (2015)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Interventions: • Vancomycin • FMT via colonoscopy				and was less costly than vancomycin as long as the cure rate for FMT via colonoscopy was ≥53%. FMT via colonoscopy was no longer dominant when the cure rate for vancomycin exceeded 90% and when the cost of FMT via colonoscopy exceeded $3,205. PSA showed that FMT via colonoscopy was the dominant strategy in all 10,000 Monte Carlo Simulations.	the model received outpatient treatment, which decreased costs since it did not incorporate hospitalisations. Data used for parameters in the model came from different studies of varying quality. The study did not incorporate the costs of AEs. **Reviewer identified:** The age of the hypothetical cohort was not specified. The study did not account for potential differences in treatment efficacy between CDI strains.
Overall applicability: Directly applicable **Overall quality: Very serious limitations**					

Abbreviations*:* AE, Adverse Event; CDI, *Clostridioides difficile*; FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost-Effectiveness Ratio; NG, Nasogastric; PSA, Probabilistic Sensitivity Analysis; QALY, Quality Adjusted Life Year.

Table 26 Economic evaluations results: You 2020

You (2020)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
Study design: Cost utility analysis (decision analytic model). **Country:** China **Population description:** Hypothetical cohort of adults (base case age: 49) with inflammatory bowel disease (IBD) with first recurrence of CDI. One subsequent CDI recurrence was modelled. **Interventions:** • Vancomycin. • Vancomycin plus bezlotoxumab. • Fidaxomicin. • FMT via lower endoscopy plus vancomycin.	**Perspective:** Public healthcare provider **Time horizon:** 12 weeks **Discounting:** NA **Data sources:** Taken from published sources.	**Interventions (per person):** Vancomycin: $14,860 Fidaxomicin: $15,470 FMT via lower endoscopy: $11,680 **Currency and cost year:** US Dollars ($); 2019	**QALY loss** Vancomycin: 0.65400 Fidaxomicin: 0.65231 FMT via lower endoscopy: 0.65082	**ICERs:** FMT via lower endoscopy dominated the other interventions. Fidaxomicin versus vancomycin: $360,947 per QALY gained. The ICER of fidaxomicin exceeded the willingness to pay threshold of $48,916 **Uncertainty:** One-way sensitivity analysis found that QALY loss and cost of the FMT via lower endoscopy group remained lower than the other intervention arms throughout variation of all clinical inputs, utility inputs and cost inputs into the model. The PSA using 10,000 Monte Carlo simulations	**Author identified:** Morality rate in all study arms is taken from that of 3,000 inflammatory bowel disease patients. The model may underestimate the direct medical costs and QALY loss for serious events in all study groups. **Reviewer identified:** They did not account for potential differences in treatment efficacy between CDI strains. They did not account for antimicrobial resistance in the costing. The 12-week time horizon may not be long enough to

You (2020)					
Study	**Methods of analysis**	**Costs**	**Effectiveness outcomes**	**Results/ incremental outcomes**	**Limitations**
N.B Bezlotuxumab was not an eligible comparator of interest in the review so data related to this intervention are not reported				showed that FMT via lower endoscopy saved QALYs at lower cost in 99.3% (versus vancomycin) and 99.7% (versus fidaxomicin) of the simulations.	capture long term effects of CDI The authors do not specify what donor screening for FMT via lower endoscopy was undertaken, and if this is included in the FMT via lower endoscopy intervention cost
Overall applicability: Partially applicable **Overall quality: Potentially serious limitations**					

Abbreviations*:* CDI, *Clostridioides difficile*; FMT, Faecal Microbiota Transplantation; IBD, inflammatory bowel disease; ICER, Incremental Cost-Effectiveness Ratio; NG, Nasogastric; PSA, Probabilistic Sensitivity Analysis; QALY, Quality Adjusted Life Year.

Eight economic evaluations studies were included that were relevant to the decision problem: Abdali 2020, Baro 2017, Konijetic 2013, Lapointe-Shaw 2016, Luo 2020, Merlo 2016, Varier 2015 and You 2020. The results of all of the included studies showed the cost-effectiveness of at least one mode of FMT in comparison to at least one other intervention for recurrent CDI.

These results are significant in showing how previous studies have evaluated FMT interventions in comparison to antibiotics for treating recurrent CDI. In terms of cost-effectiveness, seven of the eight studies found FMT to be dominant compared with antibiotic treatments, i.e. both cost saving and more effective: Abdali 2020, Konijeti 2013, Lapointe-Shaw 2016, Luo 2020, Merlo 2016, Varier 2015 and You 2020. Baro 2017 reported that FMT via enema and FMT via colonoscopy were more effective but costlier than vancomycin. Only one study reported results of effectiveness outcomes analyses other than QALYs. Lapointe-Shaw also reported on the count of recurrences of CDI, count of hospitalisations, count of CDI related deaths and average life years.

9.2 *De novo cost analysis*

The clinical and cost benefits of using FMT to treat recurrent CDI have been reported in previous studies (Abdali (2020), Baro (2017), Konijeti (2013), Lapointe-Shaw (2016), Luo (2020), Merlo (2016), Varier (2015), and You (2020)), exploring the various different routes of administrations. However, the economic studies identified did not specifically estimate the use of FMT as first line treatment for people experiencing a third episode of CDI within a UK setting. For this reason, a cohort-based cost-effectiveness model was developed to evaluate the economic impact of FMT use for adults with second recurrent CDI.

The clinical effectiveness trials identified in the systematic review specifically recruited people with recurrent CDI. The EAC notes that, due to the overlapping clinical definitions of relapse and recurrence, some trial patients may have been CDI relapse cases. Although it is also conceivable that some patients were also refractory, there is no evidence within trials to inform either supposition and therefore the economic model focuses only on recurrent CDI.

A summary of the decision problem is outlined in the table below.

Table 27: Decision problem

Element	**Description**
Population	Adults with recurrent CDI who have had 2 or more previous episodes

Intervention	FMT colonoscopy FMT enema FMT nasoduodenal tube (NDT) FMT oral capsules
Comparator	Vancomycin Fidaxomicin Vancomycin taper pulse (VTP)
Outcomes	Incremental costs
Perspective	NHS and personal social services

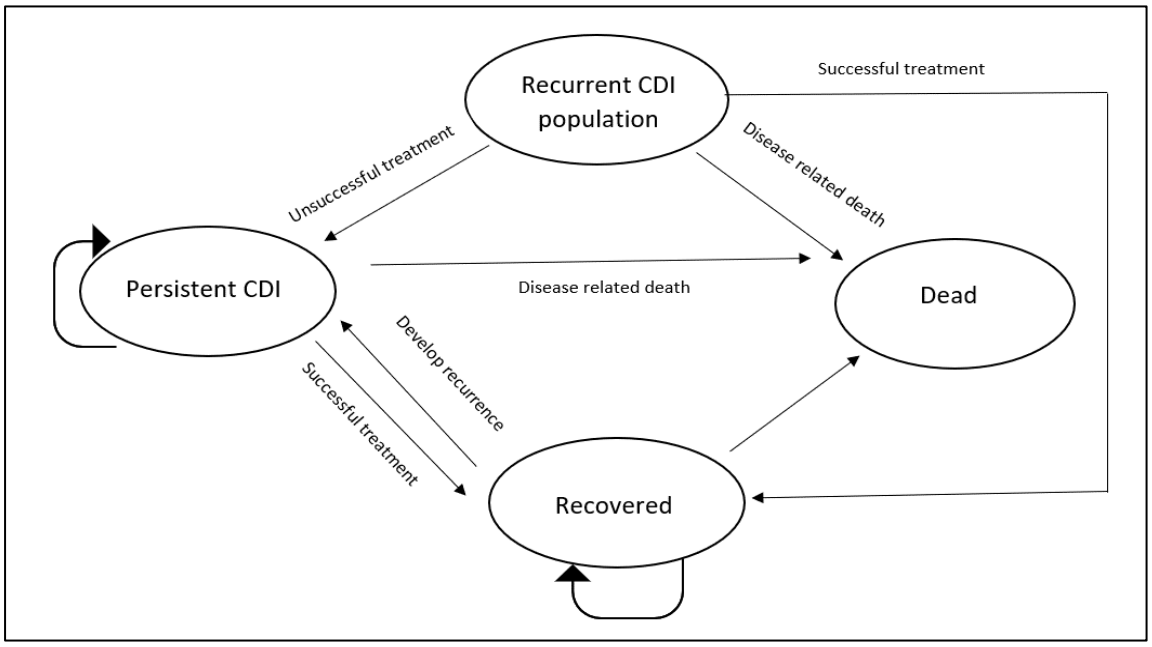
Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; NHS, National Health Service; VTP, Vancomycin taper pulse.

Four routes of FMT administration were included in the model; two for lower GI (colonoscopy and enema) and one for upper GI (NDT), and one for oral capsules. Flexible sigmoidoscopy and other forms of upper GI route such as endoscopy-based routes were not included due to lack of data in the clinical trials identified. Whilst, NGT is one of the most commonly used routes of administration in the NHS, no RCTs were identified within the clinical evidence review to inform parameters for this administration route and was, therefore, excluded from the model. However, it was assumed that any conclusions regarding the clinical benefits of NDT, as sourced from van Nood, may be applicable for NGT. This assumption is based on historical views on how comparable NGT and NDT are. For example, the clinical parameters for NGT applied in the Abdali (2020) cost-effectiveness study was synthesised by pooling results from multiple studies which included delivering FMT via nasojejunal tube and NDT. Another example includes a systematic review by Ramai (2020) which reported the outcomes for different routes of FMT administration by pooling data from multiple studies for each route. The authors combined NDT and NGT studies on the basis of anatomical proximity and clinical application of the administration mechanisms. Based on the above, economic impact of NGT was not explicitly modelled. However, the potential cost-effectiveness of FMT via NGT is explored further in the discussion based on the analyses conducted for the 4 FMT administration routes included in the model. For context, evidence on FMT via NGT cost and effectiveness is provided within the methods section, where available, along with details on the limitations of the evidence.

Vancomycin (500 mg) with or without metronidazole was not included as a comparator based on clinical advice that this is not commonly used as treatment for this population.

A cohort Markov model structure was developed and is consistent with a previous economic model published by Abdali (2020). The model structure is displayed in Figure 1 below.

Figure 1: Markov model structure



Four health states are captured in the model:

- Recurrent CDI population (i.e. third CDI episode - starting state)
- Persistent CDI (recurrent/ relapse/ refractory CDI)
- Recovered
- Dead

The economic model developed for the CDI clinical guideline (NICE 2021a) was based on a 90-day decision tree followed by a Markov model used to capture long-term outcomes. The model considered a population presenting with their first CDI infection with multiple decision trees used to capture recurrence/ relapse over the course of 90 days followed by a Markov model to capture lifetime costs and benefits. For the current decision problem this set up was not considered to be applicable. Firstly, it is difficult to assess long-term patient outcomes within the second recurrent CDI population due to scarcity of data. Therefore, the construction of a lifetime model would not be appropriate. Secondly, the primary benefit of a decision tree in this instance is the flexibility to incorporate differential treatment impact rates as people experience another recurrence or relapse. However, due to data limitations to inform variable effectiveness parameters within this population, a Markov model structure was deemed more appropriate whereby the rates of recovery and relapse are assumed to be constant.

The cohort starts in the 'recurrent CDI population' health state. Following treatment, the cohort is then divided between recovered, persistent (where people still have CDI), or dead (as a consequence of infection or other causes) health states. Individuals can recover at any time from the persistent health state. In subsequent cycles, a proportion of the recovered population may experience another recurrence or relapse of CDI, where the rate of recurrence is assumed to be the same regardless of whether people recovered from their third CDI episode or from the persistent state. Individuals can die at any point upon which they will move into the dead state.

Clinical expert opinion defined relapse as another CDI event, often caused by the same strain of CD, which occurs within 12 weeks from resolution of previous CDI episode. Recurrent CDI is defined as an infection which is often caused by another strain of CD, occurring 12 weeks after resolution of previous CDI infection (NICE 2021a). Given the clinical definitions for CDI recurrence and relapse, the use of 12-weekly cycles would be most appropriate for the decision problem. However, whilst there is possibility that the trial outcomes are capturing both recurrent and relapsed cases, it was not possible to differentiate between the two based on the evidence reported. Therefore, the cycle length was determined by outcomes as available from the clinical trials, such as time to recurrence and treatment duration, and determined to be 2 months. The rationale for this is as follows:

1. Time to recurrence was reported for 3 of the key clinical trials identified (Hota 2017, van Nood 2013, and Cammarota 2015). Hota (2017) reported median recurrence to be 9 days after FMT via enema and 35 days after initiating VTP. The regimen for VTP was an initial 14 days of vancomycin followed by a taper over 4 weeks. Van Nood (2013) reported median time to recurrence of 23 days for vancomycin with a range of 13 to 43 days. Cammarota (2015) reported a median time to recurrence of 10 days after completion of VTP. The treatment regimen was reported as 10 days treatment followed by tapering for at least 21 days. Whilst time to recurrence was not reported for fidaxomicin, vancomycin, and other routes of FMT, based on the reported values, median time to recurrence was considered to be under 90 days after treatment initiation.

2. The cycle length should be of an appropriate length to capture the full initial treatment cost, particularly as FMT can be provided in one day. VTP is associated with the longest treatment duration, and estimated to last approximately 6 weeks where this can vary. For example, Hota (2017) applied tapering for 4 weeks, following an initial 2 week treatment, but also reported that this should be given for as long as is

needed. Therefore, given the above, a 1-month cycle was not considered appropriate.

3. Within the clinical trials identified, most outcomes regarding resolution were provided at 2 months or within that time frame from treatment. However, there is large uncertainty in the time to outcome as there is variability in reporting across trials regarding from what starting point outcomes are reported; time from end of treatment versus treatment initiation.

Based on the points above a 2-month cycle was considered to be most appropriate. This is consistent with previous CDI models as identified in the economic evidence review, Abdali (2020) and Luo (2020).

A time horizon of 6 months was applied in the base case analysis. This was considered appropriate given the duration of the follow up for effectiveness reported in the key clinical trials identified, and the mortality data used to inform the model (Cammarota 2015, Hota 2017, Hvas 2019, Karas 2010, Olsen 2015, Rode 2021, van Nood 2013). Additionally, a time horizon of 6 months allows for potentially 3 further recurrences of CDI to be modelled in the recurrent CDI population.

No AEs were included as FMT related events were reported to resolve within 24 hours in the key clinical trials identified. Pre-antibiotic treatment was applied before index FMT treatment, based on clinical opinion, but not for any subsequent FMT treatments. Bowel lavage was excluded as this was not considered to be commonly used within the NHS for FMT treatment.

The key assumptions applied in the model are:

- If initial treatment failed, people are treated with the same treatment again.
- Constant response and recurrence rates for same treatment option in each cycle.
- Of those who recover from CDI, regardless of which state they recovered from (i.e. starting state or persistent state), it is assumed that the risk of death is comparable to the general population, once recovered.
- Pre-antibiotic treatment is not provided for FMT administration for subsequent treatments (only applied for the initial FMT administration).
- Initial provision of treatment is assumed to also include 5 days of hospital stay for FMT and 10 days hospital stay for antibiotics (as

applied in Abdali (2020)). Ongoing treatment after this period is assumed to occur at home (e.g. for VTP).

- Costs of tests and follow up is assumed to not differ between the intervention and comparators and excluded from the model.

Economic model parameters

The model follows a hypothetical cohort of patients diagnosed with recurrent CDI. A base case starting age of 68 was applied, calculated from the median ages of populations receiving FMT, fidaxomicin, and vancomycin in the Hvas (2019) trial. A cohort of 1,000 hypothetical patients were simulated through the model.

Four different routes of administration for FMT are included: colonoscopy and enema (both lower GI route), NDT (upper GI route), and oral capsules. The inclusion of the relevant administration routes was based on evidence available for the target population explored, although there is large uncertainty regarding the data available for the included FMT routes of administration (see below for further details). Whilst no eligible RCTs were identified comparing FMT oral capsules against antibiotics in people with a second recurrence of CDI, 2 studies were identified comparing oral capsules to FMT colonoscopy (Kao 2017, Ramai 2020). The Kao (2017) RCT compared FMT colonoscopy to oral capsules in people with at least 3 documented episodes of CDI (sample size of 116). The trial reported capsules to be non-inferior to FMT colonoscopy when comparing the proportion without recurrence at 12 weeks. The Ramai (2020) systematic review and meta-analysis estimated the pooled efficacy of specific administration routes in people with recurrent CDI. The meta-analysis estimated the efficacy of FMT colonoscopy and oral capsules to be comparable with an overall cure rate of 94.8% (CI 83.4-90.5%) and 92.1% (88.6-95.0%), respectively (Ramai (2020)). Given the above, the resolution and recurrence probabilities used to inform the transition probabilities for oral capsules were assumed to be the same as FMT colonoscopy.

Clinical parameters and variables

The key clinical parameters used to inform the model are listed in Table 28 below.

Table 28: Clinical parameters used in the model

Variable	Value used	Source

Probability of CDI resolution		
FMT colonoscopy	92.0%	Hvas 2019
FMT NDT	94.0%	Van Nood 2013
FMT oral capsule	92.0%	Assumed same as FMT colonoscopy base on Kao 2017
FMT enema	76.0%	Rode 2021
Vancomycin	19.0%	Hvas 2019
Fidaxomicin	42.0%	Hvas 2019
VTP	48.0%	Rode 2021
Probability of CDI recurrence		
FMT colonoscopy	8.3%	Hvas 2019
FMT NDT	8.3%	Assumed same as FMT colonscopy
FMT oral capsule	8.3%	Assumed same as FMT colonscopy
FMT enema	8.3%	Assumed same as FMT colonscopy
Vancomycin	69%	Hvas 2019
Fidaxomicin	46%	Hvas 2019
VTP	42%	Hota 2017

Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.

The meta-analysis conducted by Ramai and colleagues estimated the pooled, overall cure rate for NGT based on data from 6 studies, including one NDT study (van Nood 2013). 3 studies were retrospective case series, 2 of which was based in the United States (Aas 2003, Rubin 2013) and one in the UK (MacConnachie 2009). 2 studies were RCTs where one was conducted in the Netherlands (van Nood 2013), and used to inform NDT in this model, and the second was conducted in the United States (Youngster 2014). The remaining was a prospective United States study (Gundacker 2017). The overall cure rate for NDT was therefore estimated to be 78.1% (95% CI 71.86% to 81.4%). However, there were substantial differences in the number of infusions and the dose per infusion, where reported, between the studies. Additionally, there was variability regarding when outcomes were reported (e.g. 2 weeks after FMT in Gundacker 2017 compared with 12 weeks in Aas 2003). There was also variability in the number of previous episodes of CDI (e.g. more than 5 CDI episodes considered in Gundacker 2017 and up to 16 cases in Youngster 2017). Therefore, pooled estimates for NGT from Ramai 2020 may be an underestimate. However, it remains indicative of being clinically superior to the antibiotic only regimens considered in this model.

Mortality was applied in the model for the three different health states. All-

cause mortality, sourced from the Office for National Statistics (2021) life tables, was applied to people in the recovered health state. Given a starting age of 68, the 2-monthly mortality risk was estimated to be 0.2%. According to clinical opinion, mortality may not be comparable to the general population following recovery from CDI. However, based on a Danish multicentre cohort study (Hensgens 2013), the long-term impact of CDI on mortality, whilst higher than in the general population, may be small. Therefore, this assumption is likely to have a marginal impact on the results.

Those with CDI are subject to a higher mortality rate. The 6-month mortality risk for non-recurrent CDI was sourced from Karas 2010 (29.8%). The 6-month hazard ratio for mortality in the recurrent CDI population against non-recurrent CDI population was sourced from Olsen 2015 (1.33). The 6-month mortality risk for non-recurrent CDI was converted to a 6-month rate and then multiplied by the hazard ratio to estimate the 6-month mortality rate from recurrent CDI. This was divided by 3 to estimate 2 monthly mortality rates and converted into a risk, estimated to be 14.5%.

The model includes fulminant colitis (FC) as an additional complication of prolonged CDI. However, the study informing the hazard ratio for recurrent CDI mortality did not provide details on the presence of FC within the population considered for the analysis. Given that FC has an estimated prevalence of 16% (Varier 2015), additional mortality was not applied within the model because it was assumed that this was likely to be captured in the underlying non-recurrent CDI mortality risk and hazard ratio. Additionally, data used in the model for effectiveness indicate FMT has increased resolution and lower recurrence compared with all three antibiotics/regimens considered. Therefore, the addition of increased mortality for those in the persistent state would make the incremental costs larger due to more deaths in the comparator arm. However, this would be at the expense of reduced life expectancy and health-related quality of life.

Resource identification, measurement and valuation

Treatment costs

The costs for FMT colonoscopy, FMT NDT, and FMT enema are detailed in Tables 29 to 30 below. Cost of FMT colonoscopy was calculated based on resource use in Abdali (2020) (see Table 30 for details). The cost of FMT NDT was adapted based on resource use for NGT, as reported in Abdali (2020), following input from clinicians. The cost for FMT oral capsules was based on expert assumption where it was estimated to range between £500 to £600. The midpoint of £550 is applied in the model. However, the clinical expert stated that there is uncertainty regarding the true cost of providing FMT, regardless of route of administration, due to the variability in starting material

required and methods of processing. The EAC, in alignment with clinician opinion, believes the current costs applied in the model to be an underestimate. However, due to scarcity of data to inform otherwise, the values used in the model are considered to be the best available sources at present. The impact of the variability in the FMT costs are explored further through sensitivity analysis. For all routes of FMT administration, an additional consultation with a gastroenterologist was applied. This was based on clinical opinion that patients, for whom FMT may be appropriate, will have a subsequent consultation with a doctor, sometimes with a specialist nurse, to discuss the FMT treatment and provide consent. This has been costed assuming a 15-minute consultation with a gastroenterologist.

Cost breakdown for FMT colonoscopy is presented in the table below. Hvas (2019) reported that on average one infusion was required. Total unit cost was therefore estimated to be £3,355.

Table 29: Cost of FMT colonoscopy

Parameter	Value	Components	Source
FMT material	£1,992	3 units of FMT material; Unit cost of 50 ml FMT material is £664*	Abdali 2020; Mulish 2018
Gastroentrologist consultation for consent	£30	0.25 hours of HCP time; Consultant medical cost of £119 per hour applied	Assumption; PSSRU 2020
FMT administration			
Colonoscopy	£1,214	Therapeutic colonoscopy elective inpatient FE30Z	National Cost Collection 2021
Loperamide for FMT retention	£0.05	1 unit of 2mg tablet; £1.54 drug tariff for 30-pack 2mg tablets	Abdali 2020; BNF 2021d
Staff hourly (gastroenterologist)	£60	0.5 hours of HCP time; Consultant medical cost of £119 per hour applied	Abdali 2020; PSSRU 2020
Recovery time (nurse)	£60	2 hours of band 4 nurse time at £30 per hour	Abdali 2020; PSSRU 2020
Total unit cost	**£3,355**		

* Inflated using the PSSRU inflation index to 2019/2020 costs
Abbreviations: BNF, British National Formulary; FMT, Faecal Microbiota Transplantation; Personal and Social Services Unit.

Cost breakdown for FMT NDT is presented in the table below. The total unit cost of providing FMT via NDT is based on requiring 1.2 infusions (van Nood

(2013)) and was estimated to be £2,151.

Table 30: Cost of FMT NDT

Parameter	Value	Components	Source
FMT material	£664	1 unit of FMT material; Unit cost of 50 ml FMT material is £664*	Abdali 2020; Mulish 2018
Gastroentrologist consultation for consent	£30	0.25 hours of HCP time; Consultant medical cost of £119 per hour applied	Assumption; PSSRU 2020
FMT administration			
Omeprazole **	£0.04	20 mg dose; £1.08 for 28 pack 20 mg tablets	Abdali 2020; BNF 2021d
Domperidone **	£0.03	1 tablet of domperidone; £0.91 for a 30 pack	Abdali 2020; BNF 2021d & PSSRU 2020
NDT	£8.03 ***	1 unit required; 2018 cost (£7.86) inflated to 2020	Abdali 2020; PSSRU 2020
X-ray	£56.71	1 unit required; Diagnostic imaging plain film (PF)	Abdali 2020 National Cost Collection 2021
X-ray review (gastroenterologist)	£29.75	0.25 hours of staff time; consultant medical cost of £119 per hour applied	Assumption; PSSRU 2020
Endoscopic insertion of NDT	£993.19	1 unit required; endoscopic insertion of, gastrojejunostomy or jejunostomy tube (FE13Z)	Expert opinion; National Cost Collection 2021
Recovery time (nurse)	£30.00	2 hours of band 4 nurse time at £30 per hour	Abdali 2020; PSSRU 2020
Total unit cost	**£1,811**		

* Inflated using the PSSRU inflation index to 2019/2020 costs.
** Administered 2 hours prior to procedure (Abdali (2020)).
*** NGT unit cost assumed to be applicable for NDT.
Abbreviations: BNF, British National Formulary; FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; PSSRU, Personal and Social Services Unit.

Whilst NDT and NGT are considered to be similar due to anatomical proximity, the delivery of FMT via NGT is estimated to be cheaper than NDT from not requiring endoscopy guided insertion. Abdali (2020) estimated the total cost of NGT delivery to be £740.

Cost breakdown for FMT enema is presented in the table below. The total unit cost of providing FMT via enema is based on requiring 1.3 infusions (Rode

(2021)) and was estimated to be £1,041.

Table 31: Cost of FMT enema

Parameter	Value	Components	Source
FMT material	£664	1 unit of FMT material; Unit cost of 50 ml FMT material is £664*	Rode 2021; National Cost Collection 2021
Gastroentrologist consultation for consent	£30	0.25 hours of HCP time; Consultant medical cost of £119 per hour applied	Assumption; PSSRU 2020
FMT administration and recovery			
Loperamide 2mg for FMT retention	£0.05	1 unit of 2mg loperamide; £1.54 drug tariff for 30 2mg tablets	Assumed same as colonoscopy; BNF 2021d
Staff hourly (gastroenterologist)	£119	1 hour of HCP time**; Consultant medical cost of £119 per hour applied	Hota 2017 and Rode 2021; PSSRU 2020
Total unit cost	£813		

* Inflated using the PSSRU inflation index to 2019/2020 costs
** Hota (2017) reported that FMT via enema was administered over 10 to 30 minutes. Rode (2021) reported that participants were left in a lateral position during and for one hour for the procedure.
Abbreviations: BNF, British National Formulary; FMT, Faecal Microbiota Transplantation; PSSRU, Personal and Social Services Unit.

FMT oral capsules was estimated to cost £580, based on requiring one capsule and £30 for consultation for consent.

According to clinical opinion pre-antibiotic treatment is commonly used in the English health care system prior to FMT administration and was also reported in all of the clinical trials included in the clinical evidence review. Therefore, 100% of the FMT population is assumed to have a short course of vancomycin prior to index FMT treatment. Pre-antibiotic treatment cost was estimated based on a dose of 125 mg 4 times daily, as reported in Hvas (2019), where treatment was provided for 4 to 10 days. According to expert opinion, pre-antibiotic treatment is usually a short course. Therefore, the lower bound of 4 days is used to calculate total dose. Unit cost of vancomycin was sourced from the eMIT database (2021) (a 28 pack of 125 mg capsules costed £39) and the total cost of providing pre-antibiotic treatment was estimated to be £22.

Table 32 outlines the total unit cost of providing antibiotic only treatment. The dosages used to estimate costs were sourced from the appropriate trials.

Hvas (2019) provided people with 125 mg vancomycin, 4 times daily, for 10 days. For those receiving fidaxomicin, 200mg was prescribed twice daily for 10 days (Hvas (2019)).

Two of the key trials identified explored the use of VTP (Rode 2021 and Hota 2017). Rode (2021) prescribed vancomycin of 125 mg 4 times daily for 14 days followed by tapering 5 weeks, as follows: 125 mg 2 times daily for 1 week, 125 mg daily for 1 week, 125 mg every other day for 1 week, and 125 mg every third day for 2 weeks). Hota (2017), following the initial 14 days of 125 mg 4 times daily, applied tapering for a shorter duration of 4 weeks, as follows: 125 mg 2 times daily for 1 week, 125 mg daily for 1 week, 125 mg every other day for 1 week, and 125 mg every third day for 1 week. A conservative approach was adopted and the shorter treatment course for VTP from Hota (2017) was applied in the model. The product of the tablet cost and total dose was taken to estimate the total cost of providing antibiotic treatment.

Table 32: Cost of antibiotic only treatments

Parameter	Cost per tablet*	Total treatment dose (mg)	Total cost	Source [tablet cost; dose]
Vancomycin *	£1.38	5,000	**£55**	eMIT (2021); Hvas (2019)
Fidaxomicin **	£67.50	4000	**£1,350**	BNF (2021a); Hvas (2019)
VTP ***	£1.38	10,250	**£113**	eMIT; Hota (2017)

* 28 pack of 125 mg vancomycin cost £38.61 (Accessed 08.12.2021). Total dose based on 125 mg 4 times daily for 10 days (Hvas (2019))
** 20 pack of 200 mg fidaxomicin cost £1,350, undiscounted cost (Accessed 13.12.2021). Total dose based on 200 mg twice daily for 10 days (Hvas (2019)).
*** 28 pack of 125 mg vancomycin cost £38.61 (Accessed 08.12.2021). Total dose based on 125 mg 4 times daily for 2 weeks, followed by taper for 4 weeks.
Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; VTP, Vancomycin taper pulse

Hospitalisation costs are applied for the index treatment consistent with Abdali (2020). This is not applied for those requiring re-treatment if in the persistent state as a separate total hospital stay cost from recurrent CDI is applied and to avoid double counting. Those receiving their index FMT are assumed to stay in hospital for 5 days, whilst those receiving antibiotic therapy for the first time for a second recurrence remain in hospital for 10 days (Abdali 2020). Average cost of hospital stay was sourced from the National Cost Collection 2019/20 (£371 for the Inpatient, specialist palliative care, 19 years and over; currency code: SD01A) (National Cost Collection 2021). Total cost of hospital stay for first treatment was estimated to be £1,857 and £3,714 for those receiving FMT and antibiotic only treatments, respectively.

Table 33 details a summary of the costs applied in the first and subsequent model cycles for all treatments considered in the model.

Table 33: Summary of treatment costs

Parameter	First cycle*	Subsequent cycles
FMT treatments		
FMT colonoscopy	£5,234	£3,355
FMT NDT	£4,030	£2,151
FMT oral capsule	£2,459	£580
FMT enema	£2,920	£1,041
Antibiotic treatments		
Vancomycin	£3,769	£55
Fidaxomicin	£5,064	£1,350
VTP	£3,827	£113

* Includes cost of treatment, hospital stay cost (£1,857 for FMT treatment and £3,714 for antibiotic only treatments), and cost of pre-antibiotic therapy of £22 (only applicable for FMT)
Abbreviations: FMT, Faecal microbial transplant; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse

Other costs

In the persistent CDI health state, a proportion of the population will develop FC. A weighted average cost of treating FC was calculated by multiplying the cost of colectomy and medical management by the proportion undergoing each FC treatment. There was a lack of evidence to inform the proportions undergoing the 2 FC treatments. Therefore, an assumption of 10% requiring colectomy and 90% requiring medical management was applied, following the value used in the CDI clinical guidelines model (NICE 2021a). The weighted cost was multiplied by the prevalence of FC, reported to be 16% by Varier (2015) to estimate the average cost of FC in the persistent health state.

Within the eligible RCTs, no data were found to inform length of hospital stay, additional NHS resource use (e.g. ward closures and barrier nursing), and procedure related-AEs which would result in additional costs. Whilst follow up appointments and stool tests may take place in practice this was assumed to not differ between the intervention and comparator arms. As such this was excluded from the model, following a similar approach as Abdali (2020).

There was variable use of bowel lavage within the trials with 3 trials applying it prior to FMT treatment, whilst the remaining two did not. Expert opinion stated that this is not commonly applied in the English health system and therefore was excluded from the model. No other additional treatment related resources were identified to be relevant to the decision problem.

A summary of all other relevant costs is detailed in Table 34 below.

Table 34: Other costs

Parameter	Value	Components	Source
Recurrence hospitalisation cost	£7,799	Average number of bed days 21, Unit cost of hospital stay £371 (currency code: SD01A)	Wilcox 2017; National Cost Collection 2021
FC cost			
Colectomy	£13,954*	Reported cost of £12,917.33; inflated to 19/20 prices	NICE 2015b; PSSRU 2020
Medical treatment	£4,240	Average of 4 NHS non-elective spell tariff codes: FZ37K FZ37L FZ37M, and FZ37N	National Cost Collection 2021
Total cost of FC	£834	Colectomy and medical treatment weighted based on 10% requiring colectomy	Assumption

* Inflated using the PSSRU inflation index to 2019/2020 costs
Abbreviations: NICE, National Institute for Health and Care Excellence; PSSRU, Personal and Social Services Unit.

Health-related quality-of-life

Whilst trial data indicate that FMT results in increased CDI resolution and reduced recurrence, compared with antibiotics alone, they are generally associated with higher costs. For this reason, utilities have been included in the model to provide context in scenarios where FMT may not be cost saving to the system. Population norms were applied to individuals with resolved CDI, as sourced from Love-Koh 2015. For a starting age of 68 years, this was estimated to be 0.80. Utility with CDI was estimated to be 0.42, as sourced from Wilcox 2017 which was used in the previous CDI clinical guideline model (NICE 2021a).

Sensitivity analysis

There is substantial uncertainty associated with the inputs used to inform the model, in particular the resolution and recurrence data. The extent of uncertainty was quantified through deterministic sensitivity analyses (DSA), probabilistic sensitivity analyses (PSA), and various scenario analysis. These are described in further detail below.

DSA

All relevant parameters were included within the DSA analysis with the base case, upper, and lower values reported in Table 35 below. All parameters were varied by 25%, unless otherwise stated.

Table 35: DSA inputs

Parameter	Base case value	Lower value	Upper value
Age	68	47	79
Proportion pre-treated with antibiotics	100.0%	75.0%	100.0%
Number of infusions - FMT colonoscopy	1.0	1.0	2.0
Number of infusions - FMT NDT	1.2	1.0	2.0
Number of doses - FMT capsule	1.0	1.0	2.0
Number of infusions - FMT enema	1.3	1.0	2.0
Hospital stay for treatment - FMT	5.0	3.8	6.3
Hospital stay for treatment - antibiotics	10	7.5	12.5
Median hospital bed days for recurrence	21	15.8	26.3
Cost of antibiotic pre-treatment	£22	£17	£28
FMT colonoscopy unit cost of material	£1,992	£1,494	£2,490
FMT - total cost (colonoscopy)	£3,355	£2,516	£4,194
FMT unit cost of material	£664	£498	£830
FMT - total cost (NDT)	£1,811	£1,359	£2,264
FMT enema - total cost	£813	£610	£1,016
FMT oral capsules - total cost	£580	£435	£725
Comparator - Vancomycin cost	£55	£41	£69
Comparator - Fidaxomicin cost	£1,350	£1,013	£1,688
Comparator - VTP cost	£113	£85	£141
FC - colectomy	£13,954	£10,466	£17,443
FC - medical management	£4,240	£3,180	£5,300
6-month risk of CDI (nonrecurrent)	29.8%	22.4%	37.3%
Hazard ratio (recurrent CDI)	1.33	1.00	1.66
FM prevalence in persistent CDI	16.0%	12.0%	20.0%
Percentage having colectomy	10.0%	7.5%	12.5%
Resolution: FMT colonoscopy	92.0%	73.0%*	99.0%*
Resolution: FMT nasoduodenal tube	94.0%	70.5%	100.0%
Resolution: FMT oral capsule	92.0%	69.0%	100.0%
Resolution: FMT enema	76.0%	57.0%	95.0%
Resolution: Vancomycin	19.0%	4.0%*	46.0%*
Resolution: Fidaxomicin	19.0%	22.0%*	63.0%*
Resolution: VTP	19.0%	36.0%	60.0%
Recurrence: FMT colonoscopy	8.3%	6.3%	10.4%
Recurrence: FMT nasoduodenal tube	8.3%	6.3%	10.4%
Recurrence: FMT oral capsule	8.3%	6.3%	10.4%
Recurrence: FMT enema	8.3%	6.3%	10.4%
Recurrence: Vancomycin	68.8%	51.6%	85.9%
Recurrence: Fidaxomicin	68.8%	34.4%	57.3%
Recurrence: VTP	68.8%	31.5%	52.5%

* Based on 95% confidence intervals

Abbreviations: CDI, *Clostridioides difficile* Infection; FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.

PSA

PSA was conducted around all relevant parameters. Where possible evidence from literature was used to inform the variability in the base case value. For parameters where this was not possible, 15% of the mean was used to inform the alpha and beta values. The distribution, alpha, beta, and base case values are outlined in Table 36 below.

Table 36: PSA inputs

Parameter	Base case value	Distribution	Alpha	Beta
Effectiveness				
Resolution probability - FMT colonoscopy	92.0%	Beta	14.47	1.26
Resolution probability - FMT NDT	94.0%	Beta	15.00	1.00
Resolution probability - FMT oral capsule	92.0%	Beta	14.47	1.26
Resolution probability - FMT enema	76.0%	Beta	9.91	3.13
Resolution probability - Vancomycin	19.0%	Beta	2.36	10.05
Resolution probability - Fidaxomicin	42.0%	Beta	8.93	12.34
Resolution probability - VTP	48.0%	Beta	22.63	24.52
Recurrence probability - FMT colonoscopy	8.3%	Beta	2.00	22.00
Recurrence probability - FMT NDT	8.3%	Beta	2.00	22.00
Recurrence probability - FMT oral capsule	8.3%	Beta	2.00	22.00
Recurrence probability - FMT enema	8.3%	Beta	2.00	22.00
Recurrence probability - Vancomycin	68.8%	Beta	11.00	5.00
Recurrence probability - Fidaxomicin	45.8%	Beta	11.00	13.00
Recurrence probability - VTP	42.0%	Beta	25.36	35.02
Resource use				
Average hospital stay for FMT	5	Gamma	44.44	0.11
Infusions - FMT colonoscopy	1	Gamma	44.44	0.02
Infusions - FMT NDT	1	Gamma	44.44	0.03
Infusions - FMT oral capsule	1	Gamma	44.44	0.02
Infusions - FMT enema	1	Gamma	44.44	0.03

Average hospital stay for antibiotics	10	Gamma	44.44	0.23
Median hospital bed days for recurrence	21	Gamma	44.44	0.47
Fulminant colitis prevalence in CDI	16.0%	Gamma	44.44	0.00
Percentage of FM having colectomy	10.0%	Gamma	44.44	0.00
Costs				
Unit cost of FMT material	£664	Gamma	44.44	14.94
Total unit cost of FMT colonoscopy	£3,355	Gamma	44.44	74.82
Total unit cost of FMT NDT	£1,811	Gamma	44.44	18.05
Total unit cost of FMT oral capsule	£580	Gamma	44.44	12.38
Total unit cost of FMT enema	£813	Gamma	44.44	17.62
Total unit cost of Vancomycin	£55	Gamma	44.44	2.14
Total unit cost of Fidaxomicin	£1,350	Gamma	44.44	30.38
Total unit cost of VTP	£113	Gamma	44.44	4.39
Recurrence hospitalisation cost	£7,799	Gamma	44.44	190.89
Fulminant colitis - colectomy cost	£13,954	Gamma	44.44	307.18
Fulminant colitis - medical treatment cost	£4,240	Gamma	44.44	95.40
Mortality				
6-month risk - CDI (nonrecurrent)	29.8%	Gamma	44.44	0.01
Quality of life				
No CDI	0.13	Beta	2.47	16.16
Second CDI recurrence	0.07	Beta	0.26	3.47
Persistent/relapsed/recurrent CDI	0.07	Beta	0.26	3.47

Abbreviations: CDI, *Clostridioides difficile* Infection; FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.

Scenario analysis

Multiple scenarios were considered in light of the large uncertainty surrounding key parameters used within the model. These are described below.

Scenario 1: Pre-antibiotic treatment

In the base case analysis, pre-antibiotic treatment is only applied for the initial procedure and not before any subsequent FMT treatments if the CDI is unresolved or reoccurs. According to expert opinion there is variable use of pre-antibiotics before FMT, both for the initial treatment as well for any

subsequent administrations. In this scenario, pre-antibiotic treatment was applied for both initial and all subsequent FMT treatments.

Scenario 2: Everyone with CDI in subsequent cycles administered VTP

The current assumption utilised in the model is that within each treatment arm, if people have CDI in subsequent cycles, they will continue to be treated with the initial treatment administered. However, this may not occur in practice. As such a scenario was conducted in which all individuals, if left with CDI after first line treatment, will be treated with VTP regardless of initial treatment choice. This was based on the treatment approach applied by Abdali (2020).

Scenario 3: fidaxomicin cost

Fidaxomicin is associated with the largest cost of all the antibiotics/regimens considered in the model. It is understood that there is likely to be discounts in place on the cost of the drug. For this reason, threshold analysis was conducted by reducing the pack price of fidaxomicin.

Scenario 4: 1-year time horizon

The base case analysis considered a 6-month time horizon as informed by data availability. However, a 1-year time horizon was also considered to explore what impact there could be on costs over a longer term. It was assumed that the 6-month mortality calculated for the CDI population is applicable for a whole year.

9.3 *Results from the economic modelling*

Base case results

A summary of the total costs and QALYs, over a 6-month time horizon, is presented in Table 37 for all the CDI treatments considered in the model. Given the inputs, all 4 routes of FMT is associated with increased health benefits and reduced costs against all three comparators considered.

Table 37: Summary of base case results

	Costs per person	QALYs per person
FMT colonoscopy	£7,192	1.83
FMT NDT	£5,626	1.84
FMT enema	£6,181	1.74
FMT oral capsule	£4,032	1.83
Vancomycin	£17,166	1.18

Fidaxomicin	£15,718	1.39
VTP	£12,415	1.44

Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

Table 38 below depicts the cost breakdown for each treatment. For all the FMT options, the largest cost component of the total costs is from treatment (both initial treatment and subsequent treatment once individuals move into the persistent health state). For antibiotic treatment alone, the largest cost component was from recurrence-based hospitalisation.

Table 38: Cost breakdown (per person results)

	Treatment	**Hospitalisation (recurrence)**	**FC treatment**	**Total**
FMT colonoscopy	£5,699	£1,349	£144	**£7,192**
FMT NDT	£4,290	£1,207	£129	**£5,626**
FMT enema	£3,234	£2,662	£285	**£6,181**
FMT oral capsule	£2,539	£1,349	£144	**£4,032**
Vancomycin	£3,840	£12,039	£1,287	**£17,166**
Fidaxomicin	£6,287	£8,520	£911	**£15,718**
VTP	£3,919	£7,675	£821	**£12,415**

Abbreviations: FC, Fulminant Colitis; FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.

Table 39 below summarises the incremental analysis, based on per person results, comparing all FMT interventions considered against the 3 comparators. In the base case analysis, use of FMT is cost saving to the system and is always associated with increased health benefits. Largest cost savings are observed with FMT oral capsules against vancomycin (savings of £13,134) whilst largest health benefits are observed for FMT NDT against vancomycin (additional 0.66 QALYs). Consequently, all FMT routes of administration are associated with a positive net health benefit (NHB).

Table 39: Incremental analysis (per person results)

	∆Costs	**∆QALYs**	**NHB**	**ICER**
FMT vs vancomycin				
FMT colonoscopy	-£9,974	0.65	1.15	Dominant
FMT NDT	-£11,540	0.66	1.24	Dominant
FMT enema	-£10,985	0.56	1.11	Dominant
FMT oral capsule	-£13,134	0.65	1.31	Dominant
FMT vs fidaxomicin				
FMT colonoscopy	-£8,526	0.44	0.86	Dominant
FMT NDT	-£10,092	0.45	0.95	Dominant
FMT enema	-£9,537	0.35	0.83	Dominant
FMT oral capsule	-£11,686	0.44	1.02	Dominant
FMT vs VTP				

FMT colonoscopy	-£5,223	0.39	0.65	Dominant
FMT NDT	-£6,789	0.40	0.73	Dominant
FMT enema	-£6,234	0.30	0.61	Dominant
FMT oral capsule	-£8,382	0.39	0.80	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NDT, Nasoduodenal tube; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

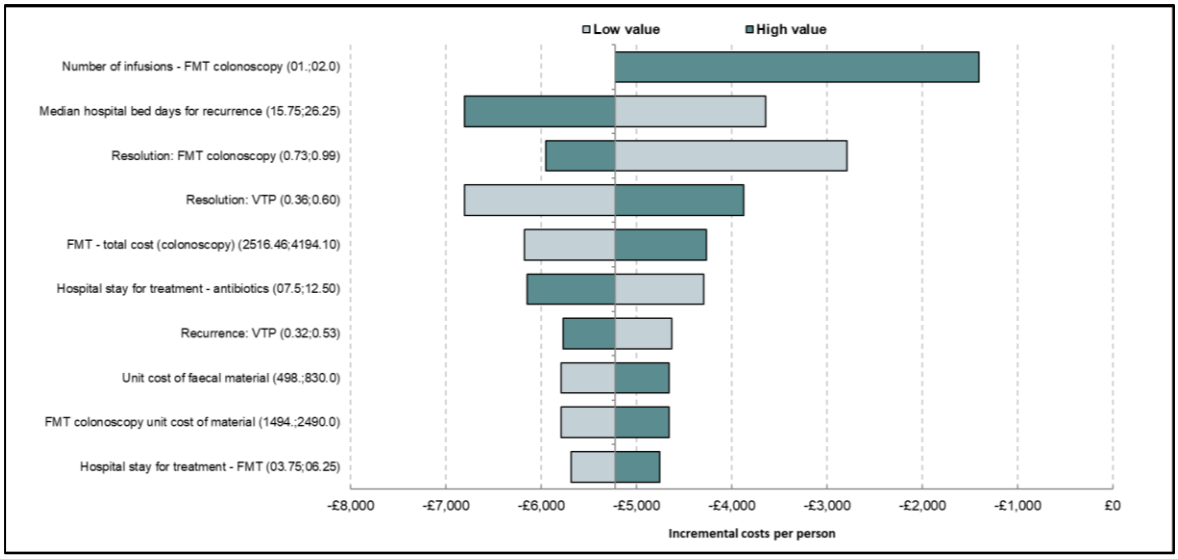
Sensitivity analysis results

For simplicity DSA and PSA results are presented in the base case for FMT colonoscopy (the least cost saving FMT) against VTP (the comparator with the lowest cost and highest health benefit of all three comparators).

DSA

The results of the DSA is presented in Figure 2 below for the FMT colonoscopy compared with VTP analysis. The largest driver of cost is the number of infusions with FMT colonoscopy, as treatment is more expensive compared with VTP. However, even with 2 infusions it is still estimated to be cost saving to the system when compared with VTP. Median hospital bed days for recurrence is also a key driver due to a larger number of people being in the persistent CDI health state for the comparator arm, where it makes up the largest cost component of the total cost. Therefore, whilst the median number of days are the same for both the comparator and intervention, the cost associated with this hospital stay has a larger impact on total pathway costs for the comparator arm. The third key driver of the costs are the resolution transition probability for FMT colonoscopy, as this determines the proportion of people who are in the persistent CDI health state which is associated with substantial costs. Even with the lower 95% CI value for resolution, FMT colonoscopy is estimated to result in cost savings.

Figure 2: Tornado diagram



PSA

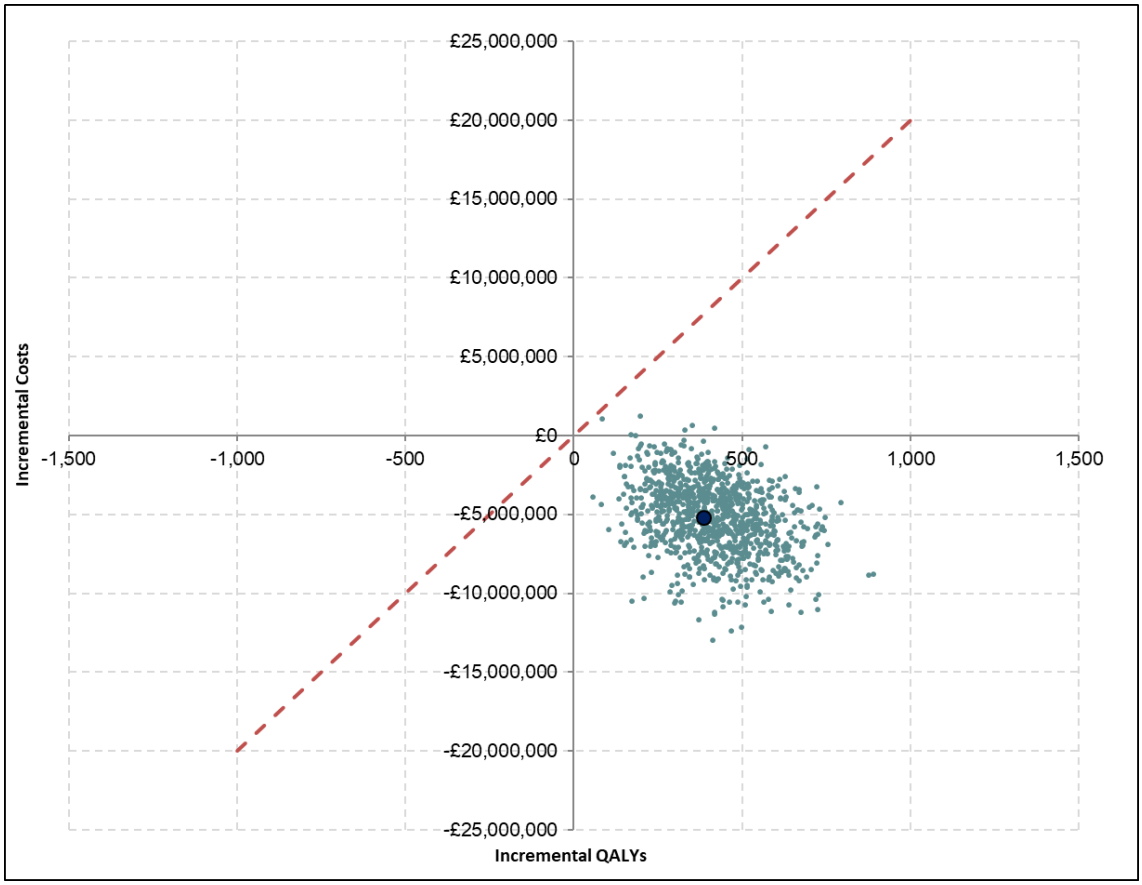
The results of the PSA are displayed in Table 40 and Figure 3 below. FMT colonoscopy is associated with cost savings and health benefits when compared with VTP. It is estimated to be cost saving 99% of the time, and cost effective 100% of the time.

Table 40: PSA results (FMT colonoscopy versus VTP)

	FMT combined	**VTP**	**Incremental**
Cost per person	£7,253	£12,407	**-£5,153**
QALYs per person	1.82	1.41	**0.41**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**0.67**

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

Figure 3: Cost-effectiveness plane



See Appendix G for PSA results for all other analyses included in the model. In summary, FMT colonoscopy is also cost saving compared with fidaxomicin and vancomycin. FMT NDT and FMT oral capsules are estimated to be cost saving 100% of the time when compared with all three comparators. FMT enema is estimated to be cost saving against fidaxomicin 100% of the time and 99% of the time against vancomycin and VTP.

Scenario results

SCENARIO 1

The results for use of pre-antibiotic treatment for subsequent FMT treatments against VTP (the second cheapest and most clinically beneficial of all antibiotics included in the model) are presented in the table below. Use of pre-antibiotic treatment results in a small increase in costs to the FMT arm. All four routes of FMT administration remain cost saving.

Table 41: Incremental analysis (per person results) - Scenario 1

	∆Costs	∆QALYs	NHB	ICER
FMT colonoscopy	-£5,219	0.39	0.65	Dominant
FMT NDT	-£6,786	0.40	0.73	Dominant
FMT enema	-£6,227	0.30	0.61	Dominant
FMT oral capsule	-£8,379	0.39	0.80	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NDT, Nasoduodenal tube; NHB, Net health benefit; QALYs, Quality-adjusted life years.

SCENARIO 2

Subsequent treatment with VTP for all arms (intervention and comparator), if individuals have CDI after first cycle, was explored. There is reduced cost savings associated with all four FMT routes against antibiotics, compared with the base case analysis. However, all four FMT routes of administration are estimated to remain cost saving against all three antibiotics considered in the model. See details in Table 42 below.

Table 42: Incremental analysis (per person results) - Scenario 2

	∆Costs	∆QALYs	NHB per person	ICER
FMT vs vancomycin				
FMT colonoscopy	-£3,972	0.34	0.54	Dominant
FMT nasoduodenal tube	-£5,325	0.35	0.62	Dominant
FMT enema	-£5,094	0.27	0.52	Dominant
FMT oral capsule	-£6,747	0.34	0.68	Dominant
FMT vs fidaxomicin				
FMT colonoscopy	-£3,553	0.23	0.41	Dominant
FMT nasoduodenal tube	-£4,906	0.24	0.49	Dominant
FMT enema	-£4,676	0.16	0.39	Dominant
FMT oral capsule	-£6,329	0.23	0.55	Dominant
FMT vs VTP				
FMT colonoscopy	-£1,870	0.21	0.30	Dominant
FMT nasoduodenal tube	-£3,223	0.21	0.38	Dominant
FMT enema	-£2,992	0.13	0.28	Dominant
FMT oral capsule	-£4,645	0.21	0.44	Dominant

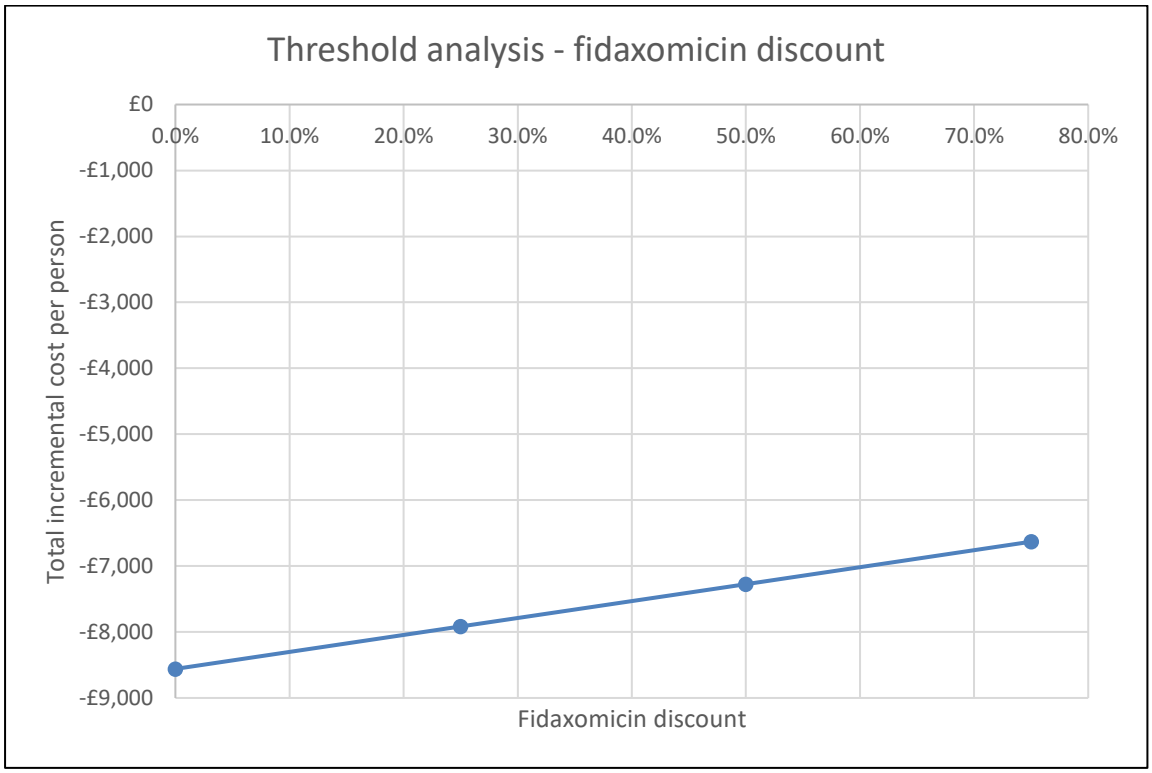
Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

SCENARIO 3

Figure 4 below depicts threshold analysis around fidaxomicin discount. As the cost of Fidaxomicin pack price decreases, cost savings with FMT

colonoscopy, the least cost saving of all four FMT considered, also decreases. However, it remains cost saving at 75% discount.

Figure 4: Fidaxomicin threshold analysis



SCNEARIO 4

A longer-term time horizon is associated with increased cost savings and health benefits for all FMT administration routes considered compared with VTP (see Table 43).

Table 43: Incremental analysis (per person results) - Scenario 4

	ΔCosts	ΔQALYs	NHB	ICER
FMT colonoscopy vs VTP				
Base case	-£5,223	0.39	0.65	Dominant
Scenario	-£10,827	1.02	1.56	Dominant
FMT NDT vs VTP				
Base case	-£6,789	0.40	0.73	Dominant
Scenario	-£12,669	1.03	1.67	Dominant
FMT enema vs VTP				
Base case	-£6,234	0.30	0.61	Dominant
Scenario	-£12,049	0.86	1.46	Dominant
FMT oral capsule vs VTP				
Base case	-£8,382	0.39	0.80	Dominant
Scenario	-£14,553	1.02	1.74	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

Impact of assumptions:

Table 44: Key model assumptions

Assumptions	Direction of results
Constant response and recurrence rates for same treatment option in each cycle	Decreased risk of resolution will result in increased costs and decreased health benefits. This will result in increased cost savings and health benefits, provided FMT is clinically better than antibiotics alone.
If initial treatment failed, people are treated with the same treatment again	Tested by applying VTP for all subsequent treatment. Against all three comparators, FMT is still associated with increased health benefits and cost savings but to a lesser extent than in the base case.
Of those who recover from CDI, regardless of from the starting state or persistent state, it is assumed that the risk of death is comparable to the general population.	Increased mortality, even within the recovered population, will result in more deaths in the comparator arm and thereby decrease incremental cost savings from FMT at the expense of forgone health benefits.
Pre-antibiotic treatment is not provided for FMT administration for subsequent treatments (only applied for the initial FMT administration)	Pre-antibiotic treatment for each round of FMT will result in decreased cost savings.
Initial provision of treatment assumed 5 days of hospital stay for FMT and 10 days hospital stay for antibiotics. Ongoing treatment after this period is assumed to occur at home (e.g. for VTP)	Increased cost savings if people remain in hospital for the full duration of their index treatment. Potentially reduced savings if reduced number of days for both treatment arms.
Costs of tests and follow up were assumed to not differ between the intervention and comparators and excluded from the model	Reduced resource use in FMT arm will result in increased cost savings and vice versa.

Abbreviations: CDI, *Clostridioides difficile* Infection; FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.

9.4 *The EAC's interpretation of the economic evidence*

All FMT administration routes are estimated to be cost-saving to the system against at least all of the antibiotic comparators considered in the base case. FMT colonoscopy is estimated to be the least cost saving whilst FMT oral capsules are estimated to the most cost saving. Whilst treatment with FMT are generally costlier than antibiotics alone, cost savings from reduced hospitalisations due to recurrence compensates for the high initial treatment costs. It should be noted that current costs for oral capsules is an assumption

based on clinical opinion. However, given the evidence supporting clinical comparability in treatment response to colonoscopy, if this cost were to be higher it is likely to remain cost saving to the system against all three comparators from reduced recurrences. This applies to all routes of administration, which are associated with substantial cost savings. Therefore, there is scope for the treatment to remain cost saving if prices are higher than currently estimated.

As detailed earlier, approximate estimates of the efficacy of FMT via NGT suggest that it is likely to be a cost-effective treatment option for recurrent CDI (overall cure rate of 78%) compared with antibiotics alone, similar to the four FMT routes of administration considered in the model. However, this may be a conservative estimate, for reasons discussed previously, where we may be understating the clinical benefit. Within the context of the FMT routes considered, this resolution rate is estimated to be higher than the resolution with FMT via enema (76%). Additionally, FMT via NGT is comparable in cost to FMT via enema (approximately £800). Taking into consideration the differences in resolution rates and similarities in costs between NGT and enema, FMT NGT is likely to be a cost-saving intervention for the second CDI recurrent population, against all three comparators considered.

DSA results show that, within the FMT colonoscopy (the most expensive of all FMT routes considered) versus VTP analysis, the cost of FMT colonoscopy is a key determinant of total incremental cost (either through the total cost or through the number of infusions required). Hvas (2019), which was used to inform FMT colonoscopy effectiveness, reported that all save one individual had 1 infusion of FMT. Therefore, the base case infusion frequency and effectiveness data used for FMT colonoscopy is considered to be broadly appropriate.

There is large uncertainty in the data used to inform transition probabilities in the model, as previously discussed. For example, though NDT was associated with the highest clinical improvements of all four FMT routes considered, the trial informing this had a low sample size and included people with only one CDI recurrence. However, results were robust following PSA analysis where all FMT routes was estimated to be cost saving at least 99% of the time and a 99% likelihood of cost-effectiveness at a threshold of £20,000 per QALY.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

Evidence from RCTs does not address the use of FMT in patients with refractory CDI.

Trial-based evidence suggests that FMT is more effective than comparator antibiotics for resolving CDI in patients with CDI recurrence. The EAC considers this treatment effect as large; 4 trials found FMT to be superior to vancomycin with absolute risk differences of 11% to 64% for CDI resolution. Comparison to fidaxomicin was assessed in 1 trial, and FMT found to be 42% more effective for this outcome.

FMT may cause more immediate AEs than antibiotics, though these were mild, quickly resolving GI symptoms that did not persist beyond the end of treatments. Furthermore, we found no reports of procedural complications, such as perforation or aspiration, and FMT was not associated with a greater number of SAEs or greater short-term mortality. This systematic review found insufficient evidence for most outcomes targeted by the decision problem, including whether FMT reduces further CDI recurrence, CDI-associated diarrhoea, or downstream interventions following treatment failure when compared with treatment with antibiotics.

The superiority of FMT for resolving CDI may not constitute an unbiased effect, since several trials used combination outcomes involving subjective components that were not completely confirmed by objective tools (such as diagnostic tests), risked measurement bias by starting follow-up times at the end of treatments, or both. In addition, 4 trials were terminated early resulting in small patient numbers, which limits the reliability of this evidence-base. Follow-up times were also short, and no trial was powered to detect a difference in mortality leading to the possibility of type II error for this outcome.

The evidence was generated by RCTs that broadly reflected the decision problem, with 2 notable exceptions concerning patients: that in 3 of the 5 trials the treatment effect incorporates a minority of patients with a first CDI recurrence, and secondly that all included studies treated patients who are likely to be in better health (less frail, fewer comorbidities, less likely hospitalised) than those in the UK NHS setting. These limitations create uncertainty regarding the size of FMT's treatment effect when used in the NHS.

10.2 *Conclusions from the economic evidence*

Given the inputs used in the model, there is potential for the use of FMT as first line treatment for individuals with second recurrent CDI to be a cost saving and cost-effective treatment compared with vancomycin, fidaxomicin, and VTP. However, there is substantial uncertainty regarding the effectiveness data used to inform the model, particularly regarding the comparability of the values from different trials. This is primarily due to heterogeneity in the population, time at which trial outcomes are reported and lack of clarity on what is considered the starting point from which time to outcomes are reported (i.e. at treatment initiation versus on treatment conclusion). Additionally, some of the trials informing key effectiveness data did not exclude individuals who had less than 3 CDI episodes, (e.g. with VTP). Therefore, the current effectiveness data for VTP may be overestimated. The key inputs used to populate the model for the base case analysis are generally optimistic values due to the data available. The effectiveness rates are considered to be higher than what may be seen for this population due to fewer frail patients being enrolled in the clinical trials used to inform these parameters. However, this is true for all the treatments considered (FMT and antibiotics) and may not have a large impact incrementally.

Uncertainty remains on the use of single and multiple infusions and the extent to which this may impact treatment effectiveness. Whilst Abdali (2020) attempted to disentangle the relationship between this by applying differential transition probabilities based on infusion frequency, this was not deemed to be possible in this model given the data available.

All 4 routes of FMT administration are estimated to be cost saving against all antibiotic comparators, where oral capsule was analysed based on clinical equivalence trials conducted against FMT colonoscopy. Additionally, FMT via NGT is also likely to be a cost saving treatment option for this population against all three comparators considered.

There is uncertainty in the true costs of both FMT and fidaxomicin. Clinical expert opinion suggests that the estimate for FMT does not fully capture the costs of processing involved in the collection and delivery of treatment. Therefore, the costs used within the model may be an underestimate. Secondly, costs for fidaxomicin may be overestimated, although it is difficult to estimate the magnitude to which this is the case. However, the current results estimate large cost savings of over £5,000 per person with FMT which may accommodate any increase in FMT treatment cost.

11 Summary of the combined clinical and economic sections

The evidence base for the clinical effects and safety of FMT is small, with short follow up, and is limited to patients with recurrent CDI. Data from the 5 included RCTs suggest that FMT is more effective than vancomycin (4 trials) or fidaxomicin (1 trial) for resolving CDI, but may cause more immediate, mild and short-term GI AEs. These trials provide insufficient evidence for most outcomes specified in the decision problem, including mortality for which all RCTs were underpowered to detect a difference. No trials were carried out in the UK, and the limited generalisability of trial participants to people who would be eligible for this procedure in the NHS creates uncertainty regarding the size of FMT's treatment effect when used in the NHS.

Based on the economic evaluation, FMT is generally considered to be cost saving against all comparators, and where not it is estimated to still incur health benefits (i.e. with FMT colonoscopy versus VTP). Costs of FMT applied are optimistic with the true cost likely being higher. However, as there is large variation in the base costs used between different administration routes, use of multiple modes of administration supports the use of FMT as a cost saving treatment option.

12 Implications for research

In order to address the uncertainties in the existing clinical and economic data for the impact of using FMT to treat patients with recurrent CDI, the EAC considers that further research should target the generation of evidence from a UK setting. These studies should provide longer-term data, which are needed to clarify any differences in downstream relapse or recurrence rates, and the impacts these have on patient morbidity, mortality and resource use. These should ideally also be able to support differentiation between effects of single infusion of FMT and multiple infusions within this patient population as infusion number impacts substantially on the costs incurred from treatment.

Although RCTs are the gold-standard design for this information, they are unlikely to be feasible in the UK given the small annual population of patients with CDI, and that FMT is already recommended for use by NICE (National Institute for Health and Care Excellence 2021a). The early termination of 4 of the 5 included RCTs would also suggest that randomised studies are too challenging to complete in this area, largely due to the ethical concerns around recruiting patients to antibiotic comparator arms once potentially large treatment effects are discovered during monitoring. An alternative solution

would be to create a national CDI registry recruiting all patients presenting with the NICE recommended 2 or more CDI recurrences, or refractory CDI, and from which prospective cohort studies could be designed. This would allow the capture of longer-term health outcome, resource use and patient-reported outcome data, which could also be examined for differences according to FMT administration routes as they continue to evolve in the NHS.

13 References

Aarhus University Hospital. *Faecal microbiota transplantation for relapsing clostridium difficile infection*. Identifier: EUCTR2015-003004-24. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2015. Available from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003004-24

Aas J, CE Gessert and JS Bakken (2003) Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. CLINICAL INFECTIOUS DISEASES 36(5): 580-585

Abdali ZI, Roberts TE, Barton P, et al. (2020) Economic evaluation of faecal microbiota transplantation compared to antibiotics for the treatment of recurrent clostridioides difficile infection. EClinicalMedicine 24**:** 100420

Academic Medical Center Amsterdam. *The FECAL trial, fecal therapy to eliminate clostridium difficile associated longstanding diarrhoea*. Identifier: NTR1177. In: Nederlands Trial Register [internet]. Amsterdam: The Dutch Cochrane Centre: 2008. Available from https://trialregister.nl/trial/1135

Administration. USFaD. Archive-it. [online; accessed 19 November 2021] Available from: https://www.archive-it.org/collections/7993?show=ArchivedPages&q=

Baro E, Galperine T, Denies F, et al. (2017) Cost-effectiveness analysis of five competing strategies for the management of multiple recurrent community-onset clostridium difficile infection in France. Plos One [Electronic Resource] 12(1)**:** e0170258

Bassler D, Briel M, Montori VM, et al. (2010) Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 303(12)**:** 1180-7

Baunwall SMD, Lee MM, Eriksen MK, et al. (2020) Faecal microbiota transplantation for recurrent Clostridioides difficile infection: An updated systematic review and meta-analysis. EClinicalMedicine 29-30**:** 100642

Baxter M, Ahmad T, Colville A et al. (2015) Fatal aspiration pneumonia as a complication of fecal microbiota transplant. CLINICAL INFECTIOUS DISEASES 61(1): 136-137

British National Formulary. (2021a). FIDAXOMICIN [online]: National Institute for Health and Care Excellence. Available from: https://bnf.nice.org.uk/medicinal-forms/fidaxomicin.html [Accessed 15.12.2021.

British National Formulary. (2021b). OMEPRAZOLE [online]: National Institute for Health and Care Excellence. Available from: https://bnf.nice.org.uk/drug/omeprazole.html [Accessed 15.12.2021.

British National Formulary. (2021c). DOMPERIDONE [online]: National Institute for Health and Care Excellence. Available from: https://bnf.nice.org.uk/drug/domperidone.html15.12.2021].

British National Formulary. (2021d). LOPERAMIDE HYDROCHLORIDE [online]: National Institute for Health and Care Excellence. Available from: https://bnf.nice.org.uk/drug/loperamide-hydrochloride.html.

Cammarota G, Masucci L, Ianiro G, et al. (2015) Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent clostridium difficile infection. Alimentary Pharmacology & Therapeutics 41(9)**:** 835-43

Catholic University of the Sacred Heart. *Fecal microbiota transplantation by colonoscopy for recurrent c. difficile infection*. Identifier: NCT02148601. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://ClinicalTrials.gov/show/NCT02148601

Clarivate (2020). EndNote [X9.3.3 for Windows & Mac]. Philadelphia, USA: Clarivate

Cold F, Baunwall SMD, Dahlerup JF, et al. (2021) Systematic review with meta-analysis: encapsulated faecal microbiota transplantation - evidence for clinical efficacy. Therapeutic Advances In Gastroenterology 14**:** 1-19

Czepiel J, Drozdz M, Pituch H, et al. (2019) Clostridium difficile infection: review. European Journal of Clinical Microbiology & Infectious Diseases 38(7)**:** 1211-1221

(eMIT) Drugs and pharmaceutical electronic market information tool (2021). [online; accessed 8 December 2021] https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

Finn E, Andersson FL, Madin-Warburton M. Burden of Clostridioides difficile infection (CDI) - a systematic review of the epidemiology of primary and recurrent CDI. BMC Infect Dis. 2021;21(1):456

Gov.UK. Alerts, recalls and safety information: drugs and medical devices. [online; accessed 19 November 2021] Available from: https://www.gov.uk/drug-device-alerts

Gundacker N, Tamhane A, Walker JB, et al. (2017) Comparative effectiveness of faecal microbiota transplant by route of administration. JOURNAL OF HOSPITAL INFECTION 96(4): 349-352

Hammeken LH, Baunwall SMD, Hvas CL, et al. (2021) Health economic evaluations comparing faecal microbiota transplantation with antibiotics for treatment of recurrent clostridioides difficile infection: a systematic review. Health Economics Review 11(1)**:** 3

Hensgens MP, Goorhuis A, Dekkers OM et al. (2013) All-cause and disease-specific mortality in hospitalized patients with Clostridium difficile infection: a multicenter cohort study. CLINICAL INFECTIOUS DISEASES 56(8): 1108-1116

Hota SS, Sales V, Tomlinson G, et al. (2017) Oral vancomycin followed by fecal transplantation versus tapering oral vancomycin treatment for recurrent clostridium difficile infection: an open-label, randomized controlled trial. Clinical Infectious Diseases 64(3)**:** 265-271

Hvas CL, Dahl Jorgensen SM, Jorgensen SP, et al. (2019) Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent clostridium difficile infection. Gastroenterology 156(5)**:** 1324-1332.e3

Hvas CL, Jorgensen SMD, Jorgensen SP, et al. (2018) Randomized controlled clinical trial: faecal microbiota transplantation (FMT) is superior to both fidaxomicin and vancomycin monotherapies for recurrent clostridium difficile-associated disease. United European Gastroenterology Journal 6(10)**:** 1596

Hvidovre University Hospital. *Rectal bacteriotherapy, fecal microbiota transplantation or oral vancomycin treatment of recurrent clostridium difficile infections*. Identifier: NCT02774382. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2017. Available from https://ClinicalTrials.gov/show/NCT02774382

Kao D, Roach B, Silva M, et al. (2017) Effect of oral capsule–vs colonoscopy-delivered fecal microbiota transplantation on recurrent Clostridium difficile infection: a randomized clinical trial. JAMA 318(20): 1985-1993.

Karas JA, Bradhsaw S, Mahmud W et al. (2010) Mortality in hospitalized older adults associated with Clostridium difficile infection at a district hospital. INFECTIOUS DISEASE REPORTS 2(1).

Khoruts A, and MJ Sadowsky (2016) Understanding the mechanisms of faecal microbiota transplantation. NATURE REVIEWS GASTROENTEROLOGY & HEPATOLOGY 13(9) 508-516.

Konijeti G, Sauk J, Ananthakrishnan A, et al. (2013) Cost-effectiveness of competing strategies for recurrent clostridium difficile infection

acg/astrazeneca fellow award. American Journal of Gastroenterology 108(Suppl 1): S473

Krogsgaard LR, Rode AA, Bytzer P, et al. (2019) Cure of recurrent clostridium difficile infection with a mix of 12 gut bacteria , faecal microbiota transplantation or oral vancomycin: results from an open-label multicentre randomised controlled trial. United European Gastroenterology Journal 7(8 Suppl): 88

Lapointe-Shaw L, Tran KL, Coyte PC, et al. (2016) Cost-effectiveness analysis of six strategies to treat recurrent clostridium difficile infection. Plos One [Electronic Resource] 11(2): e0149521

Love-Koh J, Asaria M, Cookson R, et al. (2015). The social distribution of health: estimating quality-adjusted life expectancy in England. VALUE IN HEALTH 18(5) 655-662

Luo Y, Lucas AL and Grinspan AM (2020) Fecal transplants by colonoscopy and capsules are cost-effective strategies for treating recurrent clostridioides difficile infection. Digestive Diseases & Sciences 65(4): 1125-1133

MacConnachie A, Fox R, Kennedy DR et al. (2009) Faecal transplant for recurrent Clostridium difficile-associated diarrhoea: a UK case series. QJM: An International Journal of Medicine 102(11): 781-784

Medicines & Healthcare products Regulatory Agency (2020) A guide to what is a medicinal product. MHRA Guidance Note 8. London: Agency, M. H. P. R. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/872742/GN8_FINAL_10_03_2020__combined_.pdf

Merlo G, Graves N, Brain D, et al. (2016) Economic evaluation of fecal microbiota transplantation for the treatment of recurrent clostridium difficile infection in Australia. Journal of Gastroenterology & Hepatology 31(12): 1927-1932

Mikrobiomik Healthcare Company S.L. *A phase III clinical trial in patients with recurrent clostridioides difficile (CD) infection, to evaluate the treatment with capsules of lyophilised faecal microbiota vs fidaxomicin*. Identifier: EUCTR2020-004591-17. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2020. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-004591-17/ES

Mullish B, Mohammed N, Segal J, et al. (2018) The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. London Available from: https://www.bsg.org.uk/wp-content/uploads/2018/09/The-use-of-faecal-microbiota-transplant-as-

treatment-for-recurrent-or-refractory-Clostridium-difficile-infection-and-other-potential-indications-1.pdf
National Cost Collection (2021). 2019/20 National Cost Collection data Version 2. https://www.england.nhs.uk/national-cost-collection/.
National Institute for Health and Care Excellence (2014) Faecal microbiota transplant for recurrent Clostridium difficile infection. Interventional procedures guidance [IPG485]. London Available from: https://www.nice.org.uk/guidance/ipg485
National Institute for Health and Care Excellence (2015) Clostridium difficile infection: risk with broad-spectrum antibiotics. Evidence summary [ESMPB1]. London Available from: https://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence#summary [Accessed: 17 March]
National Institute for Health and Care Excellence (2015b). Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy Available from: https://www.nice.org.uk/guidance/ta329. [Accessed: 15 December]
National Institute for Health and Care Excellence (2019) Apendix H Appraisal checklists, evidence tables, GRADE and economic profiles. London Available from: https://www.nice.org.uk/process/pmg20/resources/appendix-h-appraisal-checklists-evidence-tables-grade-and-economic-profiles-pdf-8779777885
National Institute for Health and Care Excellence (2021a) Clostridioides difficile infection: antimicrobial prescribing [NG199]. London 1-40. Available from: https://www.nice.org.uk/guidance/ng199 [Accessed: 23 July]
National Institute for Health and Care Excellence (2021b) GID-MT566 Faecal microbiota transplant for recurrent Clostridioides difficile infection. London Available from: https://www.nice.org.uk/guidance/indevelopment/gid-mt566/documents
Office for National Statistics (2021). National life tables: UK. Availabe from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
Olsen M, Yan Y, Reseke KA, et al. (2015) Recurrent Clostridium difficile infection is associated with increased mortality. Clinical Microbiology and Infection 21(2) 164-170
Personal Social Services Research Unit (2020). Unit Costs of Health and Social Care 2020 https://www.pssru.ac.uk › pub › 5-sourcesofinfo, University of Kent, Canterbury.

Pomares Bascunana RA, Veses V and Sheth CC (2021) Effectiveness of fecal microbiota transplant for the treatment of clostridioides difficile diarrhea: a systematic review and meta-analysis. Letters In Applied Microbiology 73(2): 149-158

Public Health England (2021a). Clostridioides difficile (C. difficile) infection: annual data. Annual counts and rates of C. difficile infections by acute trust and clinical commissioning group (CCG) in patients aged 2 years and over. London: 15 September 2021. Available from: https://www.gov.uk/government/statistics/clostridium-difficile-infection-annual-data

Public Health England (2021b). Annual epidemiological commentary: Gram-negative bacteraemia, MRSA bacteraemia, MSSA bacteraemia and C. difficile infections, up to and including financial year April 2020 to March 2021. London: 15 September 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1016843/Annual_epidemiology_commentary_April_2020_March_2021.pdf

Ramai D, Zakhia K, Fields P, et al. (2020) Fecal microbiota transplantation (FMT) with colonoscopy is superior to enema and nasogastric tube while comparable to capsule for the treatment of recurrent Clostridioides difficile infection: a systematic review and meta-analysis. Digestive Diseases and Sciences 66(2): 369-380

Rode AA, Chehri M, Krogsgaard LR, et al. (2021) Randomised clinical trial: a 12-strain bacterial mixture versus faecal microbiota transplantation versus vancomycin for recurrent clostridioides difficile infections. Alimentary Pharmacology & Therapeutics 53(9): 999-1009

Rubin TA, Gessert CE, Aas J, et al. (2013) Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series. ANAEROBE 19: 22-26

Stollman N, Giovanelli A, Mendolia G, et al. (2015) Frozen encapsulated stool in recurrent clostridium difficile: Exploring the role of pills in the treatment hierarchy of fecal microbiota transplant nonresponders. American Journal of Gastroenterology 110(4): 600-601

Tian H, Ding C, Gong J, et al. (2015) Freeze-dried, capsulized fecal microbiota transplantation for relapsing clostridium difficile infection. Journal of Clinical Gastroenterology 49(6): 537-538

U.S Food and Drug Administration. Fecal microbiota for transplantation: safety communication - risk of serious adverse reactions due to transmission of multi-drug resistant organisms. [online; accessed 19 November 2021] Available from: https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-communication-risk-serious-adverse-reactions-due

U.S Food and Drug Administration. Fecal microbiota for transplantation: safety alert - regarding additional safety protections pertaining to SARS-CoV-2 and COVID-19. [online; accessed 19 November 2021] Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation-0

U.S Food and Drug Administration. Fecal microbiota for transplantation: new safety information - regarding additional protections for screening donors for COVID-19 and exposure to SARS-CoV-2 and testing for SARS-CoV-2. [online; accessed 19 November 2021] Available

U.S Food and Drug Administration. Information pertaining to additional safety protections regarding use of fecal microbiota for transplantation - screening donors for COVID-19 and exposure to SARS-CoV-2 and testing for SARS-CoV-2. [online; accessed 19 November 2021] Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation-1

U.S Food and Drug Administration. Recalls, market withdrawals, and safety alerts. [online; accessed 19 November 2021] Available from: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts

U.S. Food and Drug Administration. Information pertaining to additional safety protections regarding use of fecal microbiota for transplantation – screening and testing of stool donors for multi-drug resistant organisms. [online; accessed 19 November 2021] Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation

U.S. Food and Drug Administration. Important safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse reactions due to transmission of multi-drug resistant organisms. [online; accessed 19 November 2021] Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse

U.S. Food and Drug Administration. Fecal microbiota for transplantation: safety alert - risk of serious adverse events likely due to transmission of pathogenic organisms. [online; accessed 19 November 2021] Available from: https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission

U.S. Food and Drug Administration. Information pertaining to additional safety protections regarding use of fecal microbiota for transplantation - testing of stool donors for enteropathogenic escherichia coli and

shigatoxin-producing Escherichia coli. [online; accessed 19 November 2021] Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation-0

U.S. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. [online; accessed 19 November 2021] Available from: https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program

University Health Network Toronto. *Oral vancomycin followed by fecal transplant versus tapering oral vancomycin*. Identifier: NCT01226992. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://ClinicalTrials.gov/show/NCT01226992

University of Aarhus. *Fecal microbiota transplantation for relapsing clostridium difficile infection*. Identifier: NCT02743234. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2016. Available from https://ClinicalTrials.gov/show/NCT02743234

University of Pennsylvania. *PMT for severe-CDI*. Identifier: NCT03970200. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2020. Available from https://ClinicalTrials.gov/show/NCT03970200

University of Wisconsin M. *Fecal microbiota transplantation for c. difficile infection in solid organ transplant recipients*. Identifier: NCT03617445. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2021. Available from https://ClinicalTrials.gov/show/NCT03617445

van Nood E, Vrieze A, Nieuwdorp M, et al. (2013) Duodenal infusion of donor feces for recurrent clostridium difficile. New England Journal of Medicine 368(5)**:** 407-15

Varier RU, Biltaji E, Smith KJ, et al. (2015) Cost-effectiveness analysis of fecal microbiota transplantation for recurrent clostridium difficile infection. Infection Control & Hospital Epidemiology 36(4)**:** 438-44

Wilcox MH, Ahir H, Coia J et al. (2017) Impact of recurrent Clostridium difficile infection: hospitalization and patient quality of life. Journal of Antimicrobial Chemotherapy 72(9) 2647-2656

You JHS, Jiang X, Lee WH, et al. (2020) Cost-effectiveness analysis of fecal microbiota transplantation for recurrent clostridium difficile infection in patients with inflammatory bowel disease. Journal of Gastroenterology & Hepatology 35(9)**:** 1515-1523

Youngster I, Sauk J, Pindar C, et al. (2014) Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. CLINICAL INFECTIOUS DISEASES 58(11): 1515-1522

14 Appendices

Appendix A Clinical effects and safety search strategy, search results and PRISMA flow diagram
Appendix B Clinical effectiveness trial data, quality assessments
Appendix C Economic evidence search strategy, search results and PRISMA flow diagram
Appendix D Systematic review eligibility criteria: clinical effects and safety, and economic evaluations
Appendix E Systematic review data extraction elements: clinical effects and safety, and economic evaluations
Appendix F Systematic review excluded and unobtainable studies: clinical effects and safety, and economic evaluations

Appendix A Clinical effects and safety search strategy, search results and PRISMA flow diagram

Search strategy

A MEDLINE (OvidSP) search strategy was designed to identify studies of FMT in people with CDI. The final MEDLINE strategy is presented in Figure A1.

The strategy comprised 2 concepts:

- CDI (search lines 1 to 14)
- FMT (search lines 15 to 22).

The concepts were combined as follows: CDI AND FMT.
The strategy was devised using a combination of subject indexing terms and free text search terms in the Title, Abstract and Keyword Heading Word fields. The search terms for population and intervention concepts were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The strategy was not restricted by study design or outcome, and was designed to identify both clinical and economic evidence.
The strategy excluded animal studies from MEDLINE using a standard algorithm (search line 24). The strategy also excluded some publication types which were unlikely to yield relevant study reports (editorials, news items and case reports) and records with the phrase 'case report' in the title (search line 25).

The strategy was restricted to studies published in English language. The language restriction reflected the eligibility criteria. The strategy was not restricted by date.

The performance of the draft strategy was assessed by checking retrieval of records for known studies on FMT for CDI. These studies included: 18 studies on FMT for recurrent CDI included in the 2021 systematic review by Cold et al on encapsulated FMT (Cold 2021); 7 studies included in the 2021 systematic review by Hammeken et al of economic evaluations comparing FMT with antibiotics for CDI (Hammeken 2021); 6 studies included in Table 5 (Summary of included studies: Faecal microbiota transplant (FMT)) of the NICE guideline on antimicrobial prescribing guideline for CDI (National Institute for Health and Care Excellence 2021a); 6/7 systematic reviews / NMAs included in the Appendix E.1.4 table of the same guideline, for which records could be found in MEDLINE; 44/45 studies included in the 2020 systematic review by Baunwell et al on FMT for CDI for which records could

be found in MEDLINE (Baunwall 2020); 5 studies included in the 2014 NICE overview of FMT for CDI (National Institute for Health and Care Excellence 2014). In total, 73 unique records were used to assess strategy performance. Before news items, letters and case reports were excluded, the strategy successfully retrieved all 73 records. By excluding news items, letters, and case reports, two records were not retrieved (Stollman 2015, Tian 2015). Both these records were indexed in MEDLINE with the publication type case report.

The final Ovid MEDLINE strategy was peer-reviewed by a second Information Specialist for errors in spelling, syntax, and line combinations.

Figure A1 Search strategy for MEDLINE(R) ALL

1 Clostridioides difficile/ (10223)
2 Clostridium Infections/ (9553)
3 ((clostridial or clostridioides or clostridium or peptoclostridium) adj6 difficil$).ti,ab,kf. (16288)
4 ((clostridial or clostridioides or clostridium or peptoclostridium) adj6 (disease$ or infect$ or poison$)).ti,ab,kf. (10108)
5 c diff$.ti,ab,kf. (9578)
6 cdiff$.ti,ab,kf. (173)
7 (cdad or rcdad or cdi or rcdi).ti,ab,kf. (8272)
8 (cdads or rcdads or cdis or rcdis).ti,ab,kf. (457)
9 (clostridioses or clostridiosis).ti,ab,kf. (34)
10 txid1496.ti,ab,kf. (0)
11 (bacillus adj6 difficil$).ti,ab,kf. (101)
12 b diff$.ti,ab,kf. (1408)
13 bdiff$.ti,ab,kf. (2)
14 or/1-13 (28987)
15 Fecal Microbiota Transplantation/ (1981)
16 ((faecal or fecal or faeces$ or feces$) adj6 (biotherap$ or donat$ or donor$1 or enema$ or implant$ or infus$ or install$ or reconstitut$ or restor$ or suspen$ or transfer$ or transfus$ or transplant$)).ti,ab,kf. (5405)
17 ((flora or floras or microbe$ or microbial$ or microbiome$ or microbiota$ or microflora$ or poo or poos or stool$) adj6 (biotherap$ or donat$ or donor$1 or enema$ or implant$ or infus$ or install$ or reconstitut$ or restor$ or suspen$ or transfer$ or transfus$ or transplant$)).ti,ab,kf. (10331)
18 ((flora or floras or microbe$ or microbial$ or microbiome$ or microbiota$ or microflora$ or poo or poos or stool$) adj3 (drug$ or pharmaceutical$ or treatment$ or therap$)).ti,ab,kf. (9920)
19 (bacteriotherap$ or human probiotic infusion$ or colonic restoration$ or rbx2660$).ti,ab,kf. (300)
20 (fmt or fmts).ti,ab,kf. (2617)
21 (imt or imts or hpi or hpis).ti,ab,kf. (16514)
22 or/15-21 (39203)
23 14 and 22 (1844)
24 exp animals/ not humans/ (4895630)
25 (news or editorial or case reports).pt. or case report.ti. (3050618)
26 23 not (24 or 25) (1545)
27 limit 26 to english language (1437)

Key to Ovid symbols and commands

$ Unlimited right-hand truncation symbol

$N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf) fields
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-13	Combines sets 1 to 13 using OR

Resources searched

The EAC conducted searches using the databases and information resources listed in Table A1. The information resources included a range of databases containing research published in the journal literature, conference abstracts and ongoing research. The searches were designed to identify both clinical and economic evidence, and therefore included specialist economics databases.

Table A1: Databases and information resources searched

Resource	Interface / URL
MEDLINE(R) ALL	OvidSP
Embase	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley
HTA Database	https://database.inahta.org/
ClinicalTrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform (ICTRP)	https://www.who.int/clinical-trials-registry-platform
Conference Proceedings Citation Index – Science (CPCI-S)	Web of Science
EconLit	OvidSP
NHS Economic Evaluation Database (NHS EED)	https://www.crd.york.ac.uk/CRDWeb/HomePage.asp

We also checked the reference lists of any included studies and retrieved relevant systematic reviews published in the last 5 years for any eligible studies that may have been missed by the database searches.

Running the search strategies and downloading results

We conducted searches using each database or resource listed above, translating the agreed Ovid MEDLINE strategy appropriately. Translation included consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri.

The results of database searches were downloaded in a tagged format and loaded into bibliographic software (EndNote) (Clarivate 2020). The results

were deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required.

Literature search results

The searches were conducted between 08 October 2021 and 12 October 2021. The searches identified 6,239 records (Table A2). Following deduplication, 3,893 records were assessed for relevance.

Table A2 Literature search results

Resource	Number of records identified
Databases	
MEDLINE(R) ALL	1437
Embase	3102
Cochrane Database of Systematic Reviews (CDSR)	4
Cochrane Central Register of Controlled Trials (CENTRAL)	345
HTA Database	8
ClinicalTrials.gov	760
WHO International Clinical Trials Registry Platform (ICTRP)	217
Conference Proceedings Citation Index – Science (CPCI-S)	365
EconLit	0
NHS Economic Evaluation Database (NHS EED)	1
Other sources	
Reference list checking	0
Total additional records identified through other sources	0
Total number of records retrieved	**6239**
Total number of records after deduplication	**3893**

Search strategies

A.1: Source: Ovid MEDLINE(R) ALL

Interface / URL: OvidSP
Database coverage dates: 1946 to October 07, 2021
Search date: 08/10/2021
Retrieved records: 1437
Search strategy:

1 Clostridioides difficile/ (10223)
2 Clostridium Infections/ (9553)
3 ((clostridial or clostridioides or clostridium or peptoclostridium) adj6 difficil$).ti,ab,kf. (16288)
4 ((clostridial or clostridioides or clostridium or peptoclostridium) adj6 (disease$ or infect$ or poison$)).ti,ab,kf. (10108)
5 c diff$.ti,ab,kf. (9578)
6 cdiff$.ti,ab,kf. (173)
7 (cdad or rcdad or cdi or rcdi).ti,ab,kf. (8272)
8 (cdads or rcdads or cdis or rcdis).ti,ab,kf. (457)

9 (clostridioses or clostridiosis).ti,ab,kf. (34)
10 txid1496.ti,ab,kf. (0)
11 (bacillus adj6 difficil$).ti,ab,kf. (101)
12 b diff$.ti,ab,kf. (1408)
13 bdiff$.ti,ab,kf. (2)
14 or/1-13 (28987)
15 Fecal Microbiota Transplantation/ (1981)
16 ((faecal or fecal or faeces$ or feces$) adj6 (biotherap$ or donat$ or donor$1 or enema$ or implant$ or infus$ or install$ or reconstitut$ or restor$ or suspen$ or transfer$ or transfus$ or transplant$)).ti,ab,kf. (5405)
17 ((flora or floras or microbe$ or microbial$ or microbiome$ or microbiota$ or microflora$ or poo or poos or stool$) adj6 (biotherap$ or donat$ or donor$1 or enema$ or implant$ or infus$ or install$ or reconstitut$ or restor$ or suspen$ or transfer$ or transfus$ or transplant$)).ti,ab,kf. (10331)
18 ((flora or floras or microbe$ or microbial$ or microbiome$ or microbiota$ or microflora$ or poo or poos or stool$) adj3 (drug$ or pharmaceutical$ or treatment$ or therap$)).ti,ab,kf. (9920)
19 (bacteriotherap$ or human probiotic infusion$ or colonic restoration$ or rbx2660$).ti,ab,kf. (300)
20 (fmt or fmts).ti,ab,kf. (2617)
21 (imt or imts or hpi or hpis).ti,ab,kf. (16514)
22 or/15-21 (39203)
23 14 and 22 (1844)
24 exp animals/ not humans/ (4895630)
25 (news or editorial or case reports).pt. or case report.ti. (3050618)
26 23 not (24 or 25) (1545)
27 limit 26 to english language (1437)

A.2: Source: Embase

Interface / URL: OvidSP
Database coverage dates: 1974 to 2021 October 07
Search date: 08/10/2021
Retrieved records: 3102
Search strategy:

1 clostridioides difficile/ or Clostridium difficile/ or Peptoclostridium difficile/ (17131)
2 Clostridium infection/ or Clostridium difficile infection/ or Clostridioides difficile infection/ (18347)
3 ((clostridial or clostridioides or clostridium or peptoclostridium) adj6 difficil$).ti,ab,kf,dq. (23506)
4 ((clostridial or clostridioides or clostridium or peptoclostridium) adj6 (disease$ or infect$ or poison$)).ti,ab,kf,dq. (14801)

5 c diff$.ti,ab,kf,dq. (13775)
6 cdiff$.ti,ab,kf,dq. (756)
7 (cdad or rcdad or cdi or rcdi).ti,ab,kf,dq. (13245)
8 (cdads or rcdads or cdis or rcdis).ti,ab,kf,dq. (664)
9 (clostridioses or clostridiosis).ti,ab,kf,dq. (39)
10 txid1496.ti,ab,kf,dq. (0)
11 (bacillus adj6 difficil$).ti,ab,kf,dq. (127)
12 b diff$.ti,ab,kf,dq. (1855)
13 bdiff$.ti,ab,kf,dq. (14)
14 or/1-13 (46196)
15 fecal microbiota transplantation/ or bacteriotherapy/ (5828)
16 ((faecal or fecal or faeces$ or feces$) adj6 (biotherap$ or donat$ or donor$1 or enema$ or implant$ or infus$ or install$ or reconstitut$ or restor$ or suspen$ or transfer$ or transfus$ or transplant$)).ti,ab,kf,dq. (7846)
17 ((flora or floras or microbe$ or microbial$ or microbiome$ or microbiota$ or microflora$ or poo or poos or stool$) adj6 (biotherap$ or donat$ or donor$1 or enema$ or implant$ or infus$ or install$ or reconstitut$ or restor$ or suspen$ or transfer$ or transfus$ or transplant$)).ti,ab,kf,dq. (13774)
18 ((flora or floras or microbe$ or microbial$ or microbiome$ or microbiota$ or microflora$ or poo or poos or stool$) adj3 (drug$ or pharmaceutical$ or treatment$ or therap$)).ti,ab,kf,dq. (10920)
19 (bacteriotherap$ or human probiotic infusion$ or colonic restoration$ or rbx2660$).ti,ab,kf,dq,tn. (460)
20 (fmt or fmts).ti,ab,kf,dq. (4271)
21 (imt or imts or hpi or hpis).ti,ab,kf,dq. (19516)
22 or/15-21 (48841)
23 14 and 22 (3625)
24 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6313031)
25 editorial.pt. or case report.ti. (1032510)
26 23 not (24 or 25) (3282)
27 limit 26 to english language (3102)

A.3: Source: Cochrane Central Register of Controlled Trials (CENTRAL)

Interface / URL: Cochrane Library/Wiley
Database coverage dates: Information not found. Issue searched: Issue 10 of 12, October 2021
Search date: 08/10/2021
Retrieved records: 345
Search strategy:

#1 MeSH descriptor: [Clostridioides difficile] this term only 194

#2 MeSH descriptor: [Clostridium Infections] this term only 170
#3 ((clostridial or clostridioides or clostridium or peptoclostridium) near/6 difficil*) 1473
#4 ((clostridial or clostridioides or clostridium or peptoclostridium) near/6 (disease* or infect* or poison*)) 1200
#5 (c next diff*) 894
#6 cdiff* 54
#7 (cdad or rcdad or cdi or rcdi) 985
#8 (cdads or rcdads or cdis or rcdis) 52
#9 (clostridioses or clostridiosis) 1
#10 txid1496 0
#11 (bacillus near/6 difficil*) 6
#12 (b next diff*) 296
#13 bdiff* 11
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 2738
#15 MeSH descriptor: [Fecal Microbiota Transplantation] this term only 75
#16 ((faecal or fecal or faeces* or feces*) near/6 (biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*)) 956
#17 ((flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*) near/6 (biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*)) 1354
#18 ((flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*) near/3 (drug* or pharmaceutical* or treatment* or therap*)) 2673
#19 (bacteriotherap* or human next probiotic next infusion* or colonic next restoration* or rbx2660*) 84
#20 (fmt or fmts) 613
#21 (imt or imts or hpi or hpis) 2056
#22 #15 or #16 or #17 or #18 or #19 or #20 or #21 6108
#23 #14 and #22 364
#24 #23 in Trials 345

A.4: Source: Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Cochrane Library/Wiley
Database coverage dates: Information not found. Issue searched: Issue 10 of 12, October 2021
Search date: 08/10/2021
Retrieved records: 4
Search strategy:

#1 MeSH descriptor: [Clostridioides difficile] this term only 194
#2 MeSH descriptor: [Clostridium Infections] this term only 170
#3 ((clostridial or clostridioides or clostridium or peptoclostridium) near/6 difficil*):ti,ab,kw 1389
#4 ((clostridial or clostridioides or clostridium or peptoclostridium) near/6 (disease* or infect* or poison*)):ti,ab,kw 1126
#5 (c next diff*):ti,ab,kw 819
#6 cdiff*:ti,ab,kw 52
#7 (cdad or rcdad or cdi or rcdi):ti,ab,kw 922
#8 (cdads or rcdads or cdis or rcdis):ti,ab,kw 45
#9 (clostridioses or clostridiosis):ti,ab,kw 1
#10 txid1496:ti,ab,kw 0
#11 (bacillus near/6 difficil*):ti,ab,kw 5
#12 (b next diff*):ti,ab,kw 242
#13 bdiff*:ti,ab,kw 3
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 2517
#15 MeSH descriptor: [Fecal Microbiota Transplantation] this term only 75
#16 ((faecal or fecal or faeces* or feces*) near/6 (biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*)):ti,ab,kw 849
#17 ((flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*) near/6 (biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*)):ti,ab,kw 1175
#18 ((flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*) near/3 (drug* or pharmaceutical* or treatment* or therap*)):ti,ab,kw 2561
#19 (bacteriotherap* or human next probiotic next infusion* or colonic next restoration* or rbx2660*):ti,ab,kw 81
#20 (fmt or fmts):ti,ab,kw 590
#21 (imt or imts or hpi or hpis):ti,ab,kw 1971
#22 #15 or #16 or #17 or #18 or #19 or #20 or #21 5683
#23 #14 and #22 351
#24 #23 in Cochrane Reviews, Cochrane Protocols 4

A.5: Source: EconLit

Interface / URL: OvidSP
Database coverage dates: 1886 to September 30, 2021
Search date: 08/10/2021
Retrieved records: 0
Search strategy:

1 ((clostridial or clostridioides or clostridium or peptoclostridium) adj6 difficil$).af. (4)
2 ((clostridial or clostridioides or clostridium or peptoclostridium) adj6 (disease$ or infect$ or poison$)).af. (2)
3 c diff$.af. (22)
4 cdiff$.af. (0)
5 (cdad or rcdad or cdi or rcdi).af. (31)
6 (cdads or rcdads or cdis or rcdis).af. (4)
7 (clostridioses or clostridiosis).af. (0)
8 txid1496.af. (0)
9 (bacillus adj6 difficil$).af. (0)
10 b diff$.af. (33)
11 bdiff$.af. (0)
12 or/1-11 (84)
13 ((faecal or fecal or faeces$ or feces$) adj6 (biotherap$ or donat$ or donor$1 or enema$ or implant$ or infus$ or install$ or reconstitut$ or restor$ or suspen$ or transfer$ or transfus$ or transplant$)).af. (0)
14 ((flora or floras or microbe$ or microbial$ or microbiome$ or microbiota$ or microflora$ or poo or poos or stool$) adj6 (biotherap$ or donat$ or donor$1 or enema$ or implant$ or infus$ or install$ or reconstitut$ or restor$ or suspen$ or transfer$ or transfus$ or transplant$)).af. (1)
15 ((flora or floras or microbe$ or microbial$ or microbiome$ or microbiota$ or microflora$ or poo or poos or stool$) adj3 (drug$ or pharmaceutical$ or treatment$ or therap$)).af. (1)
16 (bacteriotherap$ or human probiotic infusion$ or colonic restoration$ or rbx2660$).af. (0)
17 (fmt or fmts).af. (5)
18 (imt or imts or hpi or hpis).af. (311)
19 or/13-18 (318)
20 12 and 19 (0)
21 limit 20 to english (0)

A.6: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Database coverage dates: Information not found. Bibliographic records were published on NHS EED until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.
Search date: 08/10/2021
Retrieved records: 1
Search strategy:

1 MeSH DESCRIPTOR Clostridioides difficile 0
2 MeSH DESCRIPTOR Clostridium Infections 50

3 (((clostridial or clostridioides or clostridium or peptoclostridium) adj6 difficil*)) 106
4 ((difficil* adj6 (clostridial or clostridioides or clostridium or peptoclostridium))) 13
5 (((clostridial or clostridioides or clostridium or peptoclostridium) adj6 (disease* or infect* or poison*))) 74
6 (((disease* or infect* or poison*) adj6 (clostridial or clostridioides or clostridium or peptoclostridium))) 45
7 (c diff*) 36
8 (cdiff*)0
9 ((cdad or rcdad or cdi or rcdi)) 33
10 ((cdads or rcdads or cdis or rcdis)) 0
11 ((clostridioses or clostridiosis)) 0
12 (txid1496) 0
13 ((bacillus adj6 difficil*)) 0
14 ((difficil* adj6 bacillus)) 0
15 (b diff*) 4
16 (bdiff*)0
17 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 137
18 MeSH DESCRIPTOR Fecal Microbiota Transplantation 2
19 (((faecal or fecal or faeces* or feces*) adj6 (biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*))) 30
20 (((biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*) adj6 (faecal or fecal or faeces* or feces*))) 17
21 (((flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*) adj6 (biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*))) 8
22 (((biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*) adj6 (flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*))) 16
23 (((flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*) adj3 (drug* or pharmaceutical* or treatment* or therap*))) 44
24 (((drug* or pharmaceutical* or treatment* or therap*) adj3 (flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*))) 99
25 ((bacteriotherap* or human probiotic infusion* or colonic restoration* or rbx2660*)) 2

26 ((fmt or fmts)) 2
27 ((imt or imts or hpi or hpis)) 21
28 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 188
29 #17 AND #28 15
30 (#29) IN NHSEED 1

A.7: Source: HTA database

Interface / URL: https://database.inahta.org/
Database coverage dates: Information not found. The former database was produced by the CRD until March 2018, at which time the addition of records was stopped as INAHTA was in the process of rebuilding the new database platform. In July 2019, the database records were exported from the CRD platform and imported into the new platform that was developed by INAHTA. The rebuild of the new platform was launched in June 2020.

Search date: 08/10/2021
Retrieved records: 8
Search strategy:

22 #21 AND #20 8
21 (english)[languages] 13980
20 #19 AND #11 10
19 #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 77
18 (imt OR imts OR hpi OR hpis) 6
17 (fmt OR fmts)2
16 (bacteriotherap* OR (human AND probiotic AND infusion*) OR (colonic AND restoration*) OR rbx2660*) 2
15 ((flora OR floras OR microbe* OR microbial* OR microbiome* OR microbiota* OR microflora* OR poo OR poos OR stool*) AND (drug* OR pharmaceutical* OR treatment* OR therap*)) 42
14 ((flora OR floras OR microbe* OR microbial* OR microbiome* OR microbiota* OR microflora* OR poo OR poos OR stool*) AND (biotherap* OR donat* OR donor* OR enema* OR implant* OR infus* OR install* OR reconstitut* OR restor* OR suspen* OR transfer* OR transfus* OR transplant*)) 8
13 ((faecal OR fecal OR faeces* OR feces*) AND (biotherap* OR donat* OR donor* OR enema* OR implant* OR infus* OR install* OR reconstitut* OR restor* OR suspen* OR transfer* OR transfus* OR transplant*)) 27
12 "Fecal Microbiota Transplantation"[mh] 3
11 #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 45
10 bdiff* 0

9 txid1496 0
8 (clostridioses OR clostridiosis) 0
7 (cdads OR rcdads OR cdis OR rcdis) 0
6 (cdad OR rcdad OR cdi OR rcdi) 12
5 cdiff* 0
4 ((clostridial OR clostridioides OR clostridium OR peptoclostridium) AND (disease* OR infect* OR poison*)) 25
3 diff OR difficil* 37
2 "Clostridium Infections"[mh] 18
1 "Clostridioides difficile"[mh]24

A.8: Source: Conference Proceedings Citation Index – Science (CPCI-S)

Interface / URL: Web of Science
Database coverage dates: 1990-present
Search date: 08/10/2021
Retrieved records: 365
Search strategy:

The search was conducted in: Web of Science Core Collection. Editions: Conference Proceedings Citation Index – Science (CPCI-S) - 1990-present

The Advanced Search interface was used. The 'Exact search' option was turned on.

21 #12 and #19 and English (Languages) 365
20 #12 and #19 366
19 #13 or #14 or #15 or #16 or #17 or #18 4,685
18 TS=(imt or imts or hpi or hpis) 1,827
17 TS=(fmt or fmts) 538
16 TS=(bacteriotherap* or "human probiotic infusion*" or "colonic restoration*" or rbx2660*) 62
15 TS=((flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*) near/3 (drug* or pharmaceutical* or treatment* or therap*)) 939
14 TS=((flora or floras or microbe* or microbial* or microbiome* or microbiota* or microflora* or poo or poos or stool*) near/6 (biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*)) 1,314
13 TS=((faecal or fecal or faeces* or feces*) near/6 (biotherap* or donat* or donor* or enema* or implant* or infus* or install* or reconstitut* or restor* or suspen* or transfer* or transfus* or transplant*)) 756

12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 4,449
11 TS=bdiff* 1
10 TS="b diff*" 443
9 TS=(bacillus near/6 difficil*) 4
8 TS=txid1496 0
7 TS=(clostridioses or clostridiosis) 3
6 TS=((cdads or rcdads or cdis or rcdis)) 43
5 TS=((cdad or rcdad or cdi or rcdi)) 849
4 TS=(cdiff*) 11
3 TS=("c diff*") 1,164
2 TS=(((clostridial or clostridioides or clostridium or peptoclostridium) near/6 (disease* or infect* or poison*))) 1,338
1 TS=(((clostridial or clostridioides or clostridium or peptoclostridium) near/6 difficil*)) 2,443

A.9: Source: ClinicalTrials.gov

Interface / URL: https://clinicaltrials.gov/ct2/home
Database coverage dates: Information not found. ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). The site was made available to the public in February 2000.
Search date: 12/10/2021
Retrieved records: 760
Search strategy:

The following three searches were conducted separately. All search terms were entered using the Expert search interface. The retrieved record figure above (760) indicates the total number of records retrieved – it does not reflect duplicates found across sets.

1. (clostridial OR clostridioides OR clostridium OR peptoclostridium OR "c diff" OR "c difficile" OR cdiff OR cdifficile OR cdad OR rcdad OR cdi OR rcdi OR cdads OR rcdads OR cdis OR rcdis OR clostridioses OR clostridiosis OR txid1496 OR (bacillus AND difficile) OR "b diff" OR "b difficile" OR bdiff OR bdifficile) AND (faecal OR fecal OR faeces OR feces OR flora OR floras OR microbe OR microbes OR microbial OR microbials OR microbiome OR microbiomes OR microbiota OR microbiotas OR microflora OR microfloras OR poo OR poos OR stool OR stools) AND (biotherapy OR biotherapies OR biotherapeutic OR biotherapeutics OR donate OR donates OR donated OR donating OR donation OR donations OR donor OR donors OR enema OR enemas OR implant OR implants OR implanted OR implanting OR implantation OR implantations OR infuse OR infuses OR infused OR infusing OR infusion OR infusions OR install OR installs OR installed OR installing OR

installation OR installations OR reconstitute OR reconstitutes OR reconstituted OR reconstituting OR reconstitution OR reconstitutions OR restore OR restores OR restored OR restoring OR restoration OR restorations OR suspend OR suspends OR suspended OR suspending OR suspension OR suspensions OR transfer OR transfers OR transferred OR transferring OR transfuse OR transfuses OR transfused OR transfusing OR transfusion OR transfusions OR transplant OR transplants OR transplanted OR transplanting OR transplantation OR transplantations) = 199 results

2. (clostridial OR clostridioides OR clostridium OR peptoclostridium OR "c diff" OR "c difficile" OR cdiff OR cdifficile OR cdad OR rcdad OR cdi OR rcdi OR cdads OR rcdads OR cdis OR rcdis OR clostridioses OR clostridiosis OR txid1496 OR (bacillus AND difficile) OR "b diff" OR "b difficile" OR bdiff OR bdifficile) AND (flora OR floras OR microbe OR microbes OR microbial OR microbials OR microbiome OR microbiomes OR microbiota OR microbiotas OR microflora OR microfloras OR poo OR poos OR stool OR stools) AND (drug OR drugs OR drugged OR drugging OR pharmaceutical OR pharmaceuticals OR pharmaceutically OR treatment OR treatments OR therapy OR therapies OR therapeutic OR therapeutics) = 387 results

3. (clostridial OR clostridioides OR clostridium OR peptoclostridium OR "c diff" OR "c difficile" OR cdiff OR cdifficile OR cdad OR rcdad OR cdi OR rcdi OR cdads OR rcdads OR cdis OR rcdis OR clostridioses OR clostridiosis OR txid1496 OR (bacillus AND difficile) OR "b diff" OR "b difficile" OR bdiff OR bdifficile) AND (bacteriotherapy OR bacteriotherapies OR bacteriotherapeutic OR bacteriotherapeutics OR "human probiotic infusion" OR "human probiotic infusions" OR "colonic restoration" OR "colonic restorations" OR rbx2660 OR rbx2660r OR rbx2660tm OR fmt OR fmts OR imt OR imts OR hpi OR hpis) = 174 results

A.10: Source: WHO International Clinical Trials Registry Portal (ICTRP)
Interface / URL: http://apps.who.int/trialsearch/Default.aspx
Database coverage dates: Information not found. Data sets from data providers are updated every Friday evening according to a schedule. On the date of search, files had been imported from data providers between May 2021 and July 2021.
Search date: 12/10/2021
Retrieved records: 217
Search strategy:

The following three searches were conducted separately using the search interface at: https://apps.who.int/trialsearch/. The retrieved record figure above

(217) indicates the total number of records retrieved – it does not reflect duplicates found across sets.

For all searches 'Without synonyms' was selected.

1. (clostridial OR clostridioides OR clostridium OR peptoclostridium OR "c diff*" OR cdiff* OR cdad OR rcdad OR cdi OR rcdi OR clostridioses OR clostridiosis OR txid1496 OR (bacillus AND difficil*) OR "b diff*" OR bdiff*) AND (faecal OR fecal OR faeces* OR feces* OR flora OR floras OR microbe* OR microbial* OR microbiome* OR microbiota* OR microflora* OR poo OR poos OR stool*) AND (biotherap* OR donat* OR donor* OR enema* OR implant* OR infus* OR install* OR reconstitut* OR restor* OR suspen* OR transfer* OR transfus* OR transplant*) = 102 (104 records for 102 trials found)

2. (clostridial OR clostridioides OR clostridium OR peptoclostridium OR "c diff*" OR cdiff* OR cdad OR rcdad OR cdi OR rcdi OR clostridioses OR clostridiosis OR txid1496 OR (bacillus AND difficil*) OR "b diff*" OR bdiff*) AND (flora OR floras OR microbe* OR microbial* OR microbiome* OR microbiota* OR microflora* OR poo OR poos OR stool*) AND (drug* OR pharmaceutical* OR treatment* OR therap*) = 50 (52 records for 50 trials found)

3. (clostridial OR clostridioides OR clostridium OR peptoclostridium OR "c diff*" OR cdiff* OR cdad OR rcdad OR cdi OR rcdi OR clostridioses OR clostridiosis OR txid1496 OR (bacillus AND difficil*) OR "b diff*" OR bdiff*) AND (bacteriotherap* OR "human probiotic infusion*" OR "colonic restoration*" OR rbx2660* OR fmt or fmts OR imt OR imts OR hpi OR hpis) = 65 (65 records for 65 trials found)

Search notes for ICTRP:

The search interface at https://trialsearch.who.int/ was recently launched (source: e-mail from ICTRP Manager to ICTRPNEWS@LISTSERV.WHO.INT on 20/07/2021). On the date of search, the Search Tips page (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal/search-tips) appeared to still relate to the old interface.

Information on search functionality for a test site had previously been circulated by the ICTRP Manager (source: e-mail from ICTRP Manager to ICTRPNEWS@LISTSERV.WHO.INT on 15/03/2021). This information stated:

- Truncation disables synonym searching.

- Do not use truncation in the middle of a word e.g. bacte*mia will not return any hits.
- Individual words within phrases may be truncated e.g. “liv* canc*”.
- The minimum number of characters before the asterisk is 3 e.g. li* will not return any results.
- Now you can use parentheses when mixing Boolean operators. Parentheses may be nested to any level e.g. ((“liv* cancer*” and neoplasms) or (“Incision of liver” not malignant)) and hospital.

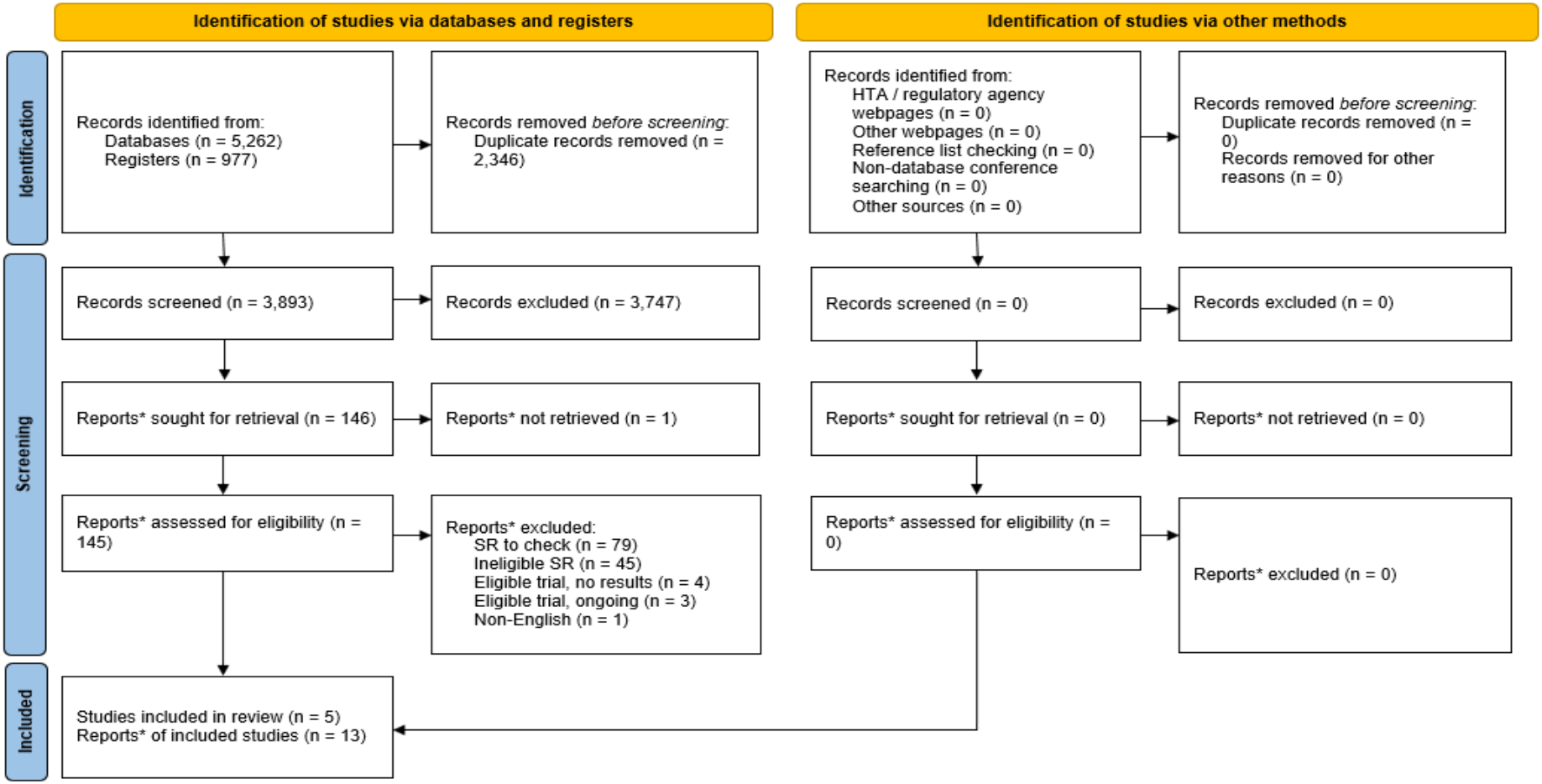
The syntax shown in the above information suggested that double quotes should now be used to search on phrases (in the previous interface, a phrase was two or more words in succession, and should not be enclosed in double-quotes).

The ICTRP Manager was contacted by e-mail (12/10/2021) to confirm if the information on search functionality previously circulated for the test site was also still correct for the new live version, and to ask if there were any up-to-date search help pages available for the new interface. No reply was received.

Test searches suggested that the following functionality was available for the new live site. This functionality matched that suggested by the information previously circulated on the test site. The search syntax was therefore developed based on the assumption that the following was correct.

- phrases should be enclosed in double quotes
- parentheses can be used when mixing Boolean operators
- individual words within phrases may be truncated e.g. "liv* canc*".

Figure A2 Clinical PRISMA flow diagram



*"Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report or any other document providing relevant information": https://www.bmj.com/content/372/bmj.n71.

Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix B Clinical effectiveness trial data, quality assessments

Table B1 PICO analysis of each included trial

Study and type	Population	Intervention	Comparator	Outcomes	Follow up and Withdrawals	EAC comment
Cammarota 2015	Adults with recurrent CDI. Italy. 41%* male. Mean age 73 years (range 29 to 93 years).	FMT by colonoscopy after vancomycin 125 mg orally QID for 3 days and bowel cleaning.	Vancomycin 125 mg orally QID for 10 days, followed by a pulse regimen (125 to 500 mg/day every 2 to 3 days) for at least 3 weeks.	• Primary: resolution of diarrhoea associated with CDI 10 weeks after the end of the treatments. • Secondary: toxin negative without recurrent CDI 5 and 10 weeks after the end of the treatments.	10 weeks from last FMT (FMT arm) or end of antibiotics (comparator arm)	After a sample size calculation, the authors planned to enrol 50 patients per group. At the planned 1-year interim analysis, FMT showed a significantly higher efficacy than vancomycin. Therefore, after consulting an independent committee (including two internists and one gastroenterologist), the study was stopped when a total of 39 patients were recruited. High risk of bias due to measuring outcomes at different timepoints, and some subjective outcomes measured without objective confirmation. Some concerns also arising from missing outcome data (treatment failure and mortality at 5-14 months), and publishing protocol toward

Study and type	Population	Intervention	Comparator	Outcomes	Follow up and Withdrawals	EAC comment
						the end of patient recruitment. Generalisability issues: unclear if the number of recurrences at study recruitment include the baseline episode.
Hota 2017 RCT with cross-over offered on further recurrence.	Adults with an acute episode of recurrent CDI. Canada. 32% male. Mean (SD) age reported by intervention: FMT 75.7 (14.5), VTP 69.6 (14.2).	FMT delivered by enema. Pre-procedural vancomycin 125 mg orally QID for 14 days. FMT delivered 48 hours after stopping vancomycin.	VTP: 14 days of vancomycin 125 mg orally QID, with taper over 4 weeks (vancomycin 125 mg orally BID for 1 week; 125 mg orally QD for 1 week; 125 mg orally every second day for 1 week; 125 mg orally every third day for 1 week.	• Recurrence CDI (laboratory-confirmed; non-laboratory confirmed). • Days of diarrhoea. • Symptom resolution. • AEs • SAEs. • CDI-specific mortality. • All-cause mortality. • CDI requiring hospital admission.	Follow up 4 months. 2 patients in comparator arm withdrew (1 repeated protocol non-compliance, 1 to seek intervention elsewhere).	Trial stopped after randomisation of 30 patients, on the basis of futility analysis (3.4% probability of finding a significant benefit for FMT, defined as the upper end of the one-sided Bayesian 95% interval for the risk reduction lying below 0). High risk of bias due to use of a PP analysis with all exclusions from 1 trial arm, and measurement of some subjective outcomes without objective confirmation. Some concerns also regarding the randomisation process, with possible differences in baseline characteristics.

Study and type	Population	Intervention	Comparator	Outcomes	Follow up and Withdrawals	EAC comment
Hvas 2019 RCT	Adults referred for recurrent CDI in a public referral gastro-enterology centre, Denmark. Median age 68 years 31% female (20/64)	FMT received by colonoscopy (19/24) or NJT (5/24). Colonoscope pre-procedure: standard lavage. NJT pre-procedure: overnight fast. 6 healthy donors delivered faeces.	Fidaxomicin 200 mg BID for 10 days (n=24) Vancomycin 125 mg QID for 10 days (n=16)	• Primary: combined clinical resolution and negative CD test result, without need for rescue FMT or colectomy 8 weeks after initial treatment. • Clinical resolution • Negative stool test for CDI • Combined clinical resolution and negative stool test for CDI	Follow up 2 months. No withdrawals or losses to follow-up.	The trial was completed after recruiting the target number of patients. High risk of bias due to the measurement of some subjective outcomes without full objective confirmation. Some concerns of selection bias due to not reporting methods of randomisation and allocation concealment.
Rode 2021	Adults with ≥2 recurrences** of CDI from primary, secondary and tertiary care. Treated at 2 university hospitals in Denmark. **randomised stratum of patients with multiple recurrences only. This study also randomised	FMT by enema after pre-treatment with vancomycin 125 mg QID for 7 to 14 days	Oral vancomycin taper (7 weeks): 125 mg QID for 14 days, 125 mg twice daily for 1 week, 125 mg once daily for 1 week, 125 mg every other day for 1 week and 125 mg every third day for 2 weeks.	Primary: • Clinical cure of CDI, defined as absence of diarrhoea or diarrhoea with a negative CD test), within 90 days after ended treatment. Secondary: • Clinical cure within 180 days after ended treatment,	180 days after treatment. All participants included in the ITT population.	Patient subgroup (randomised stratum) with multiple recurrences fully meets decision problem. As planned, the authors conducted an interim analysis for the first 90 participants. When the reported results were apparent, including the mortality data, the study was terminated due to futility and ethical concerns - even though

Study and type	Population	Intervention	Comparator	Outcomes	Follow up and Withdrawals	EAC comment
	patients with 1 recurrence (stratum #1, not extracted). Patient characteristics for multiple recurrence group not reported. (full trial population: Age range 33 to 96 years; 46% male)			• Safety (occurrence of AEs and SAEs) • 180-day mortality (all-cause and possibly CD-related mortality).		the Haybittle-Peto boundary was not met. High risk of bias due to measuring outcomes at different timepoints, and some subjective outcomes measured without full objective confirmation. Some concerns also around selective outcome reporting, with some outcomes listed in trial register not reported in the publication.
van Nood 2013	Adults (≥18 years) with relapse of CDI after at least one course of adequate antibiotic therapy (≥10 days of vancomycin at a dose of ≥125 mg QID or ≥10 days of metronidazole at a dose of 500 mg TID). Academic Medical Center in Amsterdam.	FMT by NDT after vancomycin 500 mg orally QID for 4 or 5 days, followed by bowel lavage with 4L of macrogol solution on the last day of antibiotic treatment.	Vancomycin (500 mg orally QID for 14 days); or vancomycin with bowel lavage on day 4 or 5.	Primary: cure without relapse within 10 weeks Secondary: • cure without relapse after 5 weeks • recurrence of CDI • diarrhoea • safety (AEs).	Follow up for 10 weeks. 41 (95%) patients completed the study protocol: 1 patient in the vancomycin-only group did not complete study treatment, was discharged and died (severe heart failure and COPD); this patient was considered as a treatment failure	From January 2008 through April 2010, a total of 43 patients were randomly assigned to receive FMT (17 patients), vancomycin (13), or vancomycin and bowel lavage (13). Initially, the inclusion of 40 patients per study group was planned. Because most patients in both control groups had a relapse, the data and safety monitoring board did the interim efficacy analysis and advised termination of the trial.

Study and type	Population	Intervention	Comparator	Outcomes	Follow up and Withdrawals	EAC comment
	Mean (SD) age reported by intervention: FMT 73 (13), vancomycin 66 (14), vancomycin with bowel lavage 69 (16). Male: 25 (58%).				in the mITT analysis. Another patient in the FMT arm required high-dose prednisolone because of a rapid decrease in renal-graft function. At that time, the nephrologist objected to treatment with FMT. This patient was excluded from analysis.	Generalisability issues: 8 of 43 patients included after a first relapse. Some concerns due to the unclear exclusion of 1 protocol violation patient (FMT arm) when another protocol violation patient (vancomycin arm) was included.

Abbreviations*:* AE, Adverse events; BID, Bis in die ("twice a day"); CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* Infection; COPD, Chronic obstructive pulmonary disease; EAC, External Assessment Centre; FMT, Faecal Microbiota Transplantation; ITT, Intention to treat; mITT, Modified intention to treat; NDT, Nasoduodenal tube; NJT, Nasojejunal tube; PP, Per protocol; QD, Quaque die ("once a day"); QID, Quater in die ("four times each day"); RCT, Randomised controlled trial; SAE, Serious adverse event; SD, Standard deviation; TID, Ter in die (3 times daily); VTP, Vancomycin taper pulse.

*Reviewer-calculated

Table B2 Resolution of CDI

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
Administration: Upper GI							
van Nood 2013	mITT	Cure without relapse. Cure was defined as an absence of diarrhoea or persistent diarrhoea that could be explained by other causes with three consecutive negative stool tests for CD toxin. Relapse was defined as diarrhoea with a positive stool test for CD toxin. An adjudication committee whose members were unaware of study-group assignments decided which patients were cured.	10 weeks (from initiation of therapy)	FMT (NDT); 1 to 2 infusions	16	15 (94)	p<0.001 (vs. vancomycin)[a]
				Vancomycin	13	4 (31)	p<0.001 (vs. vancomycin with bowel lavage)
				Vancomycin and bowel lavage	13	3 (23)	
				FMT (NDT); first infusion only	16	13 (81)	p<0.01 (vs. vancomycin)
				Vancomycin	13	4 (31)	p<0.01 (vs. vancomycin with bowel lavage)
				Vancomycin and bowel lavage	13	3 (23)	
Administration: Lower GI							
Cammarota 2015	ITT	Cure of CDI (single and multiple infusions). Defined as the disappearance of diarrhoea, or persistent diarrhoea explicable by other causes, with two negative stool tests for CD toxin; after one or more infusions.	10 weeks (from end of therapy)	FMT (colonoscopy); 1 or more infusions	20	18 (90)	p<0.0001
				Vancomycin	19	5 (26)	
Cammarota 2015	ITT			FMT (colonoscopy); 1 infusion	20	13 (65)	NR
				Vancomycin	19	5 (26)	

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
Cammarota 2015	ITT	CDI stool toxin negative	5 weeks (from end of therapy)	FMT (colonoscopy); 1 or more infusions	20	18 (90)	NR
				Vancomycin	19	3 (16*)	
Cammarota 2015	ITT	CDI stool toxin negative	10 weeks (from end of therapy)	FMT (colonoscopy); 1 or more infusions	20	18 (90)	NR
				Vancomycin	19	5 (26*)	
Hota 2017	PP	Symptom resolution using standardised questionnaires to record symptoms.	120 days (from initiation of therapy)	FMT (enema)	16	7* (43.8)	NR[b]
				VTP	12	7* (58.3)	
Rode 2021	ITT	Clinical cure of CDI. Defined as patient-reported absence of diarrhoea, or diarrhoea with a negative CD test.	90 days (from end of therapy)	FMT (enema); 1 to 3 infusions	14	8 (57%)	p=0.01
				VTP	13	6 (46%)	
Administration: Mixed							
Hvas 2019	ITT	Combined: clinical resolution[c] with microbiological resolution (negative CD toxin PCR test result), without need for rescue FMT or colectomy.	1 week ('after initial treatment')	FMT (colonoscopy or NJT); 1 infusion	24	13 (54)	p=0.25 (vs. Fidaxomicin); p=0.01 (vs. Vancomycin)
				Fidaxomicin	24	9 (38)	-
				Vancomycin	16	2 (13)	-
Hvas 2019[d]	ITT	Combined: clinical resolution[c] and microbiological resolution (negative CD toxin PCR	8 weeks ('after initial treatment' or last FMT)	FMT (colonoscopy or NJT); 1 infusion	24	17 (71)	p=0.009 (vs. Fidaxomicin; p=0.001 (vs. Vancomycin)

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
		test result[d]) without need for rescue FMT or colectomy (Primary Outcome)		Fidaxomicin	24	8 (33)	-
				Vancomycin	16	3 (19)	-
				FMT (colonoscopy or NJT); 1 to 2 infusions	24	18 (75*)	NR
				Fidaxomicin	24	8 (33)	
				Vancomycin	16	3 (19)	
Hvas 2019	ITT	Clinical resolution[c] without need for rescue FMT or colectomy	1 week ('after initial treatment')	FMT (colonoscopy or NJT); 1 infusion	24	21 (88)	p=0.02 (vs. Fidaxomicin); p=0.002 (vs. Vancomycin)
				Fidaxomicin	24	14 (58)	-
				Vancomycin	16	6 (38)	-
Hvas 2019	ITT	Clinical resolution[c] without need for rescue FMT or colectomy	8 weeks ('after initial treatment')	FMT (colonoscopy or NJT); 1 infusion	24	22 (92)	p=0.0002 (vs. Fidaxomicin); p=<0.0001 (vs. Vancomycin)
				Fidaxomicin	24	10 (42)	-
				Vancomycin	16	3 (19)	-
Hvas 2019	ITT	Microbiological resolution (negative CD toxin PCR test result), without need for rescue FMT or colectomy.	1 week ('after initial treatment')	FMT (colonoscopy or NJT); 1 infusion	24	16 (67)	p=0.55 (vs. Fidaxomicin); p=0.21 (vs. Vancomycin)
				Fidaxomicin	24	14 (58)	-
				Vancomycin	16	7 (44)	-
Hvas 2019	ITT	Microbiological resolution (negative CD toxin PCR test result), without need for rescue FMT or colectomy.	8 weeks ('after initial treatment')	FMT (colonoscopy or NJT); 1 infusion	24	17 (71)	p=0.08 (vs. Fidaxomicin); p=0.01 (vs. Vancomycin)
				Fidaxomicin	24	11 (46)	-

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
				Vancomycin	16	5 (31)	-

Abbreviations*:* CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* Infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; ITT, Intention to treat; mITT, Modified intention to treat; NDT, Nasoduodenal tube; NJT, Nasojejunal tube; NR, Not reported; PCR, Polymerase chain reaction; PP, Per protocol; VTP, Vancomycin taper pulse.

*Reviewer-calculated

[a] Rate ratio FMT vs vancomycin: 3.05 (99.9% CI, 1.08 to 290.05). Rate ratio FMT vs vancomycin and bowel lavage: 4.05 (99.9% CI, 1.21 to 290.12).

[b] Authors state difference is not statistically significant without reporting p value.

[c] Absence of abdominal pain using pain score (0 (no pain), 1 (mild pain), 2 (moderate pain), 3 (severe pain)), and < 3 bowel movements of Bristol 5 or lower, per day.

[d] 11 patients in each of the fidaxomicin and vancomycin arms had clinical relapse and a positive CDI test result within 8 weeks of the index treatment. All received rescue FMT, and of these 9/11 patients in the fidaxomicin arm (82%) and 10/11 patients in the vancomycin arm (91%) achieved clinical resolution confirmed by laboratory test.

Table B3 Recurrence of CDI

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
Administration: Upper GI							
van Nood 2013	mITT	Relapse was defined as diarrhoea with a positive stool test for CD toxin	5 weeks (from initiation of therapy)	FMT (NDT)	16	1 (6)	NR
				Vancomycin	13	8 (62)	
				Vancomycin and bowel lavage	13	7 (54)	
Administration: Lower GI							
Cammarota 2015	ITT	CDI recurrence after treatment. Defined as diarrhoea (at least three loose or watery stools per day for 2 or more consecutive days, or at least eight loose stools in 48 h) unexplainable by other causes, with or without positive stool toxin.	10 weeks (from end of therapy)	FMT (colonoscopy); 1 or more infusions	20	2 (10*)	NR
				Vancomycin	19	12 (63)	
Hota 2017	PP	Recurrence of symptomatic, laboratory-confirmed CDI. Symptoms CDI were self-reported and confirmed by study physicians to meet standard epidemiologic definitions of diarrhoea	120 days (from initiation of therapy)	FMT (enema)	16	9 (56.2)	Bayesian 95% CI for risk difference: -2.8%, 47.3%
				VTP	12	5 (41.7)	
Hota 2017	PP	Recurrence of symptomatic, CDI <u>without</u> laboratory confirmation. Symptoms CDI were self-reported and confirmed by study physicians to meet	14 days (from initiation of therapy)	FMT (enema)	16	0 (0)	NR
				VTP	12	0 (0)	
			120 days (from initiation of therapy)	FMT (enema)	16	0 (0)	NR
				VTP	12	0 (0)	

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
		standard epidemiologic definitions of diarrhoea					
Administration: Mixed							
Hvas 2019	ITT	Clinical recurrence and a positive CDI test result*	8 weeks ('after initial treatment')	FMT (colonoscopy or NJT)	24	2 (8*)	NR
				Fidaxomicin	24	11 (46*)	NR
				Vancomycin	16	11 (69)	NR

Abbreviations: CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* Infection; CI, Confidence interval; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; ITT, Intention to treat; mITT, Modified intention to treat; NDT, nasoduodenal tube, NJT, Nasojejunal tube; NR, Not reported; PP, Per protocol; VTP, Vancomycin taper pulse.

*Reviewer-calculated

Table B4 Time to CDI recurrence

Study	Population	Outcome definition and measure	Intervention	Number of patients analysed	Median days (range)	Difference between treatments
Administration: Upper GI						
van Nood 2013	mITT	Time to recurrence	FMT (NDT)	16	NR	NR
			Vancomycin	13	23 (13 to 43)	
			Vancomycin and bowel lavage	13	25 (18 to 70)	
Administration: Lower GI						
Cammarota 2015	ITT	Time to CDI recurrence from end of treatment	FMT (colonoscopy)	20	Median not reported; range 5 to 7 days	NR
			Vancomycin	19	10 (4 to 21)	
Hota 2017	PP	Time to CDI recurrence from administration of intervention	FMT (enema)	16	9 (NR)	NR
			VTP	12	35 (NR) 7 (NR) from end of taper	

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; ITT, Intention to treat; mITT, Modified intention to treat; NDT, nasoduodenal tube; NR, Not reported; PP, Per protocol; VTP, Vancomycin taper pulse.

Table B5 CDI-associated diarrhoea

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
Administration: Lower GI							
Hota 2017	PP	Days of diarrhoea (standardised questionnaire, not further defined)	120 days (from initiation of therapy)	FMT (enema)	16	Mean 0.8 (SD 0.8)	NR
				VTP	12	Mean 1.7 (SD 0.4)	
Administration: Mixed							
Hvas 2019	ITT	Combined (post-hoc outcome): Resolution of CDI-associated diarrhoea (clinical resolution or persistent diarrhoea with a negative CDI test result[a])	1 week ('after initial treatment')	FMT (colonoscopy or NJT)	24	24 (100)	p=0.02 (vs. fidaxomicin); p=0.003 (vs. vancomycin)
				Fidaxomicin	24	19 (79)	-
				Vancomycin	16	11 (69)	-
Hvas 2019	ITT	Combined (post-hoc outcome): Resolution of CDI-associated diarrhoea (clinical resolution or persistent diarrhoea with a negative CDI test result[a])	8 weeks ('after initial treatment')	FMT (colonoscopy or NJT)	24	22 (92)	p=0.003 (vs. fidaxomicin); p=<0.0001 (vs. vancomycin)
				Fidaxomicin	24	13 (54)	-
				Vancomycin	16	5 (31)	-

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; ITT, Intention to treat; NJT; Nasojejunal tube; NR, Not reported; PP, Per protocol; SD, Standard deviation; VTP, Vancomycin taper pulse.

[a] Using polymerase chain reaction test.

Table B6 Treatment failure leading to downstream interventions

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
Administration: Upper GI							
van Nood 2013	mITT	Patients in whom recurrent CDI developed after the first FMT were given a second infusion with FMT from a different donor	10 weeks (from initiation of therapy)	FMT (NDT)	16	3 (19)	NR
		Patients in whom antibiotic therapy failed were offered FMT off protocol.		Vancomycin with or without bowel lavage	26	18 (69)[a]	
Administration: Lower GI							
Hota 2017	PP	CDI recurrence requiring hospitalisation	120 days (from initiation of therapy)	FMT (enema)	16	0	NR
				VTP	12	0	
Cammarota 2015	PP	CDI recurrence requiring 1 to 3 courses of antibiotics	NR[b]	FMT (colonoscopy)	NR	2 (NR)[c]	NR
				Vancomycin	9[d]	7 (78%*)	

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; mITT, Modified intention to treat; NDT, nasoduodenal tube, NR, Not reported; PP, Per protocol;VTP, Vancomycin taper pulse.

*Reviewer-calculated

[a] 15/18 (83%) experienced clinical cure at an unreported time. 11/15 after 1 FMT infusion, and 4/15 after 2 infusions.

[b] reported as October 2014, occurring at between 5 and 14 months follow up from the beginning and end of patient recruitment to the trial.

[c] study reports 2 FMT patients (both with pseudomembranous colitis) receiving antibiotics during trial follow-up, but does not report whether FMT patients were contacted in October 2014 to determine further use of antibtiotics.

[d] 12 patients with a CDI recurrence during the trial, of whom 3 were lost to follow up, and 9 were contacted by telephone.

Table B7 Mortality

Study	Population	Outcome definition and measure	Timepoint of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)
Administration: Upper GI						
van Nood 2013	mITT	Mortality all cause	10 weeks (from initiation of therapy)	FMT (NDT)	16	0 (0)
				Vancomycin	13	1 (8)
				Vancomycin and bowel lavage	13	0 (0)
Administration: Lower GI						
Cammarota 2015	ITT	Mortality all-cause	10 weeks (from end of therapy)	FMT (colonoscopy)	20	2 (10)
				Vancomycin	19	2 (11)
Cammarota 2015	PP	Mortality all cause	NR[a]	FMT (colonoscopy)	20	3 (15*)
				Vancomycin	16[b]	6 (38*)
Hota 2017	PP	Mortality attributable to CDI	120 days (from initiation of therapy)	FMT (enema)	16	0 (0)
				VTP	12	0 (0)
Hota 2017	PP	Mortality all cause	120 days (from initiation of therapy)	FMT (enema)	16	0 (0)
				VTP	12	0 (0)
Rode 2021	ITT	Mortality possibly related to CDI	120 days (from initiation of therapy)	FMT (enema)	14	0 (0)
				Vancomycin	13	NR[c]
Administration: Mixed						
Hvas 2019	ITT	Mortality	8 weeks ('after initial treatment')	FMT (colonoscopy or NJT)	24	0 (0)
				Fidaxomicin	24	0 (0)
				Vancomycin	16	0 (0)

Abbreviations*:* CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; GI, Gastrointestinal; ITT, Intention to treat; mITT, Modified intention to treat; NDT, nasoduodenal tube; NJT, Nasojejunal tube; NR, Not reported; PP, Per protocol; VTP, Vancomycin taper pulse.

* Reviewer-calculated

[a] reported as October 2014, occurring at between 5 and 14 months follow up from the beginning and end of patient recruitment to the trial.

[b] 3 patients reported as lost to follow-up by October 2014

[c] 4 deaths among all 31 patients randomised to vancomycin, not reported for the multiple (≥2) recurrence subgroup.

Table B8 Risk of Bias Assessments – Efficacy and Safety

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
1. Biases arising from the randomisation process					
1.1 Was the allocation sequence random?	Yes	No information	No information	Yes	Yes
	An online random number generator software	NR	NR	Computer-generated stratified randomisation in blocks of 6 was used	Automated biased coin minimisation in randomisation software with stratification for hospitalisation status (clinical or outpatient) and the number of previous recurrences (1, 2, >2). The coin bias factor was set at 3, the bias coin lower threshold at 2.
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	No information	No information	Yes	Yes
	Randomisation was done by an external person. 'The sequence was concealed until the interventions were assigned'.	NR	NR	Allocation concealment in sealed opaque envelopes with sequential numbers for each stratum	Automated biased coin minimisation in randomisation software with stratification for hospitalisation status (clinical or outpatient) and the number of previous recurrences (1, 2, >2). The coin bias factor was set at 3, the bias coin lower threshold at 2.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No	Probably yes	No	No	No
	Baseline characteristics similar between groups	The authors state baseline characteristics were similar, although did not report statistical comparisons of	No statistical differences reported for baseline characteristics	There were no significant or clinically important differences between the groups	The authors reported no statistical differences. We noted some differences in these baseline characteristics (that did not reach statistically probable differences when

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
		baseline characteristics. We noted some differences in two characteristics: 'days from last recurrence to consent' and 'immunosuppression' (that did not reach statistically probable differences).			checked): median Charslon Comorbidity Index, number with virulent ribotype 027 strain, hospital-acquired infection.
Risk of bias judgement	Low	Some concerns	Some concerns	Low	Low
2. Bias due to deviations from the intended intervention (Effect of assignment to intervention)					
2.1 Were participants aware of their assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes
	Neither physicians nor patients were blinded to the randomisation groups	Investigators and participants were not blinded to interventions as it would be impractical due to FMT odour, and sham enemas were not endorsed by the research ethics board due to unnecessary potential risk.	Study interventions were unblinded	After allocation, the trial was open-label	Open-label
2.2 Were carers and trial people delivering the interventions aware of the participants assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes
	Neither physicians nor patients were blinded to the randomisation groups	Investigators and participants were not blinded to interventions as it would be impractical due to FMT odour, and sham enemas were not endorsed by the research	Study interventions were unblinded	After allocation, the trial was open-label	Open-label

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
		ethics board due to unnecessary potential risk.			
2.3 If Yes/probably yes/no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?	No	Yes	No	No	No
	NA	2 patients withdrew from vancomycin arm, 1 to request FMT elsewhere	NA	NA	NA
2.4 If Yes/probably yes to 2.3, were these deviations likely to have affected the outcomes?	NA	Probably yes	NA	NA	NA
	NA	All exclusions were in the vancomycin arm	NA	NA	NA
2.5 If yes/possibly yes/no information to 2.4 Were these deviations from intended intervention balanced between groups?	NA	No	NA	NA	NA
	NA	All exclusions were in the vancomycin arm	NA	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Probably no	Yes	Yes	Probably no
	An ITT analysis was done	PP analysis done	Bivariate comparisons were carried out using the $\chi 2$ test and Kruskal-Wallis analysis of variance	The authors described continuous data with the median (IQR and range), compared the 3 groups using Kruskal-Wallis test, and continued with pairwise Wilcoxon rank sum test if a significant difference was detected. Categorical data	It is unclear why 1 protocol violation was included (vancomycin arm death, imputed as failed), but FMT patient violation (renal-graft failure, received vancomycin then recurred, then was administered FMT) was excluded.

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
				were reported as numbers and proportions and compared with OR (95% CIs), chi-squared test or Fisher's exact test. Furthermore, the primary endpoint was compared in a logistic regression model adjusting for the stratification as appropriate for studies with stratified randomisation.	
2.7 If No/probably no/no information to 2.6. Was there potential for a substantial impact (on the result) of the failure to analyse the participants in the group to which they had been randomised?	NA	Probably yes	NA	NA	Probably no
	NA	Due to small numbers, the exclusion accounted for 14% of the vancomycin arm (7% of the total number randomised)	NA	NA	
Risk of bias judgement	Low	High	Low	Low	Some concerns
2. Risk of bias due to deviations from the intended interventions (Effect of adhering to intervention)					
2.1 Were participants aware of their assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes
	Neither physicians nor patients were blinded to the randomisation groups	Investigators and participants were not blinded to interventions as it would be impractical due to FMT odour, and sham enemas	Study interventions were unblinded	After allocation, the trial was open-label	Open-label

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
		were not endorsed by the research ethics board due to unnecessary potential risk.			
2.2 Were carers and people delivering the interventions aware of the participants assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes
	Neither physicians nor patients were blinded to the randomisation groups	Investigators and participants were not blinded to interventions as it would be impractical due to FMT odour, and sham enemas were not endorsed by the research ethics board due to unnecessary potential risk.	Study interventions were unblinded	After allocation, the trial was open-label	Open-label
2.3 [If applicable] If yes/probably yes/ no information to 2.1 or 2.2 Were important non-protocol interventions balanced across intervention groups?	NA	NA	NA	No	NA
	NA	NA	NA	2 patients in the FMT arm did not receive repeat infusions as indicated	NA
2.4 [If applicable] Were there failures in implementing the intervention that could have affected the outcome?	NA	NA	NA	Yes	NA
	NA	NA	NA	2 patients in the FMT arm did not receive repeat infusions as indicated	NA
2.5 [If applicable] Was there non-adherence to the assigned intervention	NA	Yes	NA	No	Probably no
	NA	2 of 14 patients in the vancomycin	NA	No non-adherence	2/43 (5%) did not receive allocated intervention

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
regimen that could have affected participant's outcomes?		taper group (14%) withdrew - one to seek FMT elsewhere and another due to repeated protocol non-compliance			
2.6. If no/probably no/no information to 2.3, or yes probably yes/no information to 2.4 or 2.5 Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	No	NA	Yes	NA
	NA	PP analysis used	NA	ITT, mITT and PP analyses	All analyses were done on a mITT basis with the exclusion of one patient who required high-dose prednisolone treatment after randomisation but before the study treatment was started.
Risk of bias judgement	Low	High	Low	Some concerns	Low
3. Bias due to missing outcome data					
3.1 Were outcome data available for all, or nearly all participants randomised?	No	Probably no	Yes	Yes	Yes
	All participants contributed data to the primary outcome and most secondary outcomes. Data missing for 2 outcomes: mortality and CDI recurrence after index treatment requiring antibiotics.	Data available for 28/30 (93%), 2 exclusions from one arm (vancomycin 86%)	Data available for all participants	mITT included 96/98 participants (98%)	All analyses were done on a mITT basis with the exclusion of one patient who required high-dose prednisolone treatment after randomization but before the study treatment was started.
3.2 If N/Probably no/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	No	Probably yes	NA	NA	NA
	For outcomes: mortality and CDI recurrence after index treatment requiring antibiotics	Authors report futility analysis using ITT and per protocol data	NA	NA	NA
	Yes	Probably no	NA	NA	NA

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
3.3 If N/Probably no/NI to 3.2: Could missingness in the outcome depend on its true value?	Possible	Reasons given for missing data	NA	NA	NA
3.4 It Y/Probably yes/NI to 3.3: Is it likely that missingmess in the outcome depended on its true value?	Probably no	Probably no	NA	NA	NA
	We have interpreted as a reporting issue	Explanation given for exclusions	NA	NA	NA
Risk of bias judgement	Some concerns	Low	Low	Low	Low
4. Bias in the measurement of the outcome					
4.1 Was the method of measuring the outcome inappropriate?	No	No	No	No	No
	The authors defined the primary outcome cure of CDI as the disappearance of diarrhoea, or persistent diarrhoea explicable by other causes, with two negative stool tests for CD toxin	The primary outcome was recurrence of symptomatic, laboratory-confirmed CDI within 120 days of the intervention, using criteria outlined in the inclusion criteria.	The primary end point was combined clinical resolution and a negative CD test result without the need for rescue FMT preceded by vancomycin or colectomy 8 weeks after the initial treatment	The primary endpoint was clinical cure, defined as absence of CDI (i.e. absence of diarrhoea or diarrhoea with a negative CD test)	Cure was defined as an absence of diarrhoea or persistent diarrhoea that could be explained by other causes with three consecutive negative stool tests for CD toxin. Relapse was defined as diarrhoea with a positive stool test for CD toxin. An adjudication committee whose members were unaware of study-group assignments decided which patients were cured.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Yes	No	No	Yes	No
	Outcome timepoints differ between arms as they are measured from the end of treatment.	Subjective symptoms but objective laboratory confirmation	Subjective symptoms but objective laboratory confirmation	Outcome timepoints differ between arms as they are measured from the end of treatments	Subjective symptoms but objective laboratory confirmation
4.3 If N/Probably no to 4.1 and 4.2: Were outcome assessors aware of the	Yes	Yes	Yes	Yes	Yes
	Because of the intrinsic difference between the two	Investigators and participants were not blinded to	Study interventions were unblinded	After allocation, the trial was open-label	Open-label

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
intervention received by the study participant?	treatments, neither physicians nor patients were blinded to the randomisation groups	interventions as it would be impractical due to FMT odour, and sham enemas were not endorsed by the research ethics board due to unnecessary potential risk.			
4.4 If Y/Probably yes/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes	Probably yes	Probably yes	Yes	No
	For subjective outcomes without laboratory confirmation (CDI recurrence)	Primary outcome: Subjective symptoms reported by patients, with objective laboratory confirmation at pre-specified intervals. Some secondary outcomes were self-reported symptoms only.	Primary outcome: subjective symptoms reported by patients, confirmed with objective laboratory test if patient reported diarrhoea. One secondary outcome fully subjective.	Absence of diarrhoea was patient-reported, with no test needed to confirm (no testing at regular intervals for all patients)	Subjective symptoms with objective laboratory confirmation, adjudicated by an independent committee
4.5 If Y/Probably yes/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably yes	Probably yes	Probably yes	Probably yes	NA
	For subjective outcomes without laboratory confirmation (CDI recurrence)	For secondary subjective outcomes	Self-reporting of diarrhoea	For subjective outcomes	NA
Risk of bias judgement	High	High	High	High	Low
	For subjective outcomes without laboratory confirmation (CDI recurrence)	For secondary subjective outcomes	For primary outcome (partial objective confirmation only) and some secondary subjective outcomes	Subjective outcome, not blinded	
5. Risk of bias in selection of the reported result					

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Probably no	Yes	Yes	No	Yes
	Protocol (NCT record) published May 28, 2014; recruitment from July 2013 through June 2014	Protocol (NCT record) published October 2010; recruitment Jan 2011 to July 2014	Protocol (NCT record) published April 2016; recruitment 5 April, 2016 to 10 June, 2018	Primary outcome different in NCT record (registered ahead of recruitment); but published outcome is more rigorous. Several secondary outcomes listed in NCT were not reported in paper, including: days diarrhoea, CDI-related hospitalisation, CDI-related outpatient hospital attendance, and further antibiotic use associated with a new recurrence of CDI.	Protocol registered January 2008; recruitment January 2008 to April 2010
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No	No	No	No	No
	Minimal number of outcome measures specified in protocol and reported	Minimal number of outcome measures pre-specified and reported	All pre-specified outcomes reported except those at 26 weeks	Paper reports key outcomes in protocol	Primary endpoint and key secondary endpoint reported; other secondary endpoints (costs, quality of life and inflammatory markers) not reported but trial terminated early.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from	No	No	No	No	No
	Minimal number of outcome measures	Minimal number of outcome measures	All pre-specified outcomes reported	The primary endpoint was analysed on ITT,	All analyses were done on a mITT basis with the exclusion of one patient who required

Cochrane Risk of Bias domain	Study				
	Cammarota 2015	**Hota 2017**	**Hvas 2019**	**Rode 2021**	**van Nood 2013**
multiple eligible analyses of the data?	specified in protocol and reported	pre-specified and reported	except those at 26 weeks	mITT and per-protocol basis; the results were consistent	high-dose prednisolone treatment after randomization but before the study treatment was started.
Risk of bias judgement	Some concerns	Low	Low	Some concerns	Low
Overall Risk of Bias	High risk	High Risk	High risk	High risk	Some concerns
	High risk of bias due to measuring outcomes from the end of treatments, creating differential timepoints between arms, as well as some subjective outcomes measured without objective confirmation. Some concerns also arising from missing outcome data (treatment failure and mortality at 5 to 14 months), and publishing protocol toward the end of patient recruitment.	High risk of bias due to use of a per protocol analysis with all patient exclusions from one trial arm (14% vancomycin patients, 7% overall randomised population); and also due to the measurement of some subjective outcomes without objective confirmation. Some concerns also regarding the randomisation process, with possible differences in baseline characteristics.	High risk of bias due to the measurement of some subjective outcomes without full objective confirmation. Some concerns of selection bias due to not reporting methods of randomisation and allocation concealment.	High risk of bias due to measuring outcomes from the end of treatments, creating differential timepoints between arms, as well as some subjective outcomes measured without full objective confirmation. Some concerns also around selective outcome reporting, with some outcomes listed in trial register not reported in the publication.	Some concerns due to the unclear exclusion of 1 protocol violation patient (FMT arm) when another protocol violation patient (vancomycin arm) was included.

Abbreviations*:* CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* Infection; CI, Confidence interval; FMT, faecal microbiota transplantation; IQR, Interquartile range; ITT, Intention to treat; mITT, Modified intention to treat; NA, not applicable; NCT, National Clinical Trial; NI, No information; NR, Not reported; OR, Odds ratio; PP, per protocol analysis.

Risk of Bias Assessments – Economic evaluations

The appraisal tables for the eight included economic evaluations studies are below.

Table B9 Risk of Bias Assessment Economic Evaluation: Abdali 2020

Abdali (2020)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	The study did not include AEs.
1.6 Are all future costs and outcomes discounted appropriately?	NA	A one year time horizon was used.
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	A longer time period would incorporate potential long-term effects of recurrent CDI.
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	

Abdali (2020)		
2.6 Are all important and relevant costs included?	Partly	Additional cost of AEs were not included. The cost of pre-FMT antibiotics did not seem to be included.
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there any potential conflict of interest?	No	None were stated.
2.12 Overall assessment: Minor limitations		
Other comments: None		

Abbreviations: AE, adverse event; FMT, faecal microbiota transplantation; QALY, quality-adjusted life year.

Table B10 Risk of Bias Assessment Economic Evaluation: Baro 2017

Baro (2017)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	NA	78-day time horizon.
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)		

Baro (2017)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	A longer time period would incorporate potential long-term effects of recurrent CDI.
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Partly	It did not include the cost of pre-FMT antibiotics, or state if they were used.
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Partly	Costs were from the best available sources in France. However, some costs were taken from individual hospitals rather than a national resource.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there any potential conflict of interest?	No	None stated
2.12 Overall assessment: Minor limitations		
Other comments: None		

Abbreviations: AE, adverse event; CDI, *Clostridioides difficile*; FMT, faecal microbiota transplantation; QALY, quality-adjusted life year.

Table B11 Risk of Bias Assessment Economic Evaluation: Konijeti 2013

Konijeti (2013)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US based study.
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	

Konijeti (2013)		
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	The study did not include AEs.
1.6 Are all future costs and outcomes discounted appropriately?	NA	A one-year time horizon was used.
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	QALYs were reported. Used willingness-to-pay threshold of $50,000 per QALY.
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	A longer time period would incorporate potential long-term effects of recurrent CDI.
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Partly	Additional cost of AEs were not included. Cost of anti-microbial resistance were not included.
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Results of the PSA were not reported in detail.
2.11 Is there any potential conflict of interest?	Yes	One author has served on scientific advisory boards for Prometheus, Inc, Janssen Pharmaceuticals, and Cubist Pharmaceuticals. All other authors report no potential conflicts
2.12 Overall assessment: Minor limitations		
Other comments: None		

Abbreviations: AE, Adverse event; CDI, *Clostridioides difficile*; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; US, United States.

Table B12 Risk of Bias Assessment Economic Evaluation: Lapointe-Shaw 2016

Lapointe-Shaw (2016)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	The study did not evaluate AEs
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	QALYs were reported. Used willingness-to-pay threshold of $50000 per QALY.
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Partly	Additional cost of AEs were not included. Cost of anti-microbial resistance were not included.
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	

Lapointe-Shaw (2016)		
2.11 Is there any potential conflict of interest?	No	None were stated.
2.12 Overall assessment: Minor limitations		
Other comments: None		

Abbreviations: AE: adverse event; QALY, quality-adjusted life year.

Table B13 Risk of Bias Assessment Economic Evaluation: Luo 2020

Luo (2020)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US based study.
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	The study did not include AEs.
1.6 Are all future costs and outcomes discounted appropriately?	NA	Six-month time horizon.
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	A longer time period would incorporate potential long-term effects of recurrent CDI.
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	

Luo (2020)		
2.6 Are all important and relevant costs included?	Partly	The study did not include the cost of antimicrobial resistance or AEs.
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there any potential conflict of interest?	Yes	One author has received lecture fees and honorarium from Merck. All other authors report no potential conflicts
2.12 Overall assessment: Minor limitations		
Other comments: None		

Abbreviations: AE: adverse event; CDI, *Clostridioides difficile*; QALY, quality-adjusted life year; US, United States.

Table B14 Risk of Bias Assessment Economic Evaluation: Merlo 2016

Merlo (2016)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	No	Not clearly stated.
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		

Merlo (2016)		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	The time period was not clearly stated, but was assumed to be lifetime.
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Partly	The study did not include the cost of antimicrobial resistance.
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	Deterministic sensitivity analysis was not conducted. The results of the PSA were not reported.
2.11 Is there any potential conflict of interest?	No	None reported
2.12 Overall assessment: Minor limitations		
Other comments: None		

Abbreviations*:* PSA, Probabilistic Sensitivity Analysis; QALY, quality-adjusted life year.

Table B15 Risk of Bias Assessment Economic Evaluation: Varier 2015

Varier (2015)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US based study.
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	AEs and hospitalisations were not included.
1.6 Are all future costs and outcomes discounted appropriately?	NA	90-day time horizon.

Varier (2015)		
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Directly applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	A longer time period would have incorporated potential long-term effects of recurrent CDI.
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	No	The model used previously defined utilities of similar disease states to CDI as estimates of colitis and recurrent CDI-associated QALYs. It was reported that CDI specific utility values had not been published yet.
2.5 Are the estimates of relative intervention effects from the best available source?	No	AEs and probability of death from FMT was taken from diagnostic colonoscopy procedure and not the FMT via colonoscopy procedure.
2.6 Are all important and relevant costs included?	Partly	The study did not include the cost of antimicrobial resistance, AEs or hospitalisation.
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Partly	Costs of FMT AEs were assumed to be same as the cost of colonoscopy AEs.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there any potential conflict of interest?	No	None stated
2.12 Overall assessment: Very serious limitations		
Other comments: None		

Abbreviations: AE: adverse event; CDI, *Clostridioides difficile*; FMT, faecal microbiota transplantation; QALY, quality-adjusted life year; US, United States.

Table B16 Risk of Bias Assessment Economic Evaluation: You 2020

You (2020)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case)	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Specifically interested in people with irritable bowel syndrome.
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	The study based in Hong Kong, which has a different health system to the UK.
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	No	IBD flare was the only AEs modelled.
1.6 Are all future costs and outcomes discounted appropriately?	NA	12 week time horizon.
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Yes	
1.9 Overall judgement: Partially applicable		
Section 2: Study limitations (the level of methodological quality)		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	A longer time period would incorporate potential long-term effects of recurrent CDI.
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	The morality rate in all study arms is taken from that of 3,000 IBD patients.
2.6 Are all important and relevant costs included?	Partly	The study did not include the cost of antimicrobial resistance or some AEs.
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	No	Costs came from 'local' sources in Hong Kong, rather than a national database. Costs for drugs that are not available in Hong Kong were taken from Drugs.com.

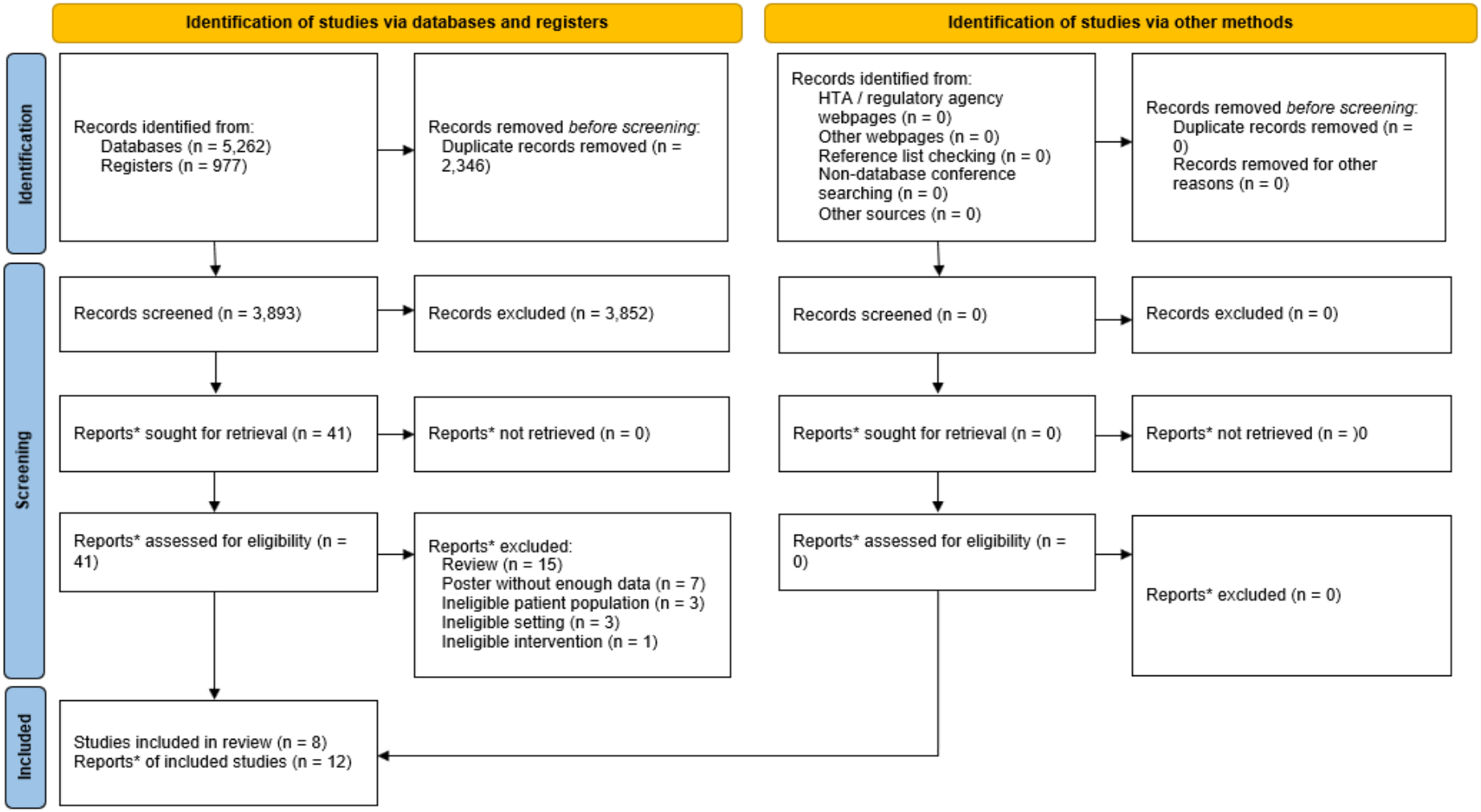
You (2020)		
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there any potential conflict of interest?	Yes	No conflict of interest was stated.
2.12 Overall assessment: Potentially serious limitations		
Other comments: None		

Abbreviations: AE: adverse event; CDI, *Clostridioides difficile*; IBD, Irritable bowel disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UK, United Kingdom.

Appendix C Economic evidence search strategy, search results and PRISMA flow diagram

A single set of searches was carried out to identify both clinical and economic evidence. Search strategies were not restricted by study design or outcome, and the selection of information resources included specialist economics databases. Full details of the EAC's search methods are provided in Appendix A.

Figure C1 Economics Evaluation PRISMA flow diagram



*"Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report or any other document providing relevant information": https://www.bmj.com/content/372/bmj.n71.

Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix D Systematic review eligibility criteria: clinical effects and safety, and economic evaluations

Systematic review of clinical effects and safety

Population

Studies of adult patients (≥18 years old) with refractory CDI or a recurrent episode of symptomatic CDI (who have had two or more CDI episodes) were eligible for inclusion in this review. We defined recurrent CDI patients as those who were recorded as having at least 2 episodes of CDI at baseline measurement of a trial. Due to the lack of consensus on the definition of refractory CDI, all author definitions were eligible.

For recurrent CDI, studies of patients with the first episode CDI were not eligible. Studies including patients without laboratory-based confirmation of CD bacteria or its toxins were not eligible, unless data for laboratory-confirmed cases could be disaggregated.

Studies including children or non-recurrent/non-refractory CDI, were only eligible if data for adults with refractory CDI or an eligible recurrent episode of CDI could be disaggregated.

Interventions

Studies assessing FMT, with or without pre-treatment with bowel lavage and/or a short course of antibiotics, were included. Eligible routes of delivery were:

- Lower GI route (rectal enema, colonoscopy, or flexible sigmoidoscopy).
- Upper GI route (endoscopy, NGT, NDT or NJT).
- Oral capsules containing frozen FMT or freeze-dried (lyophilised) faecal material.

Studies offering multiple FMT treatments, or antibiotics after failure of FMT treatment, were eligible.

Comparators

Studies comparing FMT to any of the following antibiotics recommended by NICE (National Institute for Health and Care Excellence 2021a) were eligible for inclusion in the review. YHEC note variation in dose and regimen of comparator antibiotics, so all author-defined definitions were eligible:

- Fidaxomicin (any author-defined dosing regimen).
- Vancomycin with or without Metronidazole (any author-defined dosing regimen).
- VTP (any author-defined dosing and regimen for taper and pulse).

Concomitant treatment with bowel lavage was also eligible. Trials comparing FMT to placebo were not eligible.

Outcomes

Studies assessing one or more of the following outcomes were eligible for inclusion:

- Resolution of CDI:
  - Symptomatic resolution (diarrhoea and/or other symptoms).
  - Diagnostic resolution (negative stool test for C.diff toxin during follow up period).
- Recurrence of CDI.
- Treatment failure leading to downstream interventions (e.g., retreatment with antimicrobials, repeat FMT procedures, colectomy).
- Procedural adverse events (harmful impact of undergoing intervention procedures).
- Overall treatment related adverse events (harmful effects of treatment interventions).
- Mortality.

The following patient reported, and resource use outcomes were also eligible for identification by the clinical effects and safety review to help inform the cost consequence analysis.

- Patient reported outcomes:
  - Patient acceptability of treatment modalities.
  - Health related quality of (EQ-5D).
- Resource use outcomes:
  - Length of hospital stay.
  - Follow up GP, hospital visits or telephone consultations.
  - Follow up tests such as stool testing got C.diff toxin.
  - Pre, intra and post treatment usage of medicines or procedures including antimicrobials, anti-motility drugs, proton pump inhibitors, bowel lavage.
  - Resources associated with the collection, preparation, and administration of FMT.
  - NHS resource usage such as isolation rooms, barrier nursing, ward closures, theatre or procedure room times, follow up appointments.

Study design

Randomised controlled trials (RCTs) were the only study design considered in this review. If cross-over RCTs were identified, their data was included up to the point of cross-over.

We checked the included study list of any relevant systematic reviews published in the last 5 years that were identified in the search results to ensure that all relevant

articles were identified and assessed. Data was not extracted from systematic reviews.

Non-randomised trials, observations studies, case series and case reports were not eligible for inclusion. Similarly, reviews that were not systematic (defined according to *a priori* YHEC criteria) were also excluded.

Limits

This review prioritised the synthesis of evidence for use of FMT in NHS settings, therefore studies published in non-English languages were excluded.
Studies published only as conference abstracts were only eligible for inclusion if adequate information was provided for appropriate study assessment.
Editorials and news articles were not included.

Systematic review of economic evaluations

Population

Studies of adult patients (≥18 years old) with refractory CDI or a recurrent episode of symptomatic CDI (who have had 2 or more CDI episodes) were eligible for inclusion in this review. We defined recurrent CDI patients as those who were recorded as having at least 2 episodes of CDI at baseline measurement of a trial.
Due to the lack of consensus on the definition of refractory CDI, all author definitions were eligible.

For recurrent CDI, studies of patients with the first episode CDI were not eligible.
Studies including patients without laboratory-based confirmation of CD bacteria or its toxins were not eligible, unless data for laboratory-confirmed cases could be disaggregated.

Studies including children or non-recurrent/non-refractory CDI, were only eligible if data for adults with refractory CDI or an eligible recurrent episode of CDI could be disaggregated.

Interventions

Studies assessing FMT, with or without pre-treatment with bowel lavage and/or a short course of antibiotics, were included. Eligible routes of delivery were:

- Lower GI route (rectal enema, colonoscopy, or flexible sigmoidoscopy).
- Upper GI route (endoscopy, NGT, NDT or NJT).
- Oral capsules containing frozen FMT or freeze-dried (lyophilised) faecal material.

Studies offering multiple FMT treatments, or antibiotics after failure of FMT treatment, were eligible.

Comparators

Studies comparing FMT to any of the following antibiotics recommended by NICE (National Institute for Health and Care Excellence 2021a) were eligible for inclusion in the review. YHEC note variation in dose and regimen of comparator antibiotics, so all author-defined definitions were eligible:

- Fidaxomicin (any author-defined dosing regimen).
- Vancomycin with or without Metronidazole (any author-defined dosing regimen).
- VTP (any author-defined dosing and regimen for taper and pulse).

Concomitant treatment with bowel lavage was also eligible. Trials comparing FMT to placebo were not eligible.

Outcomes

Studies assessing one or more of the following outcomes were eligible for inclusion:

- Effectiveness outcomes (e.g. quality-adjusted life years (QALYs)).
- Total costs (currency) (intervention, comparator).
- Incremental outcomes (e.g. incremental cost-effectiveness ratios (ICERs) (per QALY gained)).
- Budget impact analyses.

Study design

The following study designs were eligible:

- Health Technology Assessment (HTA) reports investigating the cost-effectiveness of treatments were eligible.
- Economic evaluations, including:
  - Cost-effectiveness analyses (including cost-utility analyses).
  - Cost-benefit analyses.
  - Cost-consequence analyses.
  - Cost-minimization analyses.
  - Budget impact analyses.

Limits

This review prioritised the synthesis of evidence for use of FMT in NHS settings, therefore studies published in non-English languages were excluded.
Studies published only as conference abstracts were only eligible for inclusion if adequate information was provided for appropriate study assessment.
Editorials and news articles were not included.

Appendix E Systematic review data extraction elements: clinical effects and safety, and economic evaluations

Systematic review of clinical effects and safety

We extracted the following elements from the eligible trials where reported:

- Trial details (bibliographic details).
- Trial characteristics:
  - Trial design.
  - Trial objective.
  - Number of participating centres and countries.
  - Eligibility criteria.
  - Number of patients randomised/analysed.
  - Number of patients lost to follow-up or withdrawn.
  - Treatment duration.
  - Follow up duration.
  - Data collection time points.
- Patient baseline characteristics:
  - Age.
  - Gender.
  - Diagnostic confirmation of current CDI.
  - Duration of symptoms (current CDI episode).
  - Stool frequency.
  - Number of prior recurrent CDI episodes.
  - Time since first CDI episode.
  - Days since last recurrence.
  - Refractory CDI.
  - CDI Ribotype 027.
  - Hospital-acquired CDI.
  - Comorbidities (Charlson comorbidity index score; inflammatory bowel disease; cancer; kidney disease).
  - Immunosuppression.
  - Creatinine count.
  - Hospitalisation (at inclusion).
  - Feeding tube present.
  - Prior hospitalisations for CDI.
  - Prior intensive care unit (ICU) admission.
  - Prior antibiotic use.
  - Proton pump inhibitor use.
- Details of intervention:
  - First FMT or repeat FMT.
  - Number of FMT doses.
  - Use of antibiotic pre-treatment (antibiotic, dose, regimen, duration).

- Use of pre-treatment bowel preparation (e.g., lavage).
- Faecal processing (Fresh vs. Frozen).
- Faeces per FMT (grams).
- Time from faecal donor collection to infusion.
- FMT delivery route of administration (Lower GI [enema, colonoscopy], Upper GI [endoscopy, NG tube, ND tube, NJ tube], oral capsules [frozen or freeze-dried]).
- Donor type (related, anonymous, mixed).
- Donor characteristics considered (age, gender, BMI, exclusions).
- Sample prep details:
  - Amount (mL or g stool).
  - Dilution liquid (type, mL).
  - Capsules (number).
  - Aerobic/anaerobic processing.
- Procedural technique details:
  - Infusion rate.
  - Infusion target (if colonoscopy or endoscopy, e.g., cecum, ileum, etc.).

- Details of statistical analyses.
- For each of the outcomes specified we will extract the following:
  - Outcome definition.
  - The unit of measurement.
  - The number of patients included in the analysis.
  - The size of the effect:
    - For dichotomous outcomes; absolute and relative risks (or odds ratios) and risk (or rate) differences.
    - For continuous outcomes; the mean change and measure of variance from baseline (or at both baseline and final visit), or mean difference between treatments.
    - For time-to-event analysis; the number of events in each arm, median time to event and a hazard ratio and p-value.
    - Where possible, absolute and relative data will be extracted.
  - A measure of precision for each estimate of effect (95% confidence intervals, standard error, or standard deviation).

For each outcome, we collected data at all-time points reported.

Systematic review of economic evaluations

We extracted the following elements from the eligible economic evaluations where reported:

- Publication details (bibliographic details).
- Study description:

    - Study design.
    - Country.
    - Population description.
    - Population size.
    - Intervention description.
    - Comparator(s) description.
- Methods of analysis:
    - Perspective.
    - Time horizon.
    - Discounting.
    - Data sources.
- Costs outcomes:
    - Intervention/comparator(s) cost.
    - Currency and cost year.
- Effectiveness outcomes:
    - Effectiveness outcomes reported (e.g. QALYs).
- Results/incremental outcomes:
    - Results e.g. ICER (per QALY gained).
    - Uncertainty.
- Limitations:
    - Author identified.
    - Reviewer identified.

Patient reported and resource use outcome data was passed on to the team doing the cost consequence assessment.

Appendix F Systematic review excluded and unobtainable studies: clinical effects and safety, and economic evaluations

Table F1 Systematic Review of clinical Effects and Safety Excluded Reports list (n=132)

Report	Exclusion reason
Abdali ZI, Roberts TE, Barton P, Hawkey PM. Economic evaluation of faecal microbiota transplantation compared to antibiotics for the treatment of recurrent clostridioides difficile infection. EClinicalMedicine. 2020;24:100420.	Ineligible SR
Abreu Y Abreu AT, Velarde-Ruiz Velasco JA, Zavala-Solares MR, Remes-Troche JM, Carmona-Sanchez RI, Aldana-Ledesma JM, et al. Consensus on the prevention, diagnosis, and treatment of clostridium difficile infection. Rev Gastroenterol Mex. 2019;84(2):204-19.	Non-English FT
Abu-Sbeih H, Ali FS, Hicklen R, Wang YH. Fecal microbiota transplantation for clostridium difficile infection in immunocompromised patients - safe or risky? Am J Gastroenterol. 2018;113:S115-S17.	SR to check
Abu-Sbeih H, Ali FS, Hicklen R, Wang YH. Taming the beast: the safety and efficacy of fecal microbiota transplantation in severe and complicated clostridium difficile Infection. Am J Gastroenterol. 2018;113:S113-S15.	SR to check
Adelman MW, Woodworth MH, Shaffer VO, Martin GS, Kraft CS. Critical care management of the patient with clostridioides difficile. Crit Care Med. 2021;49(1):127-39.	Ineligible SR
Al-Ali D, Ahmed A, Shafiq A, McVeigh C, Chaari A, Zakaria D, et al. Fecal microbiota transplants: a review of emerging clinical data on applications, efficacy, and risks (2015-2020). Qatar med. 2021;2021(1):5.	Ineligible SR
Alhifany AA, Almutairi AR, Almangour TA, Shahbar AN, Abraham I, Alessa M, et al. Comparing the efficacy and safety of faecal microbiota transplantation with bezlotoxumab in reducing the risk of recurrent clostridium difficile infections: a systematic review and bayesian network meta-analysis of randomised controlled trials. BMJ Open. 2019;9(11):e031145.	SR to check
Ali FS, Abu-Sbeih H, Hicklen R, Wang YH. Fearing the unknown - the fate of inflammatory bowel disease after fecal microbiota transplantation for clostridium difficile Infection. Am J Gastroenterol. 2018;113:S409-S11.	SR to check
Ali FS, Soin S, Abu-Sbeih H, Sundararajan N. A meta-analysis of the safety and efficay of fecal microbiota transplantation for the treatment of clostridium difficile infection in solid organ transplant recepients. Gastroenterology. 2019;156(6 Supplement 1):S901.	SR to check
Arbel LT, Hsu E, McNally K. Cost-effectiveness of fecal microbiota transplantation in the treatment of recurrent clostridium difficile infection: a literature review. Cureus. 2017;9(8):e1599.	SR to check
Bafeta A, Yavchitz A, Riveros C, Batista R, Ravaud P. Methods and reporting studies assessing fecal microbiota transplantation: a systematic review. Ann Intern Med. 2017;167(1):34-39.	SR to check
Baro E, Galperine T, Denies F, Lannoy D, Lenne X, Odou P, et al. Cost-effectiveness analysis of five competing strategies for the management of multiple recurrent community-onset clostridium difficile infection in France. PLoS ONE. 2017;12(1):e0170258.	SR to check
Baunwall SMD, Dahlerup JF, Engberg JH, Erikstrup C, Helms M, Juel MA, et al. Danish national guideline for the treatment of clostridioides difficile infection and use of faecal microbiota transplantation (FMT). Scand J Gastroenterol. 2021;56(9):1056-77.	SR to check
Baunwall SMD, Lee MM, Eriksen MK, Mullish BH, Marchesi JR, Dahlerup JF, et al. Faecal microbiota transplantation for recurrent clostridioides difficile infection: an updated systematic review and meta-analysis. EClinicalMedicine. 2020;29-30:100642.	SR to check

Report	Exclusion reason
Baxter M, Colville A. Adverse events in faecal microbiota transplant: a review of the literature. J Hosp Infect. 2016;92(2):117-27.	SR to check
Bouza E, Aguado JM, Alcala L, Almirante B, Alonso-Fernandez P, Borges M, et al. Recommendations for the diagnosis and treatment of clostridioides difficile infection: an official clinical practice guideline of the Spanish Society of Chemotherapy (SEQ), Spanish Society of Internal Medicine (SEMI) and the working group of Postoperative Infection of the Spanish Society of Anesthesia and Reanimation (SEDAR). Rev Esp Quimioter. 2020;33(2):151-75.	Ineligible SR
Burton HE, Mitchell SA, Watt M. The cost effectiveness of treatments for clostridium difficile infection: a systematic review. Value Health. 2016;19(3):A218.	SR to check
Butler M, Olson A, Drekonja D, Shaukat A, Schwehr N, Shippee N, et al. Early diagnosis, prevention, and treatment of clostridium difficile: update. United States: Agency for Healthcare Research and Quality; 2016. Available from: https://www.effectivehealthcare.ahrq.gov/ehc/products/604/2208/c-difficile-update-report-160329.pdf.	SR to check
Cammarota G, Gallo A, Ianiro G, Montalto M. Emerging drugs for the treatment of clostridium difficile. Expert Opin Emerg Drugs. 2019;24(1):17-28.	SR to check
Cammarota G, Ianiro G, Kelly CR, Mullish BH, Allegretti JR, Kassam Z, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut. 2019;68(12):2111-21.	Ineligible SR
Cammarota G, Ianiro G, Tilg H, Rajilic-Stojanovic M, Kump P, Satokari R, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017;66(4):569-80.	Ineligible SR
Chaar A, Feuerstadt P. Evolution of clinical guidelines for antimicrobial management of clostridioides difficile infection. Ther Adv Gastroenterol. 2021;14:1-16.	Ineligible SR
Chapman BC, Moore HB, Overbey DM, Morton AP, Harnke B, Gerich ME, et al. Fecal microbiota transplant in patients with clostridium difficile infection: a systematic review. J Trauma Acute Care Surg. 2016;81(4):756-64.	SR to check
Chilton CH, Pickering DS, Freeman J. Microbiologic factors affecting clostridium difficile recurrence. Clin Microbiol Infect. 2018;24(5):476-82.	Ineligible SR
Chinese University of Hong Kong. FMT for moderate to severe CDI: a randomised study with concurrent stool microbiota assessment. Identifier: NCT02570477. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://ClinicalTrials.gov/show/NCT02570477.	Eligible trial, no results
Cho JM, Pardi DS, Khanna S. Update on treatment of clostridioides difficile infection. Mayo Clin Proc. 2020;95(4):758-69.	Ineligible SR
Cold F, Baunwall SMD, Dahlerup JF, Petersen AM, Hvas CL, Hansen LH. Systematic review with meta-analysis: encapsulated faecal microbiota transplantation - evidence for clinical efficacy. Ther Adv Gastroenterol. 2021;14:1-19.	SR to check
Currier A, Michailidis L, Flomenhoft D. A comprehensive meta-analysis of prospective, randomized, controlled studies investigating the safety and adverse event rates related to FMT. Am J Gastroenterol. 2020;115:S104.	Ineligible SR
D'Aoust J, Battat R, Bessissow T. Management of inflammatory bowel disease with clostridium difficile infection. World J Gastroenterol. 2017;23(27):4986-5003.	SR to check
Dembrovszky F, Gede N, Szakacs Z, Hegyi P, Kiss S, Farkas N, et al. Fecal microbiota transplantation may be the best option in treating multiple clostridioides difficile Infection: a network meta-analysis. Infect. 2021;10(1):201-11.	SR to check
Du C, Luo Y, Walsh S, Grinspan A. Oral fecal microbiota transplant capsules are safe and effective for recurrent clostridioides difficile infection: a systematic review and meta-analysis. J Clin Gastroenterol. 2021;55(4):300-08.	SR to check
Durham SH, Le P, Cassano AT. Navigating changes in clostridioides difficile prevention and treatment. J Manag Care Spec Pharm. 2020;26(12):S3-23.	SR to check

Report	Exclusion reason
Feuerstadt P, Aroniadis OC, Svedlund FL, Garcia M, Stong L, Boules M, et al. Heterogeneity of randomized controlled trials of fecal microbiota transplantation in recurrent clostridioides difficile infection. Dig Dis Sci. 2021;18:18.	SR to check
Filip M, Tzaneva V, Dumitrascu DL. Fecal transplantation: digestive and extradigestive clinical applications. Clujul med. 2018;91(3):259-65.	Ineligible SR
Furuya-Kanamori L, Doi SAR, Paterson DL, Helms SK, Yakob L, McKenzie SJ, et al. Upper versus lower gastrointestinal delivery for transplantation of fecal microbiota in recurrent or refractory clostridium difficile infection: a collaborative analysis of individual patient data from 14 studies. J Clin Gastroenterol. 2017;51(2):145-50.	SR to check
Gallo A, Passaro G, Gasbarrini A, Landolfi R, Montalto M. Modulation of microbiota as treatment for intestinal inflammatory disorders: an uptodate. World J Gastroenterol. 2016;22(32):7186-202.	Ineligible SR
Gilca-Blanariu GE, Stefanescu G, Girleanu I, Iqbal T, Segal J, Mullish B, et al. Romanian national guideline on translating fecal microbiota transplantation applications related to clostridioides difficile infections into the local clinical practice. J Gastrointestin Liver Dis. 2021;30(1):147-63.	SR to check
Grace E, Chahine EB. Updates on clostridioides (clostridium) difficile infection with emphasis on long-term care. Sr Care Pharm. 2019;34(1):29-42.	Ineligible SR
Guery B, Galperine T, Barbut F. Clostridioides difficile: diagnosis and treatments. BMJ. 2019;366:l4609.	SR to check
Guilfoyle J, Considine J, Bouchoucha SL. Faecal microbiota transplantation and the patient experience: a systematic review. J Clin Nurs. 2021;30(9-10):1236-52.	SR to check
Gupta A, Ananthakrishnan AN. Economic burden and cost-effectiveness of therapies for clostridiodes difficile infection: a narrative review. Ther Adv Gastroenterol. 2021;14:1-13.	Ineligible SR
Gupta A, Cifu AS, Khanna S. Diagnosis and treatment of clostridium difficile infection. JAMA. 2018;320(10):1031-32.	Ineligible SR
Haber SL, Raney CRK, Larson TL, Lau JP. Fecal microbiota transplantation for recurrent clostridioides difficile infection. Am J Health Syst Pharm. 2019;76(13):935-42.	SR to check
Haifer C, Kelly CR, Paramsothy S, Andresen D, Papanicolas LE, McKew GL, et al. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice. Gut. 2020;69(5):801-10.	Ineligible SR
Hammad TA, Khan MA, Srour K, Abdelfattah T, Alastal Y, Lee WM, et al. Efficacy and safety of oral, capsulized, frozen fecal microbiota transplantation for recurrent clostridium difficile infection. A systematic review and meta-analysis. Gastroenterology. 2017;152(5 Suppl 1):S346.	SR to check
Hammeken LH, Baunwall SMD, Hvas CL, Ehlers LH. Health economic evaluations comparing faecal microbiota transplantation with antibiotics for treatment of recurrent clostridioides difficile infection: a systematic review. Health Econ Rev. 2021;11(1):3.	SR to check
Health Quality Ontario. Fecal microbiota therapy for clostridium difficile infection: OHTAC recommendation. Canada: 2016. Available from: http://www.hqontario.ca/Portals/0/Documents/evidence/reports/recommendation-fecal-microbiota-therapy-en-1607.pdf.	SR to check
Heimann SM, Cruz Aguilar MR, Mellinghof S, Vehreschild MJGT. Economic burden and cost-effective management of clostridium difficile infections. Med Maladies Infect. 2018;48(1):23-29.	Ineligible SR
Hong AS, Yu WY, Hong JM, Cross CL, Azab M, Ohning G, et al. Proton pump inhibitor in upper gastrointestinal fecal microbiota transplant: A systematic review and analysis. J Gastroenterol Hepatol. 2020;35(6):932-40.	SR to check
Hui W, Li T, Liu W, Zhou C, Gao F. Fecal microbiota transplantation for treatment of recurrent c. difficile infection: an updated randomized controlled trial meta-analysis. PLoS ONE. 2019;14(1):e0210016.	SR to check

Report	Exclusion reason
Ianiro G, Maida M, Burisch J, Simonelli C, Hold G, Ventimiglia M, et al. Efficacy of different faecal microbiota transplantation protocols for clostridium difficile infection: a systematic review and meta-analysis. United European Gastroenterol J. 2018;6(8):1232-44.	SR to check
Iqbal U, Anwar H, Karim MA. Safety and efficacy of encapsulated fecal microbiota transplantation for recurrent clostridium difficile infection: a systematic review. Eur J Gastroenterol Hepatol. 2018;30(7):730-34.	SR to check
Jiang M, Leung N-H, Ip M, You JHS. Cost-effectiveness analysis of ribotype-guided fecal microbiota transplantation in Chinese patients with severe clostridium difficile infection. PLoS ONE. 2018;13(7):e0201539.	SR to check
Khan MY, Dirweesh A, Khurshid T, Siddiqui WJ. Comparing fecal microbiota transplantation to standard-of-care treatment for recurrent clostridium difficile infection: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2018;30(11):1309-17.	SR to check
Khanna S, Aroniadis OC, Garcia M, Svedlund FL, Ong K, Stong L, et al. Reporting of randomized controlled trial methodological characteristics of fecal microbiota transplantation (FMT) for recurrent clostridioides difficile infection (RCDI). Gastroenterology. 2020;158(6 Suppl 1):S-991.	SR to check
Khurana S, Kahl A, Yu K, DuPont AW. Recent advances in the treatment of clostridioides difficile infection: the ever-changing guidelines. Fac. 2020;9:13.	Ineligible SR
Konig J, Siebenhaar A, Hogenauer C, Arkkila P, Nieuwdorp M, Noren T, et al. Consensus report: faecal microbiota transfer - clinical applications and procedures. Aliment Pharmacol Ther. 2017;45(2):222-39.	SR to check
Kukla M, Adrych K, Dobrowolska A, Mach T, Regula J, Rydzewska G. Guidelines for clostridium difficile infection in adults. Prz Gastroenterol. 2020;15(1):1-21.	SR to check
Kumar V, Fischer M. Expert opinion on fecal microbiota transplantation for the treatment of clostridioides difficile infection and beyond. Expert Opin Biol Ther. 2020;20(1):73-81.	Ineligible SR
Lai CY, Sung J, Cheng F, Tang W, Wong SH, Chan PKS, et al. Systematic review with meta-analysis: review of donor features, procedures and outcomes in 168 clinical studies of faecal microbiota transplantation. Aliment Pharmacol Ther. 2019;49(4):354-63.	SR to check
Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1-s106.	Ineligible SR
Lapointe-Shaw L, Tran KL, Coyte PC, Hancock-Howard RL, Powis J, Poutanen SM, et al. Cost-effectiveness analysis of six strategies to treat recurrent clostridium difficile infection. PLoS ONE. 2016;11(2):e0149521.	Ineligible SR
Laprise J-F, Drolet M, Gingras G, Guertin M-H, Brisson M. Mathematical modeling of the transmission dynamics of clostridium difficile infection and colonization in healthcare settings: a systematic review. PLoS ONE. 2016;11(9):e0163880.	SR to check
Le P, Nghiem VT, Mullen PD, Deshpande A. Cost-effectiveness of competing treatment strategies for clostridium difficile infection: a systematic review. Infect Control Hosp Epidemiol. 2018;39(4):412-24.	SR to check
Leung J, Pham S. A systematic review of fecal microbiota transplantation versus vancomycin for treatment of recurrent clostridioides difficile infection. Gastroenterol Nurs. 2021;44(2):106-15.	SR to check
Li KX, Grobelna A. Lyophilized versus frozen fecal microbiota transplant for recurrent clostridium difficile infection, inflammatory bowel disease, and irritable bowel syndrome: a review of clinical effectiveness, cost-effectiveness, and guidelines [internet]. Canadian Agency for Drugs and Technologies in Health. 2019;8:14.	Ineligible SR
Lin Z, Iqbal Z, Ortiz JF, Khan SA, Jahan N. Fecal microbiota transplantation in recurrent clostridium difficile infection: is it superior to other conventional methods? Cureus. 2020;12(8):e9653.	SR to check

Report	Exclusion reason
Liu X, Li Y, Wu K, Shi Y, Chen M. Fecal microbiota transplantation as therapy for treatment of active ulcerative colitis: a systematic review and meta-analysis. Gastroenterology Research & Practice. 2021;2021(6612970):1-13.	Ineligible SR
Luo Y, Lucas AL, Grinspan A. Cost-effectiveness analysis of multiple strategies for recurrent clostridium difficile infection. Gastroenterology. 2018;154(6 Suppl 1):S192.	Ineligible SR
Luo Y, Lucas AL, Grinspan AM. Fecal transplants by colonoscopy and capsules are cost-effective strategies for treating recurrent clostridioides difficile infection. Dig Dis Sci. 2020;65(4):1125-33.	Ineligible SR
Madoff SE, Urquiaga M, Alonso CD, Kelly CP. Prevention of recurrent clostridioides difficile infection: a systematic review of randomized controlled trials. Anaerobe. 2020;61(102098):1-15.	SR to check
Mamoon L, Olesen SW. Fecal microbiota transplants annually and their positive clinical impact. Clin Transl Gastroenterol. 2020;11(11):e00247.	Ineligible SR
Manthey CF, Eckmann L, Fuhrmann V. Therapy for clostridium difficile infection - any news beyond metronidazole and vancomycin? Expert Rev Clin Pharmacol. 2017;10(11):1239-50.	Ineligible SR
Marcella C, Cui B, Kelly CR, Ianiro G, Cammarota G, Zhang F. Systematic review: the global incidence of faecal microbiota transplantation-related adverse events from 2000 to 2020. Aliment Pharmacol Ther. 2021;53(1):33-42.	SR to check
Marshall LL, Peasah S, Stevens GA. Clostridium difficile infection in older adults: systematic review of efforts to reduce occurrence and improve outcomes. Consult Pharm. 2017;32(1):24-41.	SR to check
McDonald LC, Gould CV, Gerding DN, Johnson S, Bakken JS, Carroll KC, et al. Clinical practice guidelines for clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):e1-e48.	SR to check
McIlroy J, Mukhopadhya I, Hold GL, Ianiro G, Hansen R. Review article: the gut microbiome in inflammatory bowel disease-avenues for microbial management. Aliment Pharmacol Ther. 2018;47(1):26-42.	Ineligible SR
Merlo G, Graves N, Brain D, Connelly LB. Economic evaluation of fecal microbiota transplantation for the treatment of recurrent clostridium difficile infection in Australia. J Gastroenterol Hepatol. 2016;31(12):1927-32.	Ineligible SR
Messias BA, Franchi BF, Pontes PH, Barbosa DADEAM, Viana CAS. Fecal microbiota transplantation in the treatment of clostridium difficile infection: state of the art and literature review. Rev. 2018;45(2):e1609.	SR to check
Mihaescu A, Augustine AM, Khokhar HT, Zafran M, Masood SSME, Gilca-Blanariu G-E, et al. Clostridioides difficile infection in patients with chronic kidney disease: a systematic review. Biomed Res Int. 2021;2021(5466656):1-10.	SR to check
Mikrobiomik Healthcare Company S.L. A phase III clinical trial in patients with recurrent clostridioides difficile (CD) infection, to evaluate the treatment with capsules of lyophilised faecal microbiota vs fidaxomicin. Identifier: EUCTR2020-004591-17. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2020. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-004591-17/ES.	Eligible trial, ongoing
Moayyedi P, Yuan Y, Baharith H, Ford AC. Faecal microbiota transplantation for clostridium difficile-associated diarrhoea: a systematic review of randomised controlled trials. Med J Aust. 2017;207(4):166-72.	SR to check
Mullish BH, Quraishi MN, Segal JP, McCune VL, Baxter M, Marsden GL, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. J Hosp Infect. 2018;100 Suppl 1:S1-S31.	SR to check
Mullish BH, Quraishi MN, Segal JP, McCune VL, Baxter M, Marsden GL, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. Gut. 2018;67(11):1920-41.	SR to check

Report	Exclusion reason
Murphy MM, Patatanian E, Gales MA. Extended duration vancomycin in recurrent clostridium difficile infection: a systematic review. Ther. 2018;5(6):111-19.	SR to check
Nana T, Moore C, Boyles T, Brink AJ, Cleghorn J, Devenish LM, et al. South African society of clinical microbiology clostridioides difficile infection diagnosis, management and infection prevention and control guideline. S Afr J Infect Dis. 2020;35(1):1-26.	Ineligible SR
National Institute for Health and Care Excellence. Clostridioides difficile infection: antimicrobial prescribing [NG199]. London: 23 July 2021. 1-40. Available from: https://www.nice.org.uk/guidance/ng199.	SR to check
Ng SC, Kamm MA, Yeoh YK, Chan PKS, Zuo T, Tang W, et al. Scientific frontiers in faecal microbiota transplantation: joint document of Asia-Pacific Association of Gastroenterology (APAGE) and Asia-Pacific Society for Digestive Endoscopy (APSDE). Gut. 2020;69(1):83-91.	Ineligible SR
NorthShore University HealthSystem. FMT versus antimicrobials for initial treatment of recurrent CDI. Identifier: NCT02255305. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/NCT02255305.	Eligible trial, no results
Ooijevaar RE, van Beurden YH, Terveer EM, Goorhuis A, Bauer MP, Keller JJ, et al. Update of treatment algorithms for clostridium difficile infection. Clin Microbiol Infect. 2018;24(5):452-62.	SR to check
Ooijevaar RE, van Nood E, Goorhuis A, Terveer EM, van Prehn J, Verspaget HW, et al. Ten-year follow-up of patients treated with fecal microbiota transplantation for recurrent clostridioides difficile infection from a randomized controlled trial and review of the literature. Microorganisms. 2021;9(3):548.	SR to check
Per Hellström. Transplantation of cultured gut microflora to repeat antibiotic-induced diarrhea due to clostridium difficile. Identifier: NCT02857582. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://ClinicalTrials.gov/show/NCT02857582.	Eligible trial, no results
Pession A, Zama D, Muratore E, Leardini D, Gori D, Guaraldi F, et al. Fecal microbiota transplantation in allogeneic hematopoietic stem cell transplantation recipients: a systematic review. J. Pers. Med. 2021;11(2):100.	SR to check
Piekarska A, Panasiuk A, Stepien PM. Clinical practice guidelines for clostridioides (clostridium) difficile infection and fecal microbiota transplant protocol - recommendations of the Polish Society of Epidemiology and Infectious Diseases. Przegl Epidemiol. 2020;74(1):69-87.	Ineligible SR
Pomares Bascunana RA, Veses V, Sheth CC. Effectiveness of fecal microbiota transplant for the treatment of clostridioides difficile diarrhea: a systematic review and meta-analysis. Lett Appl Microbiol. 2021;73(2):149-58.	SR to check
Qazi T, Amaratunga T, Barnes EL, Fischer M, Kassam Z, Allegretti JR. The risk of inflammatory bowel disease flares after fecal microbiota transplantation: systematic review and meta-analysis. Gut Microbes. 2017;8(6):574-88.	SR to check
Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory clostridium difficile infection. Aliment Pharmacol Ther. 2017;46(5):479-93.	SR to check
Rajasingham R, Enns EA, Khoruts A, Vaughn BP. Cost-effectiveness of treatment regimens for clostridioides difficile infection: an evaluation of the 2018 Infectious Diseases Society of America guidelines. Clin Infect Dis. 2020;70(5):754-62.	Ineligible SR
Ramai D, Zakhia K, Fields PJ, Ofosu A, Patel G, Shahnazarian V, et al. Fecal microbiota transplantation (FMT) with colonoscopy is superior to enema and nasogastric tube while comparable to capsule for the treatment of recurrent clostridioides difficile infection: a systematic review and meta-analysis. Dig Dis Sci. 2021;66(2):369-80.	SR to check
Ramai D, Zakhia K, Ofosu A, Ofori E, Reddy M. Fecal microbiota transplantation: donor relation, fresh or frozen, delivery methods, cost-effectiveness. Ann Gastroenterol. 2019;32(1):30-38.	SR to check

Report	Exclusion reason
Reigadas E, van Prehn J, Falcone M, Fitzpatrick F, Vehreschild MJGT, Kuijper EJ, et al. How to: prophylactic interventions for prevention of clostridioides difficile infection. Clin Microbiol Infect. 2021	SR to check
Rokkas T, Gisbert JP, Gasbarrini A, Hold GL, Tilg H, Malfertheiner P, et al. A network meta-analysis of randomized controlled trials exploring the role of fecal microbiota transplantation in recurrent clostridium difficile infection. United European Gastroenterol J. 2019;7(8):1051-63.	SR to check
Sartelli M, Ansaloni L, Biffl WA, Coccolini F, De Simone B, Leppaniemi A, et al. World Society of Emergency Surgery-American Association for the surgery of trauma guidelines for management of clostridioides (clostridium) difficile infection in surgical patients: an executive summary. J Trauma Acute Care Surg. 2021;91(2):422-26.	Ineligible SR
Sartelli M, Di Bella S, McFarland LV, Khanna S, Furuya-Kanamori L, Abuzeid N, et al. 2019 update of the WSES guidelines for management of clostridioides (clostridium) difficile infection in surgical patients. World J Emerg Surg. 2019;14:8.	SR to check
Schmidt-Hieber M, Bierwirth J, Buchheidt D, Vehreschild JJ, Cornely OA, Hentrich M, et al. Diagnosis and management of gastrointestinal complications in adult cancer patients: 2017 updated evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). Ann Hematol. 2018;97(1):31-49.	SR to check
Shaffer SR, Witt J, Targownik LE, Kao D, Lee C, Smieliauskas F, et al. Cost-effectiveness analysis of a fecal microbiota transplant center for treating recurrent c.difficile infection. J Infect. 2020;81(5):758-65.	Ineligible SR
Siciliano V, Nista EC, Rosa T, Brigida M, Franceschi F. Clinical management of infectious diarrhea. Rev Recent Clin Trials. 2020;15(4):298-308.	Ineligible SR
Signorette JP, Oliveira RTDD, Montiel JM, Longo PL. Applications of fecal microbiota transplantation: emphasis on clostridioides difficile infections. Int J Nutrol. 2021;14(1):16-20.	SR to check
Singh T, Bedi P, Bumrah K, Gandhi D, Arora T, Verma N, et al. Fecal microbiota transplantation and medical therapy for clostridium difficile infection: meta-analysis of randomized controlled trials. J Clin Gastroenterol. 2021;0(0):1-8.	SR to check
Sokol H, Galperine T, Kapel N, Bourlioux P, Seksik P, Barbut F, et al. Faecal microbiota transplantation in recurrent clostridium difficile infection: recommendations from the French group of faecal microbiota transplantation. Dig Liver Dis. 2016;48(3):242-7.	Ineligible SR
Stalder T, Kapel N, Diaz S, Grenouillet F, Koch S, Limat S, et al. A systematic review of economic evaluation in fecal microbiota transplantation. Infect Control Hosp Epidemiol. 2020;41(4):458-66.	SR to check
Sung J, Lai CY, Cheng F, Tang W, Wong SH, Chan PK, et al. Donor characteristics and clinical outcomes of fecal microbiota transplantation: a systematic review of clinical studies published up to 2017. Gastroenterology. 2018;154(6 Suppl 1):S854.	Ineligible SR
Tang G, Yin W, Liu W. Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory clostridium difficile infection: A meta-analysis? Diagn Microbiol Infect Dis. 2017;88(4):322-29.	SR to check
Tariq R, Pardi DS, Bartlett MG, Khanna S. Low cure rates in controlled trials of fecal microbiota transplantation for recurrent clostridium difficile infection: a systematic review and meta-analysis. Clin Infect Dis. 2019;68(8):1351-58.	SR to check
Tixier EN, Verheyen E, Luo Y, Grinspan LT, Du CH, Ungaro RC, et al. Systematic review with meta-analysis: fecal microbiota transplantation for severe or fulminant clostridioides difficile. Dig Dis Sci. 2021;0(0)	SR to check
Tran M-CN, Kullar R, Goldstein EJC. Investigational drug therapies currently in early-stage clinical development for the treatment of clostridioides (clostridium) difficile infection. Expert Opin Investig Drugs. 2019;28(4):323-35.	SR to check
Trubiano JA, Cheng AC, Korman TM, Roder C, Campbell A, May MLA, et al. Australasian Society of Infectious Diseases updated guidelines for the management	Ineligible SR

Report	Exclusion reason
of clostridium difficile infection in adults and children in Australia and New Zealand. Intern Med J. 2016;46(4):479-93.	
University of Pennsylvania. PMT for severe-CDI. Identifier: NCT03970200. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2020. Available from https://ClinicalTrials.gov/show/NCT03970200.	Eligible trial, ongoing
University of Wisconsin M. Fecal microbiota transplantation for c. difficile infection in solid organ transplant recipients. Identifier: NCT03617445. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2021. Available from https://ClinicalTrials.gov/show/NCT03617445.	Eligible trial, ongoing
Voth E, Khanna S. Fecal microbiota transplantation for treatment of patients with recurrent clostridioides difficile infection. Expert Rev Anti Infect Ther. 2020;18(7):669-76.	SR to check
Waltz P, Zuckerbraun B. Novel therapies for severe clostridium difficile colitis. Curr Opin Crit Care. 2016;22(2):167-73.	Ineligible SR
Wang S, Xu M, Wang W, Cao X, Piao M, Khan S, et al. Systematic review: adverse events of fecal microbiota transplantation. PLoS ONE. 2016;11(8):e0161174.	SR to check
Wardill HR, Secombe KR, Bryant RV, Hazenberg MD, Costello SP. Adjunctive fecal microbiota transplantation in supportive oncology: emerging indications and considerations in immunocompromised patients. EBioMedicine. 2019;44:730-40.	SR to check
Wong D, Nanda N. Clostridium difficile disease in solid organ transplant recipients: a recommended treatment paradigm. Curr Opin Organ Transplant. 2020;25(4):357-63.	Ineligible SR
Wu K-S, Lee SS-J, Chen Y-S, Syue L-S, Cheng A, Yen T-Y, et al. Recommendations and guidelines for the treatment of clostridioides difficile infection in Taiwan. J Microbiol Immunol Infect. 2020;53(2):191-208.	SR to check
Yang J, Yang H. Non-antibiotic therapy for clostridioides difficile infection: a review. Crit Rev Clin Lab Sci. 2019;56(7):493-509.	Ineligible SR
Yang X, Huang Z, He J, Chen Y. The elevated risk of recurrent clostridioides difficile infection in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clin Lab. 2021;67(5):1119-29.	Ineligible SR
You JHS, Jiang X, Lee WH, Chan PKS, Ng SC. Cost-effectiveness analysis of fecal microbiota transplantation for recurrent clostridium difficile infection in patients with inflammatory bowel disease. J Gastroenterol Hepatol. 2020;35(9):1515-23.	SR to check
Young VB. Therapeutic manipulation of the microbiota: past, present, and considerations for the future. Clin Microbiol Infect. 2016;22(11):905-09.	Ineligible SR
Yuan T, Li Z. Fecal microbiota transplantation as a treatment for gastrointestinal diseases: a systemic review and meta-analysis. Gazz Med Ital. 2018;177(1-2):26-41.	SR to check
Zhou H-Y, Guo B, Lufumpa E, Li X-M, Chen L-H, Meng X, et al. Comparative of the effectiveness and safety of biological agents, tofacitinib, and fecal microbiota transplantation in ulcerative colitis: systematic review and network meta-analysis. Immunol Invest. 2021;50(4):323-37.	Ineligible SR
Zuo T, Wong SH, Lam K, Lui R, Cheung K, Tang W, et al. Bacteriophage transfer during faecal microbiota transplantation in clostridium difficile infection is associated with treatment outcome. Gut. 2018;67(4):634-43.	Eligible trial, no results

Table F2 Systematic Review of clinical Effects and Safety Unobtainable Report list (n=1)

Report	Exclusion reason
Hayes Inc. Fecal microbiota transplant for refractory or recurrent clostridium difficile infection in adults. United States: 2016. Available from: http://www.hayesinc.com/hayes/crd/?crd=48366.	Unobtainable

Table F3 Systematic Review of economic evaluations Excluded Reports list (n=29)

Report	Exclusion reason
Ahir HB, Mayes A, Marcella S, Jiang Y, Burnett H, Rajpura J. Systematic literature review of economic evaluations and healthcare resource utilisation studies in the treatment of clostridium difficile infection. Value Health. 2017;20(9):A791.	Review
Arbel LT, Hsu E, McNally K. Cost-effectiveness of fecal microbiota transplantation in the treatment of recurrent clostridium difficile infection: a literature review. Cureus. 2017;9(8):e1599.	Review
Burton HE, Mitchell SA, Watt M. The cost effectiveness of treatments for clostridium difficile infection: a systematic review. Value Health. 2016;19(3):A218.	Review
Canadian Agency for Drugs and Technologies in Health. Fecal bacteriotherapy for adult patients with recurrent clostridium difficile infection: update of clinical, cost-effectiveness, and guidelines. Canada: 2014. Available from: http://www.cadth.ca/media/pdf/htis/apr-2014/RA0667%20Fecal%20Bacteriotherapy%20Final.pdf.	Review
Durham SH, Le P, Cassano AT. Navigating changes in clostridioides difficile prevention and treatment. J Manag Care Spec Pharm. 2020;26(12):S3-23.	Review
Guo B, Harstall C, Nguyen T, Ohinmaa A. Fecal transplantation for the treatment of clostridium difficile-associated disease or ulcerative colitis. Canada: 2011. Available from: http://www.ihe.ca/advanced-search/fecal-transplantation-for-the-treatment-of-clostridium-difficile-associated-disease-or-ulcerative-colitis.	Review
Gupta A, Ananthakrishnan AN. Economic burden and cost-effectiveness of therapies for clostridiodes difficile infection: a narrative review. Ther Adv Gastroenterol. 2021;14:1-13.	Review
Gupta S, Zhu J, McCarty TR, Pruce J, Kassam Z, Kelly C, et al. Cost-effectiveness analysis of sequential fecal microbiota transplantation for fulminant clostridioides difficile infection. J Gastroenterol Hepatol. 2021;36(9):2432-40.	Ineligible intervention
Hammeken L, Ehlers LH, Jorgensen SMD, Dahlerup JF, Hvas CL. PGI33 The cost-effectiveness of faecal microbiota transplantation vs. antibiotics for patients with recurrent clostridioides difficile infection: a systematic review. Value Health. 2019;22(Suppl 3):S622.	Review
Hammeken LH, Baunwall SMD, Hvas CL, Ehlers LH. Health economic evaluations comparing faecal microbiota transplantation with antibiotics for treatment of recurrent clostridioides difficile infection: a systematic review. Health Econ Rev. 2021;11(1):3.	Review
Health Quality Ontario. Fecal microbiota therapy for clostridium difficile infection: a Health Technology Assessment. Ont Health Technol Assess Ser. 2016;16(17):1-69.	Ineligible setting
Heimann SM, Cruz Aguilar MR, Mellinghof S, Vehreschild MJGT. Economic burden and cost-effective management of clostridium difficile infections. Med Maladies Infect. 2018;48(1):23-29.	Review
Jiang M, Leung N-H, Ip M, You JHS. Cost-effectiveness analysis of ribotype-guided fecal microbiota transplantation in Chinese patients with severe clostridium difficile infection. PLoS ONE. 2018;13(7):e0201539.	Ineligible patient population
Kassam Z, Smith M, Alm E, Fridman S, Burgess J, Edelstein C, et al. The cost-effectiveness of competing strategies for managing multiply recurrent clostridium difficile infection: Examining the impact of universal stool banks and encapsulated fecal microbiota transplantation. Am J Gastroenterol. 2015;110(Suppl 1):S933-34.	Poster without enough data
Khurana S, Kahl A, Yu K, DuPont AW. Recent advances in the treatment of clostridioides difficile infection: the ever-changing guidelines. Fac. 2020;9:13.	Review
Le P, Nghiem VT, Mullen PD, Deshpande A. Cost-effectiveness of competing treatment strategies for clostridium difficile infection: a systematic review. Infect Control Hosp Epidemiol. 2018;39(4):412-24.	Review
Li KX, Grobelna A. Lyophilized versus frozen fecal microbiota transplant for recurrent clostridium difficile infection, inflammatory bowel disease, and irritable	Review

Report	Exclusion reason
bowel syndrome: a review of clinical effectiveness, cost-effectiveness, and guidelines [internet]. Canadian Agency for Drugs and Technologies in Health. 2019;8:14.	
Massachi S, Hay JW. Cost-effectiveness of various clostridium difficile infection (CDI) treatments in patients with recurrent infections. Value Health. 2014;17(3):A273-74.	Poster without enough data
Nellis E, Hickey P, Shah S, Shah H. Quality assessment of the efficacy and cost-effectiveness of fecal microbiota transplant for recurrent clostridium difficile infection. Am J Gastroenterol. 2017;112(Suppl 1):S77.	Poster without enough data
Patel SS, Grinspan A, Colombel J-F, Atreja A. Cost effectiveness analysis of fecal microbiota transplant and antibiotic treatment for recurrent clostridium difficile infection. Gastroenterology. 2014;146(5 Suppl 1):S190-91.	Poster without enough data
Rajasingham R, Enns EA, Khoruts A, Vaughn BP. Cost-effectiveness of treatment regimens for clostridioides difficile infection: an evaluation of the 2018 Infectious Diseases Society of America guidelines. Clin Infect Dis. 2020;70(5):754-62.	Ineligible patient population
Ramai D, Zakhia K, Ofosu A, Ofori E, Reddy M. Fecal microbiota transplantation: donor relation, fresh or frozen, delivery methods, cost-effectiveness. Ann Gastroenterol. 2019;32(1):30-38.	Review
Shaffer SR, Witt J, Targownik LE, Kao D, Lee C, Smieliauskas F*, et al.* Cost-effectiveness analysis of a fecal microbiota transplant center for treating recurrent c.difficile infection. J Infect. 2020;81(5):758-65	Ineligible setting
Shaffer S, Rubin DT, Targownik L, Singh H, Witt J, Bernstein C*, et al.* Cost-effectiveness analysis of starting a fecal microbiota transplantation (FMT) unit for the treatment of recurrent c. difficile infection compared with antibiotic therapy. Am J Gastroenterol. 2019;114(Suppl):S110-11.	Ineligible setting
Singh P, Udeh B, Dalton J, Udeh C, Hata J. Cost-effectiveness of 6 treatments for primary clostridium difficile infection in an ICU population. Crit Care Med. 2014;42(12 Suppl 1):A1474.	Ineligible patient population
Stalder T, Kapel N, Diaz S, Grenouillet F, Koch S, Limat S, et al. A systematic review of economic evaluation in fecal microbiota transplantation. Infect Control Hosp Epidemiol. 2020;41(4):458-66.	Review
Vaughn BP, Enns EA, Khoruts A, Rajasingham R. Cost-effectiveness of treatment regimens for clostridium difficile infection - an evaluation of the 2018 infectious diseases society of America guidelines. Gastroenterology. 2019;156(6 S1):S674.	Poster without enough data
Yang DY, Mullie T, Russell L, Roach B, Wong K, Kao DH. Economic evaluation of a fecal microbiota transplantation program for recurrent clostridioides difficile infection. Gastroenterology. 2019;156(6 S1):S-1158.	Poster without enough data
Zowall H, Brewer C, Deutsch A. Cost-effectiveness of fecal microbiota transplant in treating clostridium difficile infection in Canada. Value Health. 2014;17(7):A676.	Poster without enough data

Appendix G Additional results

FMT colonoscopy results

Table 1: PSA results of FMT colonoscopy

	FMT colonscopy	Comparator	Incremental
Compared with vancomycin			
Cost per person	£7,220	£17,294	**-£10,074**
QALYs per person	1.82	1.12	**0.70**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**1.20**
Probability that intervention is cost saving			**100.0%**
Probability that intervention is cost effective			**100.0%**
Compared with fidaxomicin			
Cost per person	£7,216	£15,760	**-£8,545**
QALYs per person	1.82	1.35	**0.47**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**0.89**
Probability that intervention is cost saving			**100.0%**
Probability that intervention is cost effective			**100.0%**

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental cost-effectiveness ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years.

FMT NDT results

Table 2: PSA results of FMT NDT

	FMT NDT	Comparator	Incremental
Compared with vancomycin			
Cost per person	£5,607	£17,241	**-£11,635**
QALYs per person	1.83	1.11	**0.72**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**1.30**
Probability that intervention is cost saving			**100.0%**
Probability that intervention is cost effective			**100.0%**
Compared with fidaxomicin			
Cost per person	£5,581	£15,883	**-£10,302**
QALYs per person	1.83	1.35	**0.47**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**0.99**
Probability that intervention is cost saving			**100.0%**
Probability that intervention is cost effective			**100.0%**
Compared with VTP			
Cost per person	£5,621	£12,540	**-£6,919**
QALYs per person	1.83	1.41	**0.42**

ICER (using a threshold of £20,000 per QALY)	**Dominant**
NHB per person (using a threshold of £20,000 per QALY)	**0.77**
Probability that intervention is cost saving	**100.0%**
Probability that intervention is cost effective	**100.0%**

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental cost-effectiveness ratio; NDT, Nasoduodenal tube; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

FMT enema results

Table 3: PSA results of FMT enema

	FMT enema	**Comparator**	**Incremental**
Compared with vancomycin			
Cost per person	£6,170	£17,319	**-£11,149**
QALYs per person	1.72	1.12	**0.61**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**1.15**
Probability that intervention is cost saving			**99.9%**
Probability that intervention is cost effective			**99.9%**
Compared with fidaxomicin			
Cost per person	£6,354	£15,857	**-£9,503**
QALYs per person	1.72	1.35	**0.37**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**0.85**
Probability that intervention is cost saving			**100.0%**
Probability that intervention is cost effective			**100.0%**
Compared with VTP			
Cost per person	£6,309	£12,490	**-£6,182**
QALYs per person	1.72	1.41	**0.31**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**0.62**
Probability that intervention is cost saving			**99.8%**
Probability that intervention is cost effective			**99.9%**

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental cost-effectiveness ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

FMT oral capsules results

Table 4: PSA results of FMT oral

	FMT oral capsule	**Comparator**	**Incremental**
Compared with vancomycin			
Cost per person	£4,006	£17,185	**-£13,178**
QALYs per person	1.83	1.13	**0.71**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**1.37**

Probability that intervention is cost saving			**100.0%**
Probability that intervention is cost effective			**100.0%**
Compared with fidaxomicin			
Cost per person	£4,061	£15,798	**-£11,737**
QALYs per person	1.81	1.35	**0.47**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**1.06**
Probability that intervention is cost saving			**100.0%**
Probability that intervention is cost effective			**100.0%**
Compared with VTP			
Cost per person	£4,053	£12,479	**-£8,427**
QALYs per person	1.82	1.41	**0.41**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**0.83**
Probability that intervention is cost saving			**100.0%**
Probability that intervention is cost effective			**100.0%**

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental cost-effectiveness ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

NICE National Institute for Health and Care Excellence

Assessment Report Fact Check

GID-MT566 Faecal microbiota transplant for recurrent *Clostridioides difficile* infection

There were 6 consultees who responded to the factual inaccuracy and key assumptions check of the external assessment centre's assessment report. This included:

- 5 Clinical experts
- 1 Patient organisation
- 1 NHS organisation

The 1 NHS organisation did not have any comments and so were excluded from the below table.

The technology

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response
1	Are there any factual inaccuracies in the way the technology has been described? (pages 14-15)	1	Patient Organisation	I wonder if it is worth stating in the document technology description an alternative way of describing FMT as intestinal microbiota transplantation (IMT).	IMT would be perhaps a more acceptable means of describing the technology for patients who might have treatment than faecal microbiota transplantation.	The EAC defers to MTAC as the project title is declared by NICE. The EAC notes that changing the nomenclature to IMT to increase acceptability has been suggested in published letter form.
		2	Clinical Expert	Relatively minor point (page 14): perhaps indicate that in majority of the studies, faecal matter was diluted using 0.9% saline	In the RCTs that compared FMT with antibiotics, the faecal matter was diluted using 0.9% saline	We thank the expert for highlighting this, and have amended the following report sections:

						Section 2 Overview of the technology describes FMT as a procedure rather than the evidence identified in the systematic review, so we have amended wording to reflect the predominance of saline as the diluting agent. Section 5.1 Overview of methodologies of included studies – we have added a sentence that all trials used saline as the mixing agent (Hota 2017 did not specify concentration).
		3	Clinical Expert	'…implants a sample of gut microorganisms from a healthy donor…'	We think it is not just the microorganisms that provide efficacy of FMT but also, for instance, the metabolites produced by those chemicals. Consider rewording to something like: '…implants a sample of gut microorganisms (and of the	We thank the expert for this information and have clarified this point in the report.

					surrounding environment in which they are found) from a screened healthy donor…'.	
		4	Clinical Expert	P9/203 (and similarly P14/203). Suggested opening sentence for P9 (with similar alteration to the sentence on P14): 'Faecal microbiota transplant (FMT) for Clostridiodes difficile infection involves the transfer of faecal matter from a healthy donor into the gastrointestinal (GI) tract of an infected individual.' P9/203. Bowel lavage or preparation, rather than wash.	I would suggest changing these opening sentences to improve clarity. The verb 'implant' is not usually used in this context. This is the usual terminology.	We have amended our terminology as suggested.
		5	Clinical Expert	Page 14, final paragraph "Each transplant of a faecal sample is referred to as an infusion". Infusions are instillations of a liquid, so this term would not cover capsules (which are ingested). Page 14, final paragraph "All 3 methods of delivery use the same mechanism of action". The underlying mechanism(s) of action is poorly understood, so difficult to state this is the case with certainty.		We thank the expert for this information and have clarified both these points in the report.
2	Have all appropriate equality considerations been	1	Patient Organisation	As current treatment is application by endoscopy or enteral tube this might not be applicable, but if FMT is given by	Gelatine components are avoided by certain religious or cultural	We thank the organisation for this important

	considered? (page 16)			capsule there might be religious considerations to be made depending on the capsule components.	groups if it is derived from pork.	information. Although we did not include any trials evaluating oral capsules, we have examined excluded studies and can confirm that gelatine has been used in oral capsule preparation, so we have added this to the special considerations section. We have also checked the reported sampling processes in included trials and note that glycerol (which can be made using animal product, generally beef) was used for producing the frozen product in one trial (Hvas 2019). We have inserted this knowledge into the special considerations section.
		2	Clinical Expert	Appear appropriate	-	-

		3	Clinical Expert	-	-	-
		4	Clinical Expert	I think the current statement is appropriate.		
		5	Clinical Expert	No additional considerations identified		

Clinical evidence

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response
3	The included evidence focused on published RCTs in which FMT was compared to antibiotic treatment (in line with the scope of the assessment). Has any key clinical evidence been missed from this report? (pages 18-40)	1	Patient Organisation	-	-	-
		2	Clinical Expert	Not aware of additional key evidence with the specified scope		
		3	Clinical Expert	Was this study considered? https://www.acpjournals.org/doi/full/10.7326/M16-0271 - in this study, patients randomised to the placebo arm received their own stool. I think this study would not qualify on the definition of FMT – but was this study considered? https://www.nejm.org/doi/full/10.1056/NEJMoa2106516	I think would reach the criteria of 'comparator' set in Table 2. I would expect that Firmicutes spore from human donor stool is too far removed to be considered as 'FMT', but perhaps this merits a comment?	These two RCTs were identified during searching, but were excluded on the following grounds: Kelly 2020: This trial was ineligible for inclusion in the systematic review as it compared FMT vs FMT. Only trials comparing FMT to a comparator arm receiving antibiotics

						only were eligible for inclusion based on the NICE scope. All RCTs comparing FMT to FMT, or FMT to placebo, were therefore excluded. Feuerstadt 2022: we did not identify the full text as it was published after our searches were conducted. However, we did identify the NCT record (NCT03183128). We excluded this trial on the basis that the intervention is not an FMT product, and that the comparator is placebo and not antibiotics. Antibiotics were used prior to the interventions, but as a study eligibility criterion for patients entering the trial. Placebo is not an eligible comparator

						for the systematic review.
		4	Clinical Expert	Not as far as I am aware.		
		5	Clinical Expert	None identified		
4	Are there any factual inaccuracies in the results presented from the evidence base? (pages 35-57)	1	Patient Organisation	-	-	-
		2	Clinical Expert	Not identified	-	
		3	Clinical Expert	-	-	-
		4	Clinical Expert	No. But on P60, 'No trials reported on the effectiveness of FMT to treat patients with refractory CDI', I think it is worth commenting on the looseness of the terms 'recurrent / refractory' in this context, as per our discussion during the video conference.	This is contentious, as we discussed in the video conference.	Thank you for reminding us of the important discussion around terminology, we have added a paragraph of explanatory text at the beginning of section 8 (Interpretation of the clinical evidence) to draw attention to this. The EAC would like to emphasise that although the patient eligibility criteria of the 5

						included RCTs may have included some refractory patients, the focus of these trials was very much relapse/recurrence.
		5	Clinical Expert	None identified		
5	Do you know of any UK-based adverse events not listed in pages 62 to 64?	1	Patient Organisation	No		
		2	Clinical Expert	Aware of US-based adverse events		
		3	Clinical Expert	An often quoted case report from the UK of a serious adverse event after FMT is: https://academic.oup.com/cid/article/61/1/136/340816	I am not aware of any literature from UK experience reporting FMT-related adverse events other than this	Thank you for highlighting this reference. As the scope was limited to RCTs, case report evidence has not been systematically searched for and identified as part of the safety review and therefore the EAC does not consider it appropriate to include one specific report as evidence. However, considering this case is referred to often, we have inserted a

						justification of our findings of no serious harm in section 8.
		4	Clinical Expert	I recall publication of a case of aspiration pneumonia in the UK.		Thank you for highlighting this case report. As the scope was limited to RCTs, case report evidence has not been systematically searched for and identified as part of the safety review and therefore the EAC does not consider it appropriate to include one specific report as evidence. However, considering this case is referred to often, we have inserted a justification of our findings of no serious harm in section 8.
		5	Clinical Expert	None identified		
6	Do you know of any ongoing studies not listed on page 74?	1	Patient Organisation	No		
		2	Clinical Expert	Not aware of additional involving FMT		

		3	Clinical Expert	-	-	-
		4	Clinical Expert	No.		
		5	Clinical Expert	None identified		

Economic evidence

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response
7	Eight economic evaluation studies were included that were relevant to the decision problem, are there any additional studies that should be included that are not reported here? (pages 75-79)	1	Patient Organisation	-	-	-
		2	Clinical Expert	Not aware of relevant additional		
		3	Clinical Expert	-	-	-
		4	Clinical Expert	No.		
		5	Clinical Expert	None identified		
8	Are the interventions and comparators used in the economic model appropriate for the NHS population needing FMT?	1	Patient Organisation	-	-	-
		2	Clinical Expert	Appear appropriate to me. Page 98, second paragraph, suggest change “pathogen” to “strain of *C. difficile*”		Thank you, the wording has been amended in the report.
		3	Clinical Expert	Should the intervention be ‘nasogastric tube’ rather than nasoduodenal?	As discussed before, NG tube is used much more	Whilst the EAC acknowledges that NGT FMT delivery is

					frequently than ND tube for FMT administration in the UK. However, note that page 96 says that no RCTs identified with NG tube to inform results of economic model.	commonly used in the UK it has not been included in the model due to insufficient RCT evidence within this population to inform parameters. Additional context has been added to the methods section and conclusion to reflect the potential benefits of NGT based on results for the other routes of administering FMT included in the model.
		4	Clinical Expert	The points made about NG versus ND and NJ tube administration on P96 are valid and correct. However, the conclusion of this section should be clarified.		Thank you for the feedback. Additional text has been added to page 96 to conclude how the gaps in evidence regarding NGT is addressed in the report.
		5	Clinical Expert	Yes, although fidaxomicin as an extended-pulsed dose regimen is not included as a comparator and may result in less recurrence than the standard dosing regimen.		Thank you for the feedback. The comparators included were based on those reported in the NICE scope and for which data could be obtained for the

						selected population for this assessment (third episode of CDI) from RCTs.
9	Is the rationale for the model design listed on page 98 to 99 appropriate for using FMT in this population?	1	Patient Organisation	-	-	-
		2	Clinical Expert	Believe appropriate based on the identified clinical trials.		
		3	Clinical Expert	-	-	-
		4	Clinical Expert	Yes.		
		5	Clinical Expert	Yes		
10	Are the key assumptions listed on page 99 to 100 appropriate for using FMT in this population?	1	Patient Organisation	-	-	-
		2	Clinical Expert	"…it is assumed that the risk of death is comparable to the general population, once recovered." Clinical experience suggests this may not be the case. There may be publications that have addressed this issue. "..include 5 days of hospital stay for FMT and 10 days hospital stay for antibiotics.." Based on clinical experience, is likely to be shorter.		Thank you for the feedback, we acknowledge this is a limitation of the model. However, no quantitative evidence was found to inform parameters to inform increased mortality in this population following a targeted literature search. A multi-centre cohort study (Hensgens 2013)

						stated that the long-term excess mortality associated with CDI may be higher, but small. Therefore, the impact on results are likely marginal. However, this will be addressed qualitatively in the report. The impact of this assumption is also described in the results section. The impact of the length of stay of assumption on the results has been included in the report.
		3	Clinical Expert	-	-	-
		4	Clinical Expert	I appreciate the discussions about NG/ND/NJ tubes on P96 and the lack of RCT evidence for NG. But NG tube administration remains one of the most common routes for administration in the UK and so the use of ND data (P100 onwards) makes for difficult reading from a UK perspective. I think a further comment about this is necessary on P100.	See comments in the box on the left.	Thank you for the feedback. Additional text has been added to the clinical parameters section for context on what evidence is available for NGT. This is discussed further in the conclusion section to provide an

						indication of the economic impact of FMT via NGT against the comparators considered.
		5	Clinical Expert	Table 28 – clinical parameters used for the model. Is the rate of CDI resolution used for vancomycin (19%) and fidaxomicin (42%) on the low side, and what is the rationale for using Hvas 2019 to populate this parameter? Louie 2011 found a clinical cure rate of 85.8% for vanclomycin and 88.2% for fidaxomicin (NJEM 2011;364:422-31). In a similar RCT Cornely found clinical cure rates of 90.6% and 91.7% respectively (Lancet Infect Dis 2012;12:281-9. Similarly for recurrence rates, the Hvas reference has high recurrence rates for fidaxomicin (46%) compared with Louie (15.4%).		Thank you for providing the additional studies. We identified 5 randomised clinical trials based on the evidence review criteria. Of those, van Nood 2013 and Hvas 2019 included vancomycin treatments. van Nood included people with 1st CDI recurrence cases as well and had a smaller sample size. For this reason, the Hvas RCT was used to inform effectiveness data for vancomycin. Of the 5 eligible studies, Hvas 2019 was also the only study which reported outcomes for fidaxomicin. Whilst there are limitations with all of the evidence, we

						considered Hvas 2019, the most appropriate to inform model parameters. We note that in Cornely 2012 and Louie 2011 more than 80% of the populations were not recurrent CDI cases. Therefore, we considered these data should not be applied to the recurrent population.
11	Are the cost parameters used in the model appropriate (tables 29-32)? Are there any costs to the NHS missed in the total calculation of treatment costs?	1	Patient Organisation	-	-	-
		2	Clinical Expert	Suggest consider additional time of Consultant Gastroenterologist for initial consultation and consent for the procedure. Page 96: "…, it was assumed that any conclusions regarding the clinical benefits of NDT, as sourced from van Nood, may be applicable for NGT." Should Table 30 therefore consider cost of NGT, instead of NDT?		Assuming that treatment options will be discussed with the patient and that this would be applicable for both arms, suggest not updating the costs currently applied in the model. Regarding NDT/NGT cost, additional text has been added outlining the total cost of administering FMT via NGT.

		3	Clinical Expert	-	-	
		4	Clinical Expert	An NG tube insertion would not involve the £1000 ND insertion cost.		Additional text has been added to the cost section to clarify that the cost of providing NGT is lower than for NDT. Cost reported in Abdali (2020) is included for context.
		5	Clinical Expert	These are reasonable estimates, however real costs are likely to be subject to significant variation.		Thank you for this feedback.
12	Are there any areas of key uncertainty in which additional scenario analysis would be warranted? (pages 110-111)	1	Patient Organisation	-	-	
		2	Clinical Expert	-	-	
		3	Clinical Expert	-	-	
		4	Clinical Expert	No.		
		5	Clinical Expert	None identified		

Further comments

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response

13	Please add any further comments relating to factual inaccuracies on the assessment report.	1	Patient Organisation	-	-	-
		2	Clinical Expert	-	-	-
		3	Clinical Expert	Page 12 - Negative stool test for CD toxin during follow up period (experts state that this measure may be unreliable for up to 3 months post procedure).	I think most expert authorities would say positivity lasts typically for up to 30 days, I am not aware of evidence saying up to 3 months but I may be incorrect.	This comment is in relation to the wording of the NICE scope .
		4	Clinical Expert	P120: I acknowledge these sentences: 'Previous analyses have combined NDT and NGT data when pooling results. Therefore, based on the assumption that NDT efficacy data is comparable to NGT, FMT via NGT is also likely to be a cost saving treatment option for this population against all three comparators considered. Particularly, since the cost of NGT (Abdali (2020)) is approximately 50% cheaper than NDT.' This is a vitally important point for UK users. I think that (brief) statements to this effect should be included each time NDT is mentioned and referenced in the economic modelling section, to ensure	See comments in the box on the left.	The conclusion section has been updated to provide more clear application of the model results to the NGT context. This includes comparing what evidence is available to indicate the cost and effectiveness of NGT to other forms of FMT administration included in the model.

				that this work remains relevant to the UK and to a UK audience.		
		5	Clinical Expert	None identified		

Economic model comments (if requested to review the model)

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response
14	Please add comments relating to errors or omissions within the economic model.	1	Patient Organisation	-	-	-
		2	Clinical Expert	-	-	-
		3	Clinical Expert	-	-	-
		4	Clinical Expert	-	-	-
		5	Clinical Expert	NA		

YHEC
York Health Economics Consortium

GID-MT566 External Assessment Centre (EAC) Addendum on Economic Model Input Updates

1.1 Base Case Analysis

The base case analysis was updated following feedback from clinical experts on costs and a correction to the FMT via enema resolution rate. Table 1 outlines the corrections made to the model. The following updates were made to the base case analysis.

Table 1: Correction to model inputs

#	Model correction	Section in Assessment report
1	FMT enema resolution probability changed from 76% to 57% to reflect cure rate in second plus recurrent CDI patients	**Table 28**
2	Addition of bowel cleansing cost prior to colonoscopy procedure for delivery of FMT via colonoscopy (2 sachets required, costing £3.39)	**Table 29**
3	Update of FMT unit material cost from £664 to £850 per unit (if 3 units, these are costed for the price of 2 according to expert opinion, therefore cost of 2 FMT materials used to cost for FMT colonoscopy). This change was applicable for all FMT routes considered, excluding via oral capsules.	**Tables 29, 30 and 31.**

The effectiveness data used to inform the FMT enema resolution probability was questioned. The previous base case analysis utilised 76%, which is the 10-week resolution probability for all individuals considered in the trial (i.e. those with first recurrence of CDI and 2 or more recurrence of CDI), in accordance with the cycle length considered in the model. The trial also reported the number of people with resolution at 90-days by population subgroups. There were 14 people with 2 or more recurrences who received FMT treatment via enema, of which, 8 were cured (57%).

Clinical experts also stated that prior to FMT colonoscopy a bowel cleansing is required, where this may also be conducted with other routes of FMT administration. The new base case analysis applies bowel cleansing cost to FMT colonoscopy. Clinical experts stated the use of macrogol and sodium picosulfate for bowel cleansing. The latter is used in the model, however, price differences between the two are minor (£5 and £3.25 for 2 sachets of macrogol and picosulfate, respectively).

Additionally, one clinical expert stated that the current cost of FMT material is not reflective of the true costs associated with FMT production, considering additional costs such as covid-19 screening. One expert reported the unit cost of a 50ml sample to be £850, where if 3 samples are provided this will be costed for the price of two. Unit cost of FMT colonoscopy was calculated by applying 3 units of FMT material and updated to £1,700 (based on 3 units being costed for the price of 2). FMT NDT and FMT enema were modelled to require 1 unit of FMT material.

The results of the updated base case analyses are presented in the tables below.

Table 2: Summary total cost per person for comparators

	Costs	QALYs
FMT colonoscopy	£6,864	1.83
FMT NDT	£5,873	1.84
FMT enema	£9,046	1.61
FMT oral capsule	£4,032	1.83

Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube.

Table 3: Cost breakdown (per person results)

	Treatment	Hospitalisation (recurrence)	FC treatment	Total
FMT colonoscopy	£5,370	£1,349	£144	**£6,864**
FMT NDT	£4,537	£1,207	£129	**£5,873**
FMT enema	£3,854	£4,691	£501	**£9,046**
FMT oral capsule	£2,539	£1,349	£144	**£4,032**

Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube.

Table 4: Incremental analysis (per person results)

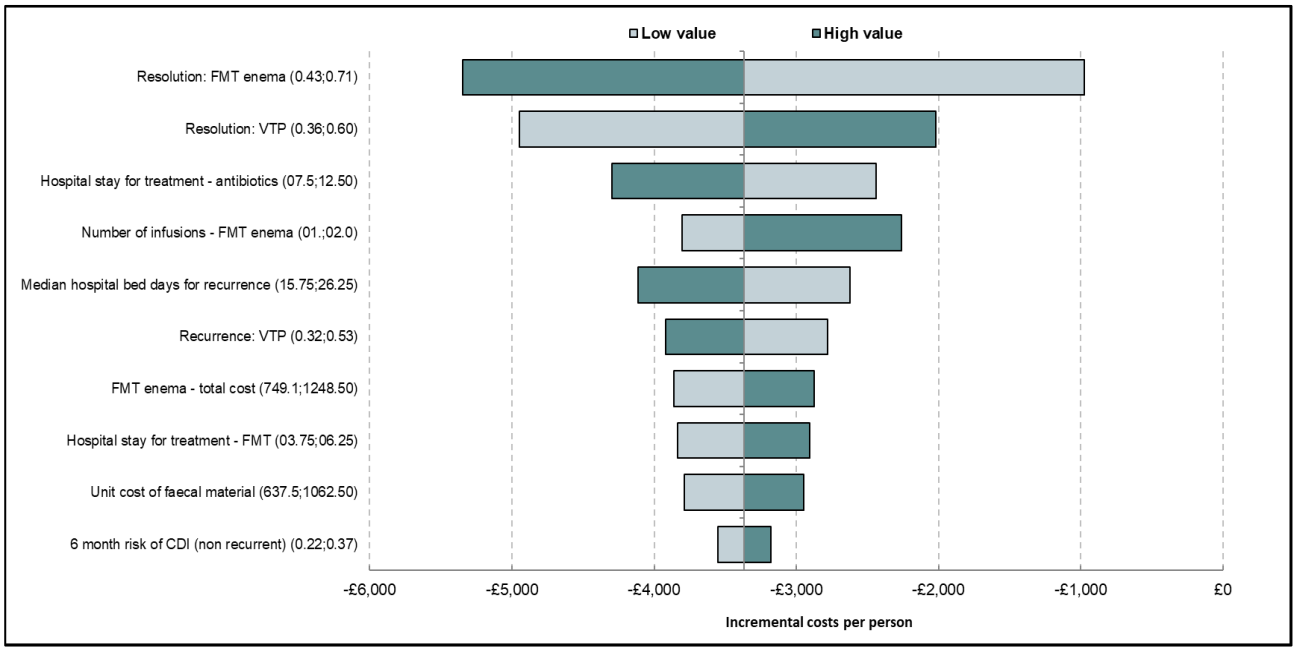
	∆Costs	∆QALYs	NHB	ICER
FMT vs vancomycin				
FMT colonoscopy	-£10,303	0.65	1.17	Dominant
FMT NDT	-£11,293	0.66	1.22	Dominant
FMT enema	-£8,120	0.43	0.84	Dominant
FMT oral capsule	-£13,134	0.65	1.31	Dominant
FMT vs fidaxomicin				
FMT colonoscopy	-£8,854	0.44	0.88	Dominant
FMT NDT	-£9,844	0.45	0.94	Dominant
FMT enema	-£6,672	0.22	0.55	Dominant
FMT oral capsule	-£11,686	0.44	1.02	Dominant
FMT vs VTP				
FMT colonoscopy	-£5,551	0.39	0.66	Dominant
FMT NDT	-£6,541	0.40	0.72	Dominant
FMT enema	-£3,369	0.17	0.34	Dominant
FMT oral capsule	-£8,382	0.39	0.80	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NDT, Nasoduodenal tube; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

DSA

The key drivers of the results for FMT enema (the least cost saving FMT) versus VTP are the resolution probability for FMT enema and VTP, followed by the hospital stay for any cases of CDI in subsequent cycles. Resolution probability determines the proportion of the cohort in the recurrence CDI health state which is associated with large costs. However, FMT enema was still found to be cost saving when compared with VTP.

Figure 2: Tornado plot for FMT enema versus VTP



Note: FMT enema resolution lower and upper bound was calculated as 25% of the mean (43% and 71%)

PSA

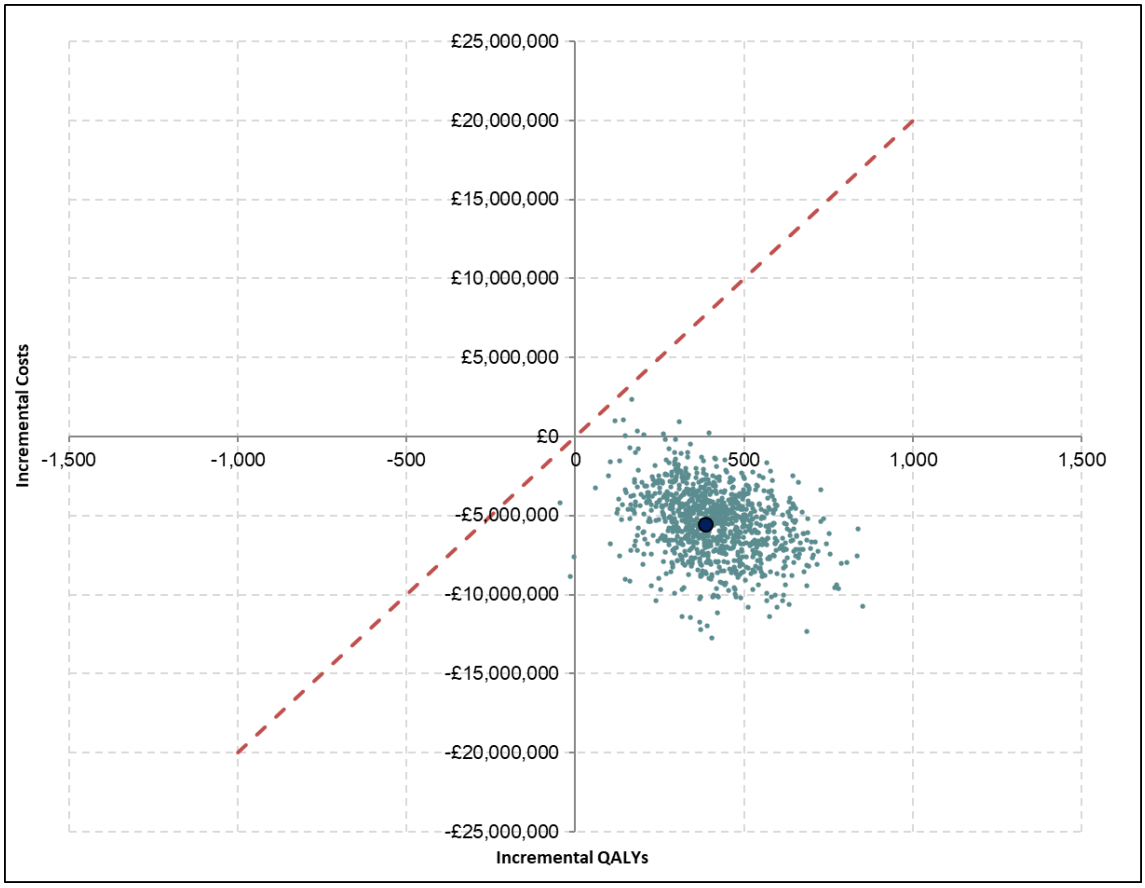
The results of the PSA for FMT colonoscopy are displayed in Table 5 and Figure 3 below. FMT colonoscopy is estimated to be cost saving 99% of the time and cost effective 100% of the time against VTP.

Table 5: PSA results (FMT colonoscopy versus VTP)

	FMT combined	**VTP**	**Incremental**
Cost per person	£6,906	£12,392	**-£5,486**
QALYs per person	1.82	1.41	**0.41**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**0.68**

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

Figure 3: Cost-effectiveness plane (FMT colonoscopy versus VTP)



FMT colonoscopy was found to be 100% cost saving and cost-effective when compared with both vancomycin and fidaxomicin.

The base case results were found to be robust for FMT NDT and FMT oral capsules with a 100% likelihood of cost savings and cost-effectiveness when compared with all three comparators.

FMT enema was found to be 100% cost saving and cost-effective when compared with vancomycin. It was found to be cost saving 99.6% and cost-effective 99.5% of the time when compared with fidaxomicin (figure 4). When compared with VTP, the likelihood of FMT enema being cost saving and cost-effective was estimated to be 96% and 97%, respectively (figure 5).

Figure 4: Cost-effectiveness plane (FMT enema versus fidaxomicin)

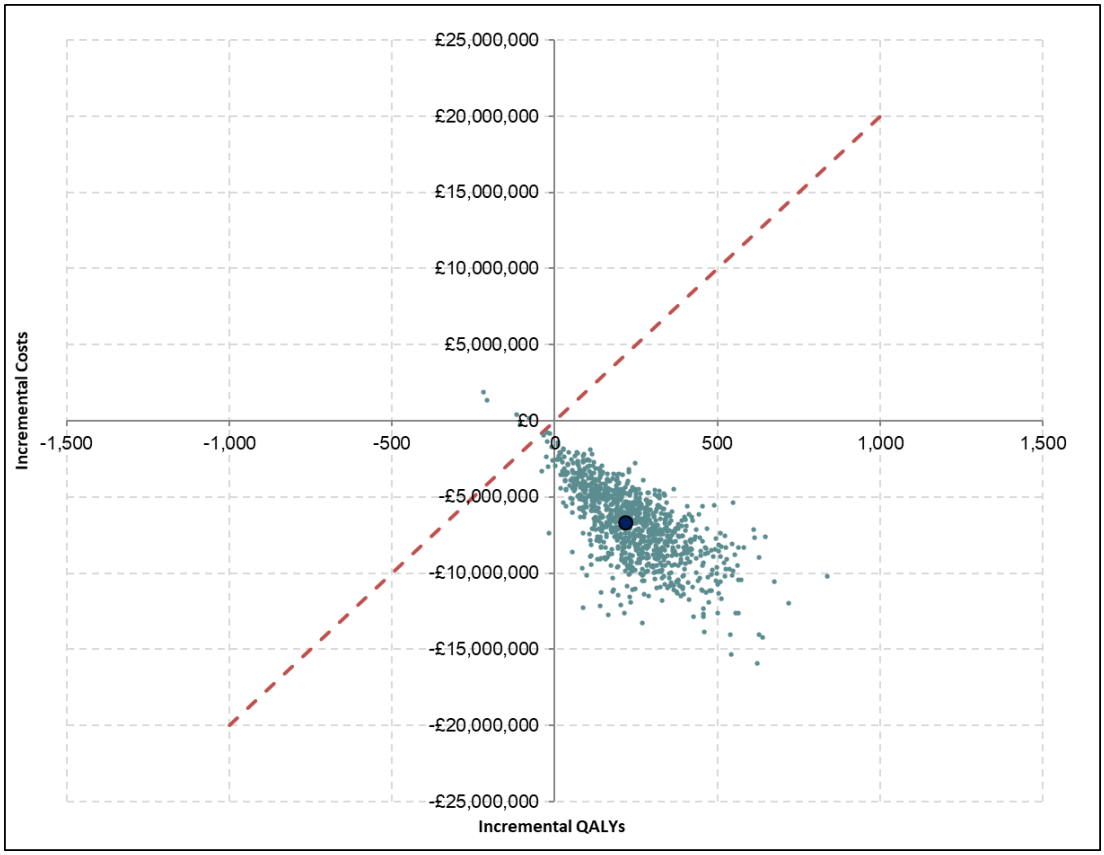
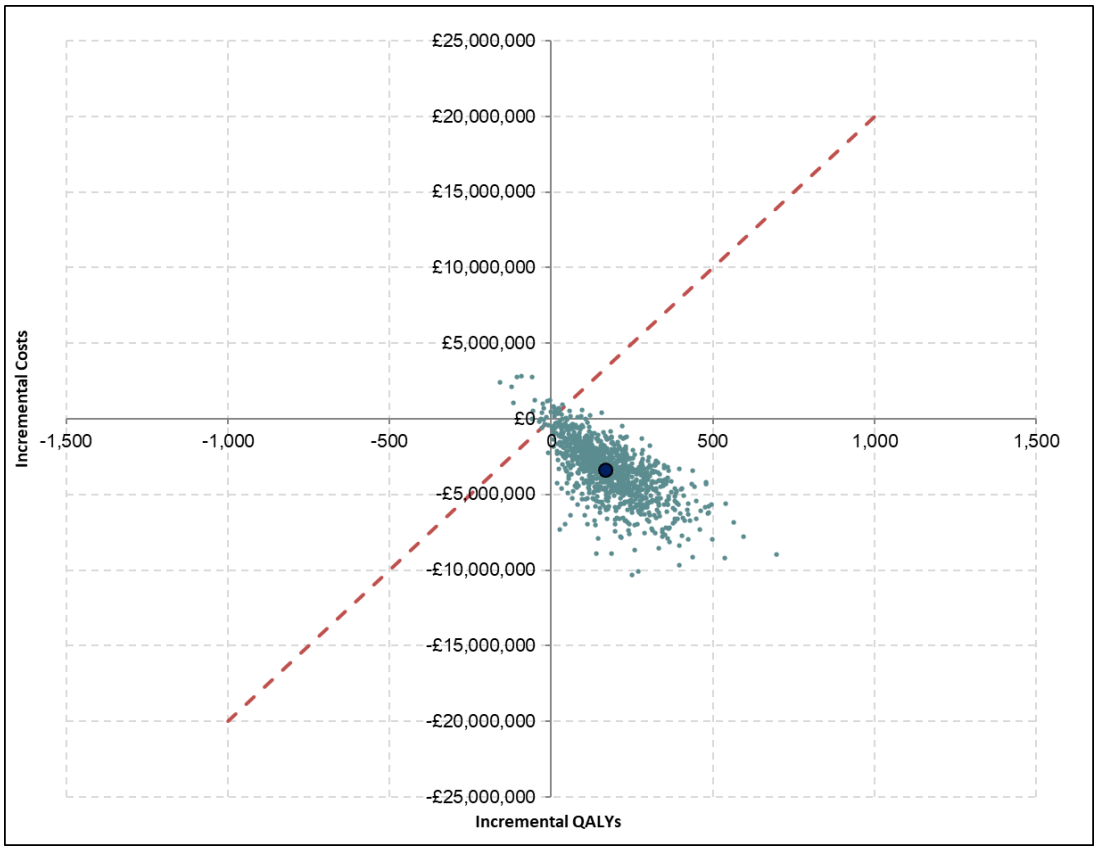


Figure 5: Cost-effectiveness plane (FMT enema versus VTP)



1.2 Scenario Analyses

SCENARIO 1

The results for use of pre-antibiotic treatment for subsequent FMT treatments against VTP (the second lowest cost and most clinically beneficial of all antibiotics included in the model) are presented in the table below.

Table 6: Incremental analysis (per person results) - Scenario 1

	∆Costs	∆QALYs	NHB	ICER
FMT colonoscopy	-£5,548	0.39	0.66	Dominant
FMT NDT	-£6,538	0.40	0.72	Dominant
FMT enema	-£3,357	0.17	0.34	Dominant
FMT oral capsule	-£8,379	0.39	0.80	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NDT, Nasoduodenal tube; NHB, Net health benefit; QALYs, Quality-adjusted life years.

SCENARIO 2

Subsequent treatment with VTP for all arms (intervention and comparator), if individuals have CDI after first cycle, was explored. There is reduced cost savings associated with all four FMT routes against antibiotics, compared with the base case analysis, though all routes of FMT remain cost saving.

Table 7: Incremental analysis (per person results) - Scenario 2

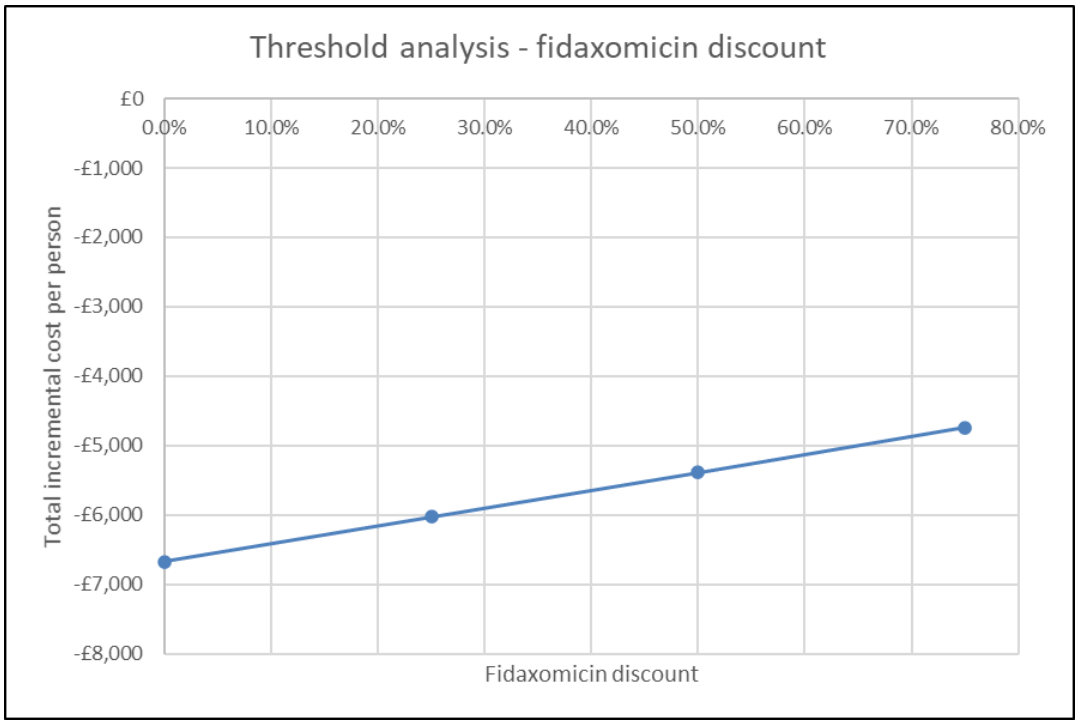
	∆Costs	∆QALYs	NHB per person	ICER
FMT vs vancomycin				
FMT colonoscopy	-£4,260	0.34	0.55	Dominant
FMT nasoduodenal tube	-£5,104	0.35	0.60	Dominant
FMT enema	-£3,440	0.18	0.35	Dominant
FMT oral capsule	-£6,747	0.34	0.68	Dominant
FMT vs fidaxomicin				
FMT colonoscopy	-£3,842	0.23	0.43	Dominant
FMT nasoduodenal tube	-£4,686	0.24	0.48	Dominant
FMT enema	-£3,022	0.07	0.22	Dominant
FMT oral capsule	-£6,329	0.23	0.55	Dominant
FMT vs VTP				
FMT colonoscopy	-£2,158	0.21	0.31	Dominant
FMT nasoduodenal tube	-£3,002	0.21	0.36	Dominant
FMT enema	-£1,338	0.04	0.11	Dominant
FMT oral capsule	-£4,645	0.21	0.44	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

SCNEARIO 3

Figure 6 below depicts the threshold analysis around fidaxomicin discount for FMT enema versus fidaxomicin. As the cost of fidaxomicin pack price decreases, cost savings with FMT enema, the least cost saving of all four FMT considered, also decreases. However, it remains cost saving at 75% discount.

Figure 6: Fidaxomicin threshold analysis



SCENARIO 4

A 12-month time horizon was applied and is associated with increased cost savings.

Table 8: Incremental analysis (per person results) - Scenario 4

	ΔCosts	ΔQALYs	NHB per person	ICER
FMT colonoscopy vs VTP				
Base case	-£5,551	0.39	0.66	Dominant
Scenario	-£11,214	1.02	1.58	Dominant
FMT NDT vs VTP				
Base case	-£6,541	0.40	0.72	Dominant
Scenario	-£12,377	1.03	1.65	Dominant
FMT enema vs VTP				
Base case	-£3,369	0.17	0.34	Dominant
Scenario	-£8,518	0.61	1.03	Dominant
FMT oral capsule vs VTP				
Base case	-£8,382	0.39	0.80	Dominant
Scenario	-£14,553	1.02	1.74	Dominant

SCENARIO 5

The base case analysis utilises inputs from Abdali (2020) for costing hospital stay for the index procedure. This was estimated to be 5 days for FMT treatment, and 10 days for antibiotic only treatment. Expert feedback suggests that these days are too long with same day discharge often taking place in practice and should not differ between the FMT and antibiotic only treatments. A scenario was run by setting both treatment arms to a 1-day hospital stay for the index treatment. This is associated with a reduction in estimated cost savings for all FMT routes against all three comparators but still remained cost-saving.

Table 9: Incremental analysis (per person results)

	∆Costs	∆QALYs	NHB	ICER
FMT vs vancomycin				
FMT colonoscopy	-£8,446	0.65	1.07	Dominant
FMT NDT	-£9,436	0.66	1.13	Dominant
FMT enema	-£6,263	0.43	0.75	Dominant
FMT oral capsule	-£11,277	0.65	1.21	Dominant
FMT vs fidaxomicin				
FMT colonoscopy	-£6,997	0.44	0.79	Dominant
FMT NDT	-£7,987	0.45	0.85	Dominant
FMT enema	-£4,815	0.22	0.46	Dominant
FMT oral capsule	-£9,829	0.44	0.93	Dominant
FMT vs VTP				
FMT colonoscopy	-£3,694	0.39	0.57	Dominant
FMT NDT	-£4,684	0.40	0.63	Dominant
FMT enema	-£1,512	0.17	0.24	Dominant
FMT oral capsule	-£6,525	0.39	0.71	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NDT, Nasoduodenal tube; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

YHEC
York Health Economics Consortium

GID-MT566 External Assessment Centre (EAC) Addendum on Economic Model Input Updates – Post Committee Meeting

1.1 Base Case Analysis

The base case analysis was updated following the committee meeting to include pre-antibiotic treatment for all FMT administrations (index and for repeat treatments if CDI persisted or reoccurred). The hospital stay for index treatment administration was also updated to 1 day for the FMT and antibiotic alone treatment arms following clinical opinion.

The results of the updated base case analyses are presented in the tables below.

Table 1: Summary total cost per person for comparators

	Costs	QALYs
FMT colonoscopy	£5,381	1.83
FMT NDT	£4,391	1.84
FMT enema	£7,572	1.61
FMT oral capsule	£2,550	1.83
Vancomycin	£13,824	1.18
Fidaxomicin	£12,375	1.39
VTP	£9,072	1.44

Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.

Table 2: Cost breakdown (per person results)

	Treatment	Hospitalisation (recurrence)	FC treatment	Total
FMT colonoscopy	£3,888	£1,349	£144	**£5,381**
FMT NDT	£3,055	£1,207	£129	**£4,391**
FMT enema	£2,380	£4,691	£501	**£7,572**
FMT oral capsule	£1,057	£1,349	£144	**£2,550**
Vancomycin	£497	£12,039	£1,287	**£13,824**
Fidaxomicin	£2,944	£8,520	£911	**£12,375**
VTP	£576	£7,675	£821	**£9,072**

Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.

Table 3: Incremental analysis (per person results)

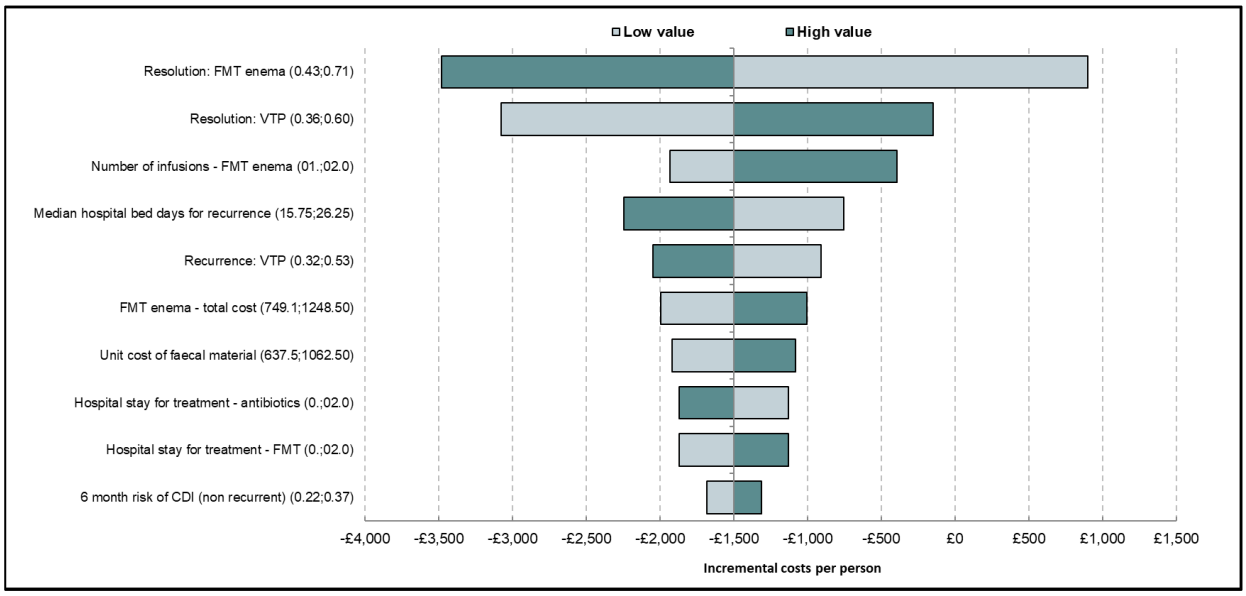
	∆Costs	∆QALYs	NHB	ICER
FMT vs vancomycin				
FMT colonoscopy	-£8,443	0.65	1.07	Dominant
FMT NDT	-£9,433	0.66	1.13	Dominant
FMT enema	-£6,251	0.43	0.74	Dominant
FMT oral capsule	-£11,274	0.65	1.21	Dominant
FMT vs fidaxomicin				
FMT colonoscopy	-£6,994	0.44	0.79	Dominant
FMT NDT	-£7,985	0.45	0.85	Dominant
FMT enema	-£4,803	0.22	0.46	Dominant
FMT oral capsule	-£9,826	0.44	0.93	Dominant
FMT vs VTP				
FMT colonoscopy	-£3,691	0.39	0.57	Dominant
FMT NDT	-£4,682	0.40	0.63	Dominant
FMT enema	-£1,500	0.17	0.24	Dominant
FMT oral capsule	-£6,522	0.39	0.71	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NDT, Nasoduodenal tube; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

DSA

The key drivers of the results for FMT enema (the least cost saving FMT) versus VTP are the resolution probability for FMT enema and VTP, followed by number of infusions of FMT required, where variation in FMT resolution could result in FMT being cost incurring. Resolution probability determines the proportion of the cohort in the recurrence CDI health state which is associated with large costs, and number of infusions impacts the total cost unit cost of administrating FMT.

Figure 1: Tornado plot for FMT enema versus VTP



Notes: FMT enema resolution lower and upper bound was calculated as 25% of the mean (43% and 71%). Lower and upper bound for hospital stay with index treatment was set to 0 and 2 days for both the FMT and antibiotic alone treatment arms.

PSA

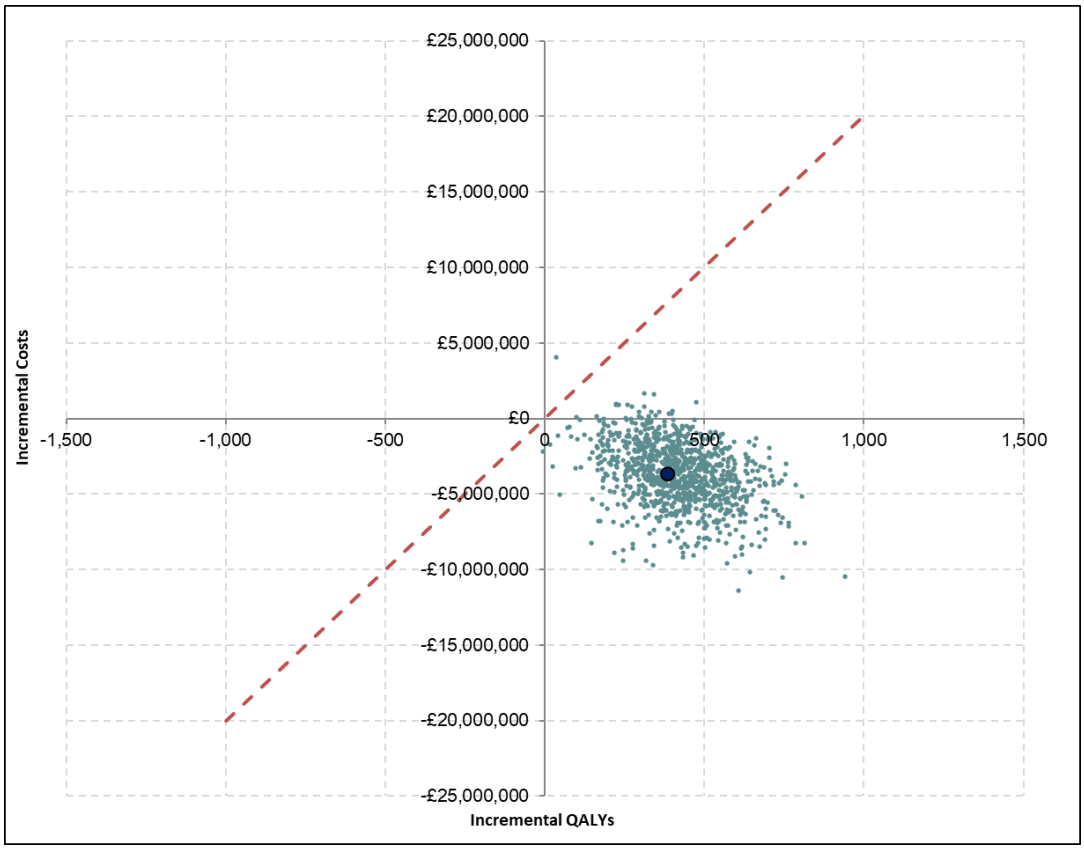
The results of the PSA for FMT colonoscopy are displayed in Table 4 and Figure 2 below. FMT colonoscopy is estimated to be cost saving 97.7% of the time and cost effective 99.9% of the time against VTP.

Table 4: PSA results (FMT colonoscopy versus VTP)

	FMT combined	**VTP**	**Incremental**
Cost per person	£5,385	£9,105	**-£3,721**
QALYs per person	1.82	1.41	**0.42**
ICER (using a threshold of £20,000 per QALY)			**Dominant**
NHB per person (using a threshold of £20,000 per QALY)			**0.60**

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

Figure 2: Cost-effectiveness plane (FMT colonoscopy versus VTP)



FMT colonoscopy was found to be cost saving 99.9% and 99.7% of the time when compared with vancomycin and fidaxomicin respectively. FMT was cost-effective 100% of the time (£20,000 threshold) when compared with both comparators.

The base case results were found to be robust for FMT oral capsules with a 100% likelihood of cost savings and cost-effectiveness when compared with all three comparators. We estimated FMT NDT was cost-saving 100% of the time when compared with vancomycin and fidaxomicin respectively. When compared with VTP, FMT NDT was estimated to be cost-saving 99% of the time. FMT NDT was estimated to be cost-effective 100% of the time against all three comparators.

FMT enema was found to be 99.5% cost saving and 99.9% cost-effective when compared with vancomycin. It was found to be cost saving and cost-effective 98% of the time when compared with fidaxomicin (figure 3). When compared with VTP, the likelihood of FMT enema being cost saving and cost-effective was estimated to be 80% and 91%, respectively (figure 4).

Figure 3: Cost-effectiveness plane (FMT enema versus fidaxomicin)

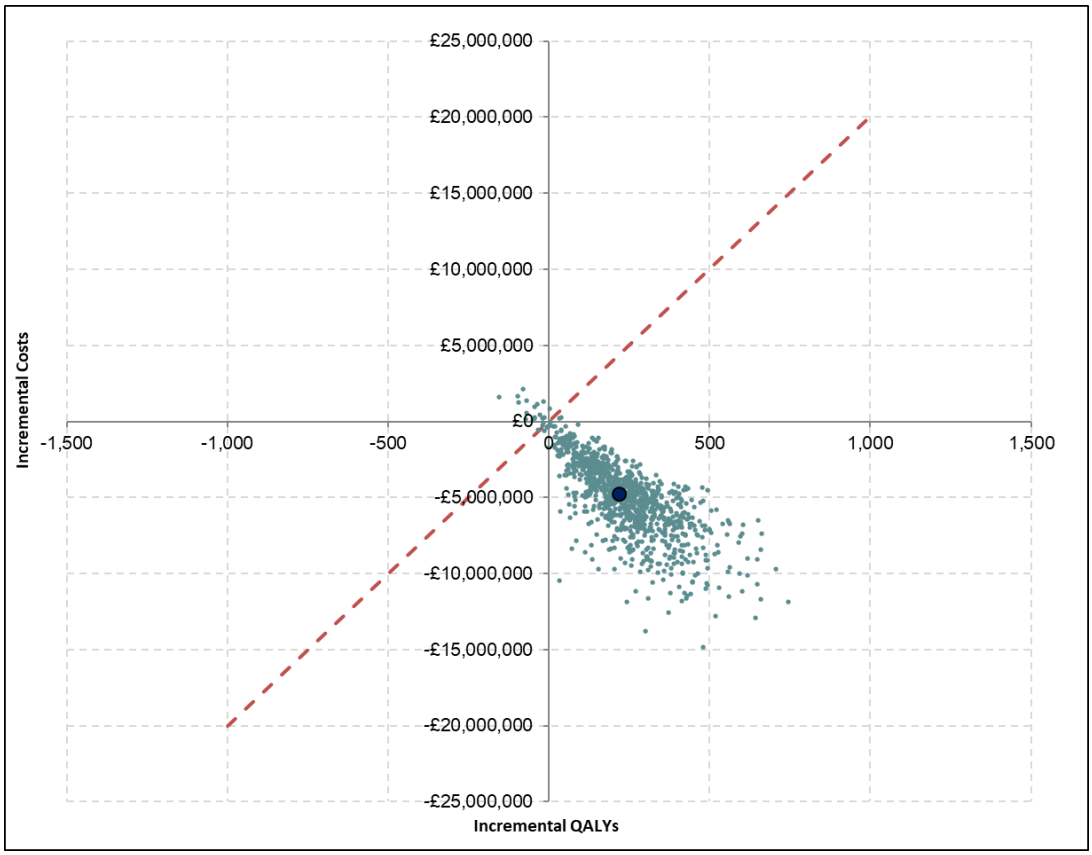
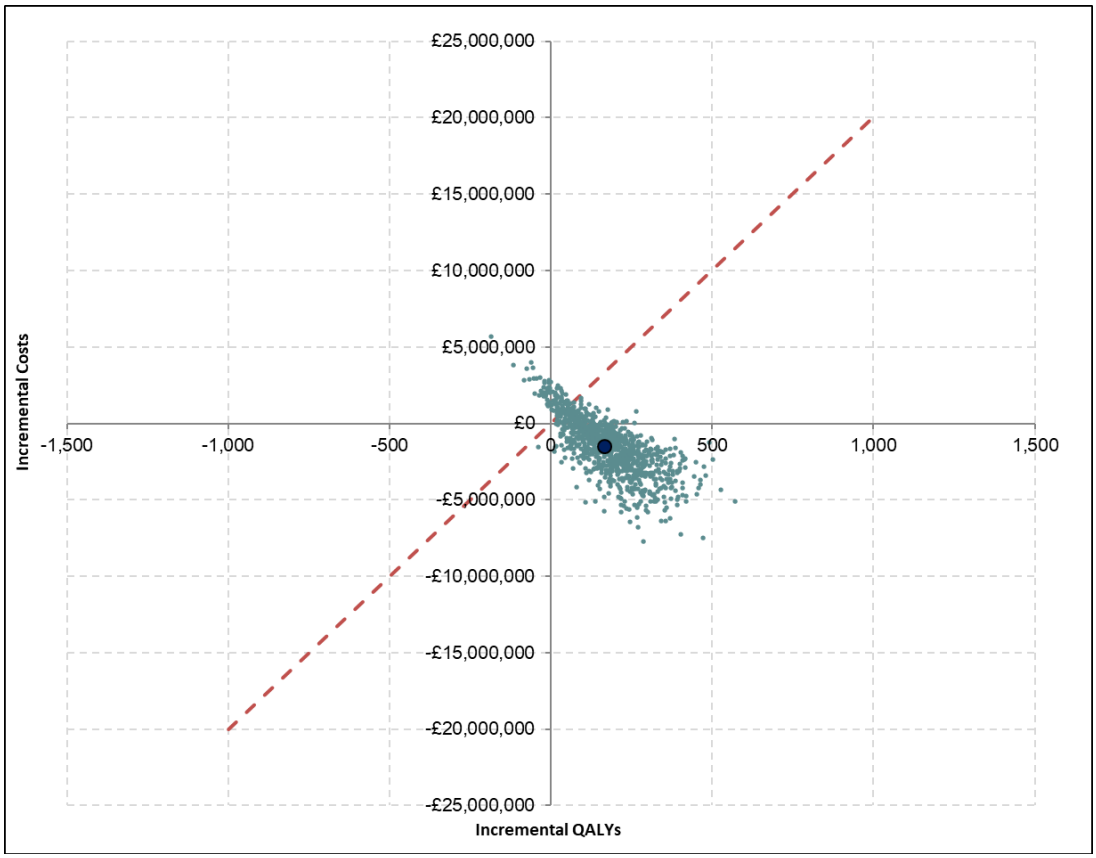


Figure 4: Cost-effectiveness plane (FMT enema versus VTP)



1.2 Scenario Analyses

SCENARIO 1

Subsequent treatment with VTP for all arms (intervention and comparator), if individuals have CDI after first cycle, was explored. There is reduced cost savings associated with all four FMT routes against antibiotics, compared with the base case analysis, with FMT enema incurring costs when compared with VTP but remains cost-effective at a threshold of £20,000 per QALY. It should be noted that the model programming for this scenario does not account for differential transition probabilities of recurrence for people who recovered following the initial FMT treatment and after subsequent VTP treatment. Therefore, the incremental costs savings are potentially higher than estimated.

Table 5: Incremental analysis (per person results) - Scenario 1

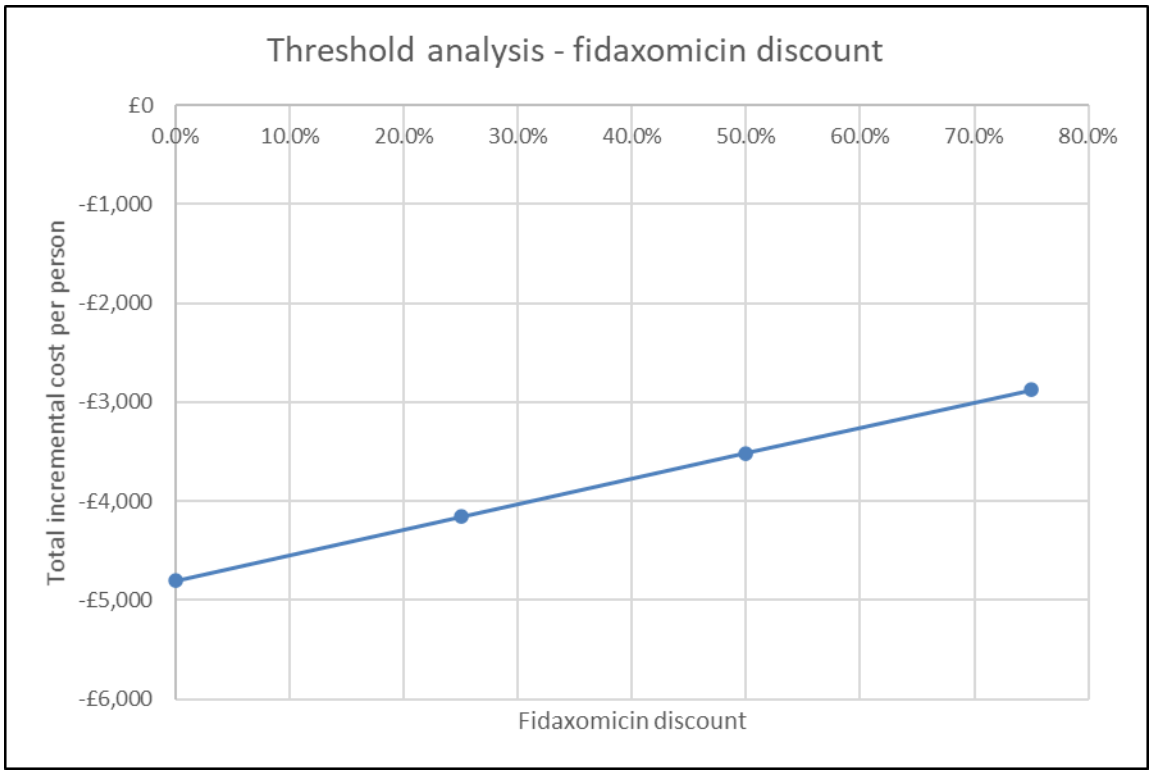
	∆Costs	∆QALYs	NHB per person	ICER
FMT vs vancomycin				
FMT colonoscopy	-£2,403	0.34	0.46	Dominant
FMT nasoduodenal tube	-£3,247	0.35	0.51	Dominant
FMT enema	-£1,584	0.18	0.26	Dominant
FMT oral capsule	-£4,890	0.34	0.58	Dominant
FMT vs fidaxomicin				
FMT colonoscopy	-£1,985	0.23	0.33	Dominant
FMT nasoduodenal tube	-£2,829	0.24	0.38	Dominant
FMT enema	-£1,165	0.07	0.13	Dominant
FMT oral capsule	-£4,472	0.23	0.46	Dominant
FMT vs VTP				
FMT colonoscopy	-£301	0.21	0.22	Dominant
FMT nasoduodenal tube	-£1,145	0.21	0.27	Dominant
FMT enema	£518	0.04	0.02	£12,359
FMT oral capsule	-£2,788	0.21	0.34	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

SCNEARIO 2

Figure 5 below depicts the threshold analysis around fidaxomicin discount for FMT enema versus fidaxomicin. As the cost of fidaxomicin pack price decreases, cost savings with FMT enema, the least cost saving of all four FMT considered, also decreases. However, it remains cost saving at 75% discount.

Figure 5: Fidaxomicin threshold analysis



SCENARIO 3

A 12-month time horizon was applied and is associated with increased cost savings.

Table 6: Incremental analysis (per person results) - Scenario 3

	ΔCosts	ΔQALYs	NHB per person	ICER
FMT colonoscopy vs VTP				
Base case	-£3,691	0.39	0.57	Dominant
Scenario	-£9,350	1.02	1.48	Dominant
FMT NDT vs VTP				
Base case	-£4,682	0.40	0.63	Dominant
Scenario	-£10,513	1.03	1.56	Dominant
FMT enema vs VTP				
Base case	-£1,500	0.17	0.24	Dominant
Scenario	-£6,642	0.61	0.94	Dominant
FMT oral capsule vs VTP				
Base case	-£6,522	0.39	0.71	Dominant
Scenario	-£12,689	1.02	1.65	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Faecal microbiota transplant for recurrent *Clostridioides difficile* infection

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations

1. The procedure

Faecal microbiota transplants (FMT) aim to restore a healthy gut microbiome in people who have recurrent or refractory *Clostridioides difficile* (*C. difficile*) infections. FMT is a medical procedure rather than a device that can be purchased. The treatment involves transferring intestinal bacteria and other microorganisms from healthy donor faeces into the gut of the recipient. It has been suggested that the procedure is termed intestinal microbiota transfer, instead of FMT, to increase its acceptability by patients, donors and healthcare workers (Craven et al. 2020).

Currently there is variation between institutions on how the FMT procedure is done, with differences in the quantification, preparation, and storage of donor material, as well as the mode of delivery into the intestine. FMT can be used as a fresh preparation, frozen or capsulised. According to joint British Society of Gastroenterology and Healthcare Infection Society guidelines, frozen FMT is considered preferable. To prepare a sample, donor faeces are taken and diluted with water or saline, then filtered to remove large particles. For frozen FMT, the suspension is then emulsified with a cryoprotectant and frozen and stored for up to 6 months in aliquots of filtered suspension at -80°C. Commonly used cryoprotectants are glycerol and trehalose. Frozen FMT is thawed at room temperature prior to use.

There are different routes of administration for frozen or fresh FMT:

- lower gastrointestinal route (rectal enema, colonoscopy or flexible sigmoidoscopy)
- upper gastrointestinal route (endoscopy or using a nasogastric tube, nasoduodenal tube or nasojejunal tube).

Alternatively, FMT can be given via oral capsules containing frozen FMT or freeze-dried (lyophilised) faecal material.

FMT administration via nasogastric tube and colonoscopy are the most used procedures in the NHS. Capsulised FMT is less commonly used. This is

because capsulised FMT options are more complicated to prepare than other methods of FMT preparation. Some capsule preparations may require taking a high number of large capsules in a single day. However, advanced preparations, such as lyophilised capsules, could reduce the number of pills needed.

Other variations in preparation and treatment procedures include whether samples are processed aerobically or anaerobically, bowel lavage prior to the procedure (Cold et al. 2021, Mullish et al. 2018), other treatments needs alongside FMT (such as prokinetics prior to upper gastrointestinal [GI] administration, or loperamide following lower GI delivery), and dose of delivery. People receiving FMT may also have a short course of antibiotics (vancomycin or fidaxomicin), prior to FMT treatment. It is recommended to have a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT to minimise any effects of antimicrobials on the FMT material.

In line with recommendations from the British Society of Gastroenterology and Healthcare Infection Society, a strict donor screening program should be in place for FMT. Before the procedure, healthy donors (who can be family members or unrelated) are screened using a questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota. Donors are also restricted by age and body mass index (BMI; aged 18 to 60 years with a BMI between 18 and 30 kg/m^2). Blood and stool screening is also done to check for pathogens to ensure there are no transmissible blood or gut infections. When using frozen FMT, it is recommended that the stool is stored in 'quarantine' until donors have successfully completed a donor health questionnaire and laboratory screening assays both before and after the period of stool donation. When using fresh FMT, it is recommended that a repeat health questionnaire is done at the time of each stool donation, with donor health questionnaires and laboratory screening being repeated regularly. It is also recommended to do PCR testing for SARS-CoV-2 using nasopharyngeal swab testing and checking genetic material in donor stool.

FMT must be manufactured in accordance with Medicines and Healthcare products Regulatory Agency (MHRA) guidance for human medicines regulation. When FMT is supplied on a named patient basis, within a single organisation, a pharmacy exemption may be used, subject to ensuring proper governance and traceability. Before establishing an FMT service, NHS centres are legally required to seek advice from the MHRA and, if necessary, obtain licences to process, distribute and carry out FMT.

2. Proposed use of the technology

2.1. Disease or condition

The aim of this evaluation is to review the use of faecal microbiota transplant (FMT) in adults with a refractory *C. difficile* infection or a recurrent episode of *C. difficile* infection who have had 2 or more previous episodes.

NICE's evidence summary on *C. difficile* infection: risk with broad-spectrum antibiotics states that a *C. difficile* infection occurs when the other harmless bacteria in the gut are disrupted (for example, by taking antibiotics) or when the immune system is compromised, allowing the numbers of *C. difficile* bacteria to increase to high levels. Aside from broad-spectrum antibiotics, other factors increase the risk of *C. difficile* infection including older age, underlying morbidity, hospitalisation, exposure to other people with the infection, long duration of antibiotic treatment, taking multiple antibiotics concurrently or taking multiple antibiotic courses, use of proton pump inhibitors and inflammatory bowel disease.

C. difficile infection symptoms can range depending on the severity of the infection. Symptoms of mild *C. difficile* infections include watery diarrhoea, abdominal cramps, nausea and dehydration. In more severe cases the infection can cause bloody diarrhoea and fever. In a few people *C. difficile* infection can lead to pseudomembranous colitis, sepsis, toxic megacolon, colonic rupture, and death. The risk of death increases in those with multiple comorbidities.

2.2. Patient group

NHS Trusts in England reported a total of 12,503 cases of *C. difficile* infection during 2020/2021. While the overall incidence (22.2 per 100,000 population) has decreased since the start of mandatory surveillance in 2008 (108 per 100,000) (Public Health England 2021a), the rate of hospital-onset *C. difficile* infection cases has increased each year from 2018 (12.2 per 100,000) to March 2021 (15.4 per 100,000) (Public Health England 2021b).

Approximately 21% of people with *C. difficile* infection in the UK develop recurrent infection (Finn et al. 2021), which is associated with higher mortality (Olsen et al. 2015), greater morbidity, longer hospital stays, and higher resource use and costs (Wilcox et al. 2017). UK experts estimate that approximately 450 to 500 people will have 2 or more recurrent episodes of *C. difficile* infection every year (EAC correspondence log).

2.3. Current management

First-line treatment for a *C. difficile* infection involves rehydration and antibiotic therapy. Clinical responses are generally favourable, but some people have recurrent, relapsing, or refractory *C. difficile* infections. For these people, further courses of antibiotics are used.

There is a lack of clear distinction between recurrent, refractory and relapsing *C. difficile* infections. NICE's guideline on *C. difficile* infection: antimicrobial prescribing states a relapsing infection is more likely to be with the same *C. difficile* strain whereas a recurrent infection is more likely to be with a with a different *C. difficile* strain. However, the guideline acknowledges that there is no agreement on the precise definition of relapse and recurrence, and it is difficult to distinguish between them in clinical practice as tests are not routinely done for distinction according to clinical experts. The joint British Society of Gastroenterology and Healthcare Infection Society guidelines also states that there is little consensus on the definition of refractory *C. difficile*, with some studies using the terms refractory and recurrent interchangeably (as well as other terms such as salvage therapy). As a result, the quality of

evidence for the utility of FMT in refractory cases of *C. difficile* is lower than for recurrent *C. difficile*.

NICE's guideline on *C. difficile* infection: antimicrobial prescribing says offer an oral antibiotic to treat suspected or confirmed *C. difficile* infection in adults (oral metronidazole, vancomycin or fidaxomicin based on recommendations in table 1 below). It is also recommended to manage fluid loss and symptoms associated with suspected or confirmed *C. difficile* infection, but not to offer antimotility medicines such as loperamide.

Table 1: Antibiotics for adults aged 18 years and over (taken from NICE's guideline on C. difficile infection: antimicrobial prescribing)

Treatment	**Antibiotic, dosage and course length**
First-line antibiotic for a first episode of mild, moderate or severe *C. difficile* infection	Vancomycin: 125 mg orally four times a day for 10 days
Second-line antibiotic for a first episode of mild, moderate or severe *C. difficile* infection if vancomycin is ineffective	Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for *C. difficile* infection if first- and second-line antibiotics are ineffective	Seek specialist advice. Specialists may initially offer: Vancomycin: Up to 500 mg orally four times a day for 10 days With or without Metronidazole: 500 mg intravenously three times a day for 10 days
Antibiotic for a further episode of *C. difficile* infection within 12 weeks of symptom resolution (relapse)	Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for a further episode of *C. difficile* infection more than 12 weeks after symptom resolution (recurrence)	Vancomycin: 125 mg orally four times a day for 10 days Or Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for life-threatening *C. difficile* infection	Seek urgent specialist advice, which may include surgery. Antibiotics that specialists may initially offer are: Vancomycin: 500 mg orally four times a day for 10 days With Metronidazole: 500 mg intravenously three times a day for 10 days

NICE's guideline on *C. difficile* infection: antimicrobial prescribing recommends considering a FMT for a recurrent episode of *C. difficile* infection in adults who have had 2 or more previous episodes. NICE's interventional procedures guidance on FMT for recurrent *C. difficile* infection states that current evidence on the efficacy and safety of FMT for recurrent *C. difficile* infection is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit.

2.4. Proposed management with the technology

FMT is intended for adults with a refractory *C. difficile* infection or a recurrent episode of *C. difficile* infection who have had 2 or more previous episodes. The aim of the procedure is to treat the infection with transplanted gut microbiota instead of prescribing further courses of antibiotics. In the NHS this procedure is currently done in a small number of specialist centres, within secondary care. The University of Birmingham Microbiome Treatment Centre is the first MHRA licensed facility in the UK to provide FMT for people with recurrent and refractory *C. difficile* infection. It is responsible for the largest number of FMT administrations in NHS hospitals.

FMT procedures in the NHS are generally carried out as an inpatient or day case procedure in hospital. The setting and hospital department varies depending on the route of delivery. If FMT is delivered using a nasogastric (or other nasoenteric) tube, the procedure is usually done by a healthcare professional in a hospital ward or in a day case unit. If FMT is delivered using endoscopy, a trained endoscopist is required and it is usually done in an endoscopy unit. Capsulised FMT can also be done as a less invasive option and does not need specialist care or the use of an endoscopy unit. It is recommended that multidisciplinary teams are formed to deliver the FMT service.

3. The decision problem

NICE commissioned the EAC to perform a systematic review of the clinical and economic evidence, alongside a cost-consequence analysis, for the use

of FMT in people with recurrent or refractory *C. difficile* infection. Since FMT is a medical procedure without a specific manufacturer there is no company submission, and the case for adopting FMT in the NHS has been reviewed solely by the EAC.

The decision problem is described in the scope in Appendix D. The EAC did not propose any variation to the decision problem (see table 1 of the EAC's assessment report). However, the EAC said that some outcomes were included with more detail than specified in the scope. It also found no evidence found on patient acceptability, health related quality of life, or resource use such as NHS resource usage and length of hospital stay. The EAC also defined the recurrent *C. difficile* infection population as those with 2 or more episodes at trial baseline for their literature search.

4. The evidence

The EAC undertook a literature search (see section 4.1 and Appendix A of the EAC's assessment report), to identify randomised controlled trials (RCTs) evaluating the efficacy and safety of FMT. This included any RCTs reporting FMT by any route of delivery, against NICE recommended comparators, to treat recurrent *C. difficile* infection in those with at least 2 episodes of *C. difficile* infection at trial inclusion. In total 5 RCTs (reported in 13 papers) were included that were relevant to the decision problem. The 5 main publications were: Cammarota et al. 2015; Hota et al. 2017; Hvas et al. 2019; Rode et al. 2021 and van Nood et al. 2013.

4.1. Summary of evidence of clinical benefit

Trial design and quality

On the 5 included RCTs, 2 were 2-arm RCTs comparing FMT to vancomycin taper pulse (VTP; Cammarota et al. 2015, Hota et al. 2017). Two of the trials had 3 arms with Hvas et al. (2019) randomising people between FMT, vancomycin and fidaxomicin treatments, and van Nood et al. (2013) randomising people between FMT, vancomycin only and vancomycin with

bowel lavage. Rode et al. (2021) also had 3-arms but is considered here as a 2-arm trial as rectal bacteriotherapy was not an eligible comparator.

The included studies had relatively small sample sizes with a median of 39 and a range of 27 (Rode et al. 2021) to 64 adults (Hvas et al. 2019). This is in part due to 4 of the trials being terminated early, 2 for greater than expected treatment effect at interim analysis (Cammarota et al. 2015 and van Nood et al. 2013), 1 for futility of FMT compared with the antibiotic comparator (Hota et al. 2017), and 1 for futility of rectal bacteriotherapy compared with the antibiotic comparator (Rode et al. 2021). Only Hvas et al. (2019) completed after recruiting the target number of people.

The eligibility criteria were relatively similar between trials and included adults with symptomatic *C. difficile* infection recurrence confirmed by positive diagnostic test for CD toxin (a toxin produced by *C. difficile*), and after at least 1 prior failed course of antibiotics. However, 3 trials (Cammarota et al. 2015, Hota et al. 2017 and van Nood et al. 2013) included a mixed number of *C. difficile* infection recurrences, including those with a first recurrence of *C. difficile* infection. The EAC note however that those with a first recurrence appear to be the minority of cases in these trials. Rode et al. (2021) also recruited those with any *C. difficile* infection recurrence but stratified randomisation according to the number of prior recurrences allowing extraction of the multiple recurrence subgroup. No trials reported on the effectiveness of FMT to treat people with refractory *C. difficile* infection, although this could be a result of the difficulties in defining refractory *C. difficile* infection as discussed in section 2.3.

The included studies used different routes of FMT administration. Two trials assessed FMT delivered via enema (Hota et al. 2017 and Rode et al. 2021), 1 using colonoscopy (Cammarota et al. 2015), 1 using nasoduodenal tube (NDT; van Nood et al. 2013) and 1 using mixed routes (colonoscopy as first preference or by nasojejunal tube [NJT] in those unable to have colonoscopy; Hvas et al. 2019). No included trials evaluated FMT delivered by capsule, nasogastric tube (NGT), or flexible sigmoidoscopy.

There was variation in the number of times FMT was given (the number of infusions), ranging from 1 (Hota et al. 2017), 1 to 2 (van Nood et al. 2013 and Hvas et al. 2019), 1 to 3 (Rode et al. 2021) or up to 4 infusions (Cammarota et al. 2015). FMT samples used were from fresh product in 3 trials (Cammarota et al. 2015, Hota et al. 2017 and van Nood et al. 2013) or frozen product in 2 trials (Hvas et al. 2019, Rode et al. 2021). All trials gave vancomycin prior to FMT treatment, ranging from 3 days (Cammarota et al. 2015) to 14 days of treatment (Hota et al. 2017). Clinical experts advised that pre-treatment with short-course antibiotics (stopped 24 to 48 hours before FMT treatment) is not standard of care in the UK but is common due to the hospitalised status of the people needing FMT. Bowel lavage was also done prior to FMT in 3 trials (Cammarota et al. 2015, Hvas et al. 2019 and van Nood et al. 2013), although clinical experts advised that this is not routinely done in the UK.

The EAC acknowledged weaknesses in the evidence base. None of the studies were done in a UK NHS setting and the trial populations (in all treatment arms) appear to have fewer comorbidities and were less likely to be hospitalised than the population eligible UK population. The van Nood et al. (2013) study also used a higher dose of vancomycin (500 mg, 4 times a day, for 14 days) than would be used in the NHS (125 mg or 250 mg, 4 times a day). The EAC assessed the risk of bias (using Cochrane risk of bias 2.0 tool) and found that 4 trials have a high risk of bias (Cammarota et al. 2015, Hota et al. 2017, Hvas et al. 2019 and Rode et al. 2021) due to the open label design and measurement of at least one subjective outcome without systematic microbiological confirmation. Cammarota et al. (2015) and Rode et al. (2021) were judged to have an increased risk of bias due to the measurement of outcomes at different timepoints between trial arms. van Nood et al. (2013) was assessed as having some concerns due to its open label design.

Overall, the EAC stated that the results from the evidence base are difficult to interpret due to the small number of people evaluated and the between-study heterogeneity relating to the methods of FMT delivery, the number of infusions and differences in outcome measurements and timepoints.

Resolution of *C. difficile* infection

Four trials found FMT to be significantly better than vancomycin (Cammarota et al. 2015, Hvas et al. 2019, Rode et al. 2021 and van Nood et al. 2013) or fidaxomicin (Hvas et al. 2019), with *C. difficile* infection resolution being achieved in 57% (Rode 2021) to 94% (van Nood et al. 2013) of those having FMT (when any number of infusions were considered). A single FMT infusion was found to be superior to vancomycin in 2 trials (Hvas et al. 2019 and van Nood et al. 2013) and fidaxomicin in 1 trial (Hvas et al. 2019). Cammarota et al. (2015) also reported a difference after 1 infusion but did not state whether this was statistically significant. However, Hota et al. (2017) showed less *C. difficile* infection resolution in the FMT group compared to VTP (43.8% compared to 58.3%, respectively), although no statistical significance was reported.

C. difficile infection recurrence

Recurrence of *C. difficile* infection following treatment was reported by 4 trials. Hota et al. (2017) reported comparable *C. difficile* infection recurrence after FMT (by enema, 56.2%) when compared to VTP (41.7%). Cammarota et al. (2015), Hvas et al. (2019) and van Nood et al. (2013) reported lower *C. difficile* infection recurrences to those having FMT (range of 6% to 10%) compared with those receiving antibiotics (vancomycin range of 62% to 69%, fidaxomicin 46%). No trials stated whether observed differences were statistically significant.

C. difficile infection associated diarrhoea

Two trials reported data for *C. difficile* infection associated diarrhoea, both of which showed a reduction following FMT treatment. Hota et al. (2017) found that those in the FMT (by enema) group had a mean (SD) of 0.8 (0.8) days diarrhoea compared with 1.7 (0.4) in those receiving VTP by 120 days following the end of treatments. Hvas et al. (2019) found FMT (by colonoscopy or NJT) was significantly better than fidaxomicin and vancomycin for eliminating diarrhoea caused by *C. difficile* infection, with an absence of

diarrhoea in more people at both 1-week follow-up (100% in FMT group compared to 79% and 69% for fidaxomicin and vancomycin groups, respectively) and 8 weeks follow-up (92% in FMT group compared to 54% and 31% for fidaxomicin and vancomycin groups, respectively).

Mortality and adverse events

Comparative mortality was reported by 4 trials (Cammarota 2015, Hota 2017, Hvas 2019 and van Nood 2013), none of which reported a statistically significant difference between FMT and comparator antibiotics.

The data suggests that FMT, regardless of infusion modality used, leads to short term gastrointestinal side effects. These procedural adverse events were reported by 4 trials (Cammarota et al. 2015, Hota et al. 2017, Hvas et al. 2019 and van Nood et al. 2013). The most common adverse events after FMT treatment include diarrhoea, bloating with abdominal cramps and abdominal pain or cramps. These symptoms lasted (where reported) between 3 hours (van Nood et al. 2013) and 12 hours (Cammarota et al. 2015), with those in the Hvas et al. (2019) trial described as ‘transient’.

A serious adverse event happened shortly after FMT in one person in the Hvas et al. (2019) trial. This involved sepsis-like symptoms after an uncomplicated FMT by colonoscopy and resolved without hospitalisation within 24 hours.

Table 2:Clinical evidence summary

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Cammarota 2015 2-arm RCT	39 adults with laboratory confirmed recurrent CDI Mean age (years): FMT: 71 Control: 75 Male (%): FMT: 40 Control: 42 Italy	Intervention: FMT via colonoscopy (preceding short regimen vancomycin and bowel cleaning) n=20 Comparator: Vancomycin oral taper regimen (125 mg QID 10 days, with pulse: 125 to 500 mg a day every 2 to 3 days, for at least 3 weeks) n=19	Primary: resolution of diarrhoea associated with CDI 10 weeks after the end of treatments Secondary: negative CDI stool toxin at 5 and 10 weeks after the end of the treatments, CDI recurrence after treatment, time to CDI recurrence from end of treatment, immediate AEs, overall AEs, treatment failure leading to downstream interventions (5 to 14 months	Resolution of CDI: FMT: 13/20 (65%; after single infusion) and 18/20 (90%; multiple FMT infusions in 6 people) VTP: 5/19 (26%) (p<0.0001 VTP vs multiple FMT infusions) CDI stool toxin negative (10 weeks after end of treatment): FMT: 18/20 (90%) VTP: 5/19 (26%) CDI recurrence (10 weeks after end of treatment): FMT: 2/20 (10%) VTP: 12/19 (63%) Time to CDI recurrence from end of treatment: FMT: 5 to 7 days VTP: 4 to 21 days	None	Part funded by the Catholic University of Rome	Study terminated early after a planned 1-year interim analysis showed a significantly higher efficacy for FMT over VTP. Small sample size (n=39) is a limitation, a priori power calculation estimated 82 people would be needed to demonstrate significant difference in primary outcome. Population may have fewer

			after the end of treatments), mortality	CDI recurrence requiring 1 to 3 further courses of antibiotics: FMT: 2 (number assessed not reported) VTP: 7/9 (78%) All-cause mortality (10 weeks after treatment): FMT: 2/20 (10%) VTP: 2/19 (11%) Immediate AEs: FMT: 19/20 (94%). Consisted of diarrhoea (19/20, 94%), bloating and abdominal cramping (12/20, 60%), all resolving within 12 hours. VTP: None Overall AEs: None reported during remainder of trial			comorbidities than a UK population, but most were hospitalised at inclusion (75% for FMT and 84% for VTP) and were predominantly older (mean age 73 years).
Hota 2017 2-arm RCT	30 adults with laboratory confirmed recurrent CDI and a history of ≥2 episodes of CDI Mean age (years): FMT: 75.7 Control: 69.6	Intervention: FMT delivered by enema (preceded by long course antibiotics) n=16 Comparator: vancomycin oral taper regimen (125 mg QID 14	Primary: recurrence of symptomatic toxin-confirmed CDI within 120 days of starting the intervention Secondary: early recurrence of symptoms within 14 days,	Recurrence of CDI (120 days; lab confirmed): FMT: 9/16 (56.2%) VTP: 5/12 (41.7%) No one in either arm had recurrence of symptomatic CDI without laboratory confirmation at 14 days or 120 days Resolution of CDI (by 120 days): FMT: 7/16 (43.8%)	2 withdrawals in control group; one to seek FMT elsewhere and another due to repeated protocol non-compliance	Physicians Services Incorporated Foundation; Public Health Ontario; University of Toronto Department of Medicine	The study was terminated at the interim analysis after randomising 30 people due it being unlikely to find a difference between treatments. The small sample size of

	Male (%): FMT: 31 Control: 33 Canada	days, with pulse: 125 mg BID 1 week, 125 mg QID 1 week, 125 mg every 2 days 1 week, 125 mg every 3 days 1 week) n=14	relapse within 120 days (same strain of CD), days diarrhoea, mortality, CDI-associated hospitalisation, AEs and SAEs	VTP: 7/12 (58.3%) Symptom resolution using standardised questionnaires: FMT: 7/16 (43.8%) VTP: 7/12 (58.3%) Time to CDI recurrence from administration of intervention: FMT: 9 days VTP: 35 days Days of diarrhoea: FMT: Mean 0.8 (SD 0.8) VTP: Mean 1.7 (SD 0.4) No immediate AEs after FMT or during antibiotic use were reported. Early AEs (0 to 7 days after treatment) FMT: 55 separate events VTP: 36 events Late AEs (7 to 14 days after treatment): FMT: 33 events VTP: 59 events		Integrating Challenge Grant; University Health Network; and Sinai Health System (in kind)	this trial (n=30) is a limitation, a priori power calculation estimated 114 people would be needed to demonstrate a significant difference in the primary outcome. Prior to FMT a longer antibiotic pre-treatment (125 mg QID for 14 days) was given then would be expected in the UK.

				No CDI recurrence needing hospitalisation, or all-cause mortality in either group			
Hvas 2019 3-arm RCT	64 adults with recurrent CDI documented within 8 weeks of stopping anti-CDI treatment and at least 1 prior treatment for CDI. Mean age (years): FMT: 68 Fidaxomicin: 64 Vancomycin: 72 Male (%): FMT: 17 Fidaxomicin: 46 Vancomycin: 31 Denmark	Intervention: FMT via colonoscopy or NJT (preceded by short course antibiotics and bowel lavage (colonoscopy only)) n=24 Comparator: fidaxomicin (200 mg BID 10 days) or vancomycin (125 mg QID 10 days). n=24 (fidaxomicin) and n=16 (vancomycin)	Primary: combined clinical resolution and a negative PCR result for CD toxin 8 weeks after the allocated treatment. Secondary: clinical resolution at week 8, negative CD test at week 8, combined clinical resolution and negative CD test result at week 1, clinical resolution at week 1, negative CD test result at week 1, CDI-associated diarrhoea, mortality, immediate	Clinical and microbiological resolution of CDI (1 week after treatment): FMT: 13/24 (54%) Fidaxomicin: 9/24 (38%; p=0.25 vs FMT) Vancomycin: 2/16 (13%; p=0.01 vs FMT) Clinical and microbiological resolution of CDI (8 weeks after treatment): FMT: 17/24 (71%) Fidaxomicin: 8/24 (33%; p=0.009 vs FMT) Vancomycin: 3/16 (19%; p=0.001 vs FMT) Clinical resolution without the need for rescue FMT or colectomy (1 week): FMT: 21/24 (88%) Fidaxomicin: 14/24 (58%; p=0.02 vs FMT) Vancomycin: 6/16 (38%; p=0.002 vs FMT) Clinical resolution without the need for rescue FMT or colectomy (8 weeks): FMT: 22/24 (92%)	None	Danish Regions grant	Small sample size of trial (n=64) is a limitation. People included in study likely to have fewer comorbidities than UK population. Most people were not hospitalised at inclusion (6/64 (9%).

			AEs, overall AEs.	Fidaxomicin: 10/24 (42%; p=0.0002 vs FMT) Vancomycin: 3/16 (19%; p<0.0001 vs FMT) <u>Recurrence of CDI:</u> FMT: 2/24 (8%) Fidaxomicin: 11/24 (46%) Vancomycin:11/16 (69%) <u>CDI-associated diarrhoea (1 week):</u> FMT: 24/24 (100%) Fidaxomicin:19/24 (79%; p=0.02 vs FMT) Vancomycin 11/16 (69%; p=0.003 vs FMT) <u>CDI-associated diarrhoea (8 weeks):</u> FMT:22/24 (92%) Fidaxomicin 13/24 (54%; p=0.003 vs FMT) Vancomycin: 5/16 (31%; p<0.0001 vs FMT). <u>Procedural AEs:</u> Immediate AEs in 10/24 FMT group (42%) but were transient. 1 person had a SAE with 24 hours of FMT which resolved in 24 hours without hospitalisation. AEs during antibiotic			

				treatment were not reported separately from all events by the end of follow up. No statistical difference in those experiencing at least 1 AE or SAE between 2 days and 8 weeks after intervention. No mortality reported during follow up.			
Rode 2021 3-arm RCT	98 adults with laboratory-confirmed recurrent CDI within 90 days after a former episode of CDI and have received at least one course of antibiotic Extraction of multiple (≥2) recurrence group only Mean age (years): FMT: 75 Control (VTP): 76 Male (%): FMT: 41	Intervention: FMT via enema (preceded by long course antibiotics) n=14 Comparator: vancomycin (standard or extended taper) n=13 Rectal bacteriotherapy not eligible for this review, no further details are reported	Primary: clinical cure of CDI, defined as absence of diarrhoea or diarrhoea with a negative CD test, within 90 days after end of treatment Secondary: (not reported for extracted subgroup)	Clinical cure of CDI: FMT:8/14 (57%; after 1 to 3 FMT infusions) VTP: 6/13 (46%) No mortality related to CDI in FMT group. Outcome not reported for vancomycin subgroup with multiple (≥2) CDI recurrences.	None	Hvidovre Hospital; The Research fund of the Department of Infectious Disease, Hvidovre Hospital; Region Sjælland; The Christenson-Cesons Family Foundation; Ministeriet Sundhed Forebygge lse; The Research Council for Naestved/ Ringsted/	Study terminated due to futility of rectal bacteriotherapy. A limitation is the small subgroup of people with ≥2 recurrences (n=27). Data could only be extracted for 1 outcome. Those having FMT were given a longer pre-treatment of vancomycin (125 mg QID for 7 to 14 days) which may be longer than that seen in the UK.

	Control (VTP): 55 Denmark					Slagelse Hospital	
van Nood 2013 3-arm RCT	43 adults presenting with CDI relapse after ≥1 course of antibiotic therapy Mean age (years): FMT: 73 Vancomycin: 66 Vancomycin with bowel lavage: 69 Male (%): FMT: 50 Vancomycin: 46 Vancomycin with bowel lavage: 77 The Netherlands	Intervention: FMT delivered by NDT (preceded by short course antibiotics and bowel lavage) n=17 Comparator: vancomycin (500 mg QID 14 days) or vancomycin with bowel lavage n=13 in each group	Primary: cure without relapse within 10 weeks after the initiation of therapy Secondary: cure without relapse after 5 weeks, CDI recurrence, treatment failure leading to downstream interventions, mortality, immediate AEs, overall AEs	Clinical cure of CDI: FMT (single infusion): 13/16 (81%) After 1 to 2 FMT infusions: 15/16 (94%) Vancomycin only: 4/13 (31%) Vancomycin with bowel lavage: 3/13 (23%) p<0.01 for both comparisons after 1 infusion and p<0.001 for 1 to 2 infusions CDI recurrence (after 5 weeks): FMT: 1/16 (6%) Vancomycin only: 8/13 (62%) Vancomycin with bowel lavage: 7/13 (54%) Treatment failure leading to downstream interventions: FMT: those whom recurrent CDI developed after the first infusion were given a second FMT infusion 3/16 (19%) Vancomycin: 18/26 (69%) had a relapse within 10 weeks of beginning treatment and received off-protocol FMT infusions Procedural AEs and SAEs: 15 (94%) FMT group had an AE which resolved within 3 hours of the procedure	41/43 (95%) completed the study protocol; 1 person in vancomycin-only group did not complete study treatment, 1 person in FMT was excluded due to needing treatment for another condition.	Supported by grants from the Netherlands Organization for Health Research and Development and a Spinoza Award from the Netherlands Organization for Scientific Research	Trial terminated following an unplanned interim analysis due to low treatment response rate in the vancomycin control arm. A minority of people in the trial presented with a first CDI recurrence. Trial included a lower proportion of hospitalised cases at inclusion than might be expected in the NHS (13/42; 31%). Comparator antibiotic was at a higher dose than would be used in the UK

				<u>Overall treatment-related AEs:</u> By 10 weeks after the initiation of treatments, 3 (19%) in FMT group had an AE. The total number AEs during follow-up was not reported in either vancomycin arm <u>Overall treatment-related SAEs:</u> One SAE within 10 weeks of receiving FMT but unrelated to the intervention. <u>Mortality:</u> Death of one person in the vancomycin-only group (8%) but considered to be unrelated to the study drug.			(500mg QID for 14 days).
Abbreviations used: AE, Adverse event; BID, Bis in die ("twice a day"); CD, *Clostridioides difficile*; CDI, *Clostridioides difficile* infection; FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal Tube; NJT, Nasojejunal tube; PCR, Polymerase chain reaction; QID, Quater in die ("four times each day"); RCT, Randomised controlled trial; SAE, Serious adverse event; SD, Standard deviation; TID, Ter in die ("three times a day"); VTP, Vancomycin taper pulse.							

4.2. Summary of economic evidence

The EAC carried out a single set of searches to identify both clinical and economic evidence (see section 4). Search strategies were not restricted by study design or outcome, and the selection of information resources included specialist economics databases. Eight economic evaluation studies (reported in 12 papers) were included that were relevant to the decision problem (Abdali et al. 2020, Baro et al. 2017, Konijeti et al. 2013, Lapointe-Shaw et al. 2016, Luo et al. 2020, Merlo et al. 2016, Varier et al. 2015 and You et al. 2020) and are discussed in full in the EAC's assessment report (section 9.1).

Of the studies identified, Abdali et al. (2020) was identified as being directly applicable with minor limitations and was done using a UK NHS perspective. It was a cost-utility analysis comparing four treatments for recurrent *C. difficile* infection: FMT via NGT, FMT via colonoscopy, oral fidaxomicin, and oral vancomycin. The population was a hypothetical cohort of hospitalised people over 65 years who had at least one *C. difficile* infection recurrence. The analysis used a Markov model with four health states (relapsed, recovered, recurrent *C. difficile* infection and dead) and had a cycle length of 2 months and time horizon of 1 year. The analysis found that fidaxomicin and vancomycin are dominated by FMT via NGT and FMT via colonoscopy. The EAC noted minor methodological limitations including the short time horizon and not including the cost of pre-FMT antibiotics and adverse events. These were not expected to significantly change the conclusions.

De novo analysis

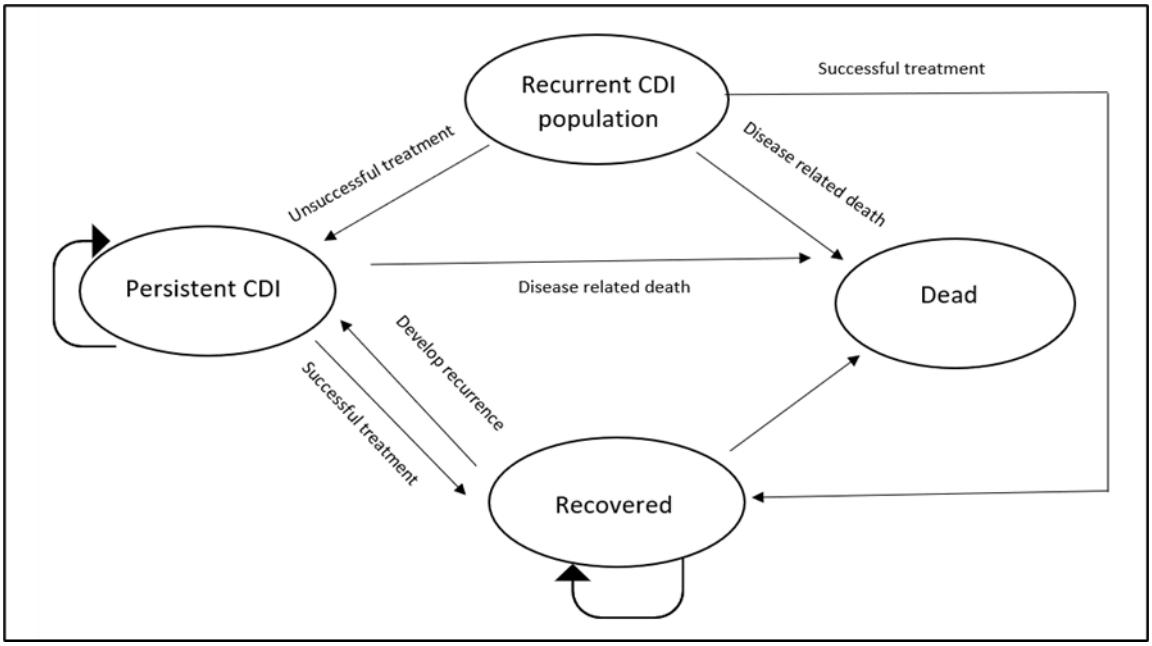
The EAC created a new cohort-based cost-effectiveness model to evaluate the economic impact of FMT use for adults with recurrent *C. difficile* infection who have had 2 or more previous episodes. A cohort Markov model structure (Figure 1) was used, consistent with Abdali et al. (2020). A starting age of 68 was used, based on the median age in the Hvas et al. (2019) trial. A cohort of 1,000 hypothetical patients were simulated through the model.

The model includes 4 routes of FMT administration (colonoscopy, enema, NDT and oral capsules) and 3 antibiotic comparators (vancomycin, fidaxomicin and VTP). Other routes of FMT administration were excluded due to a lack of RCT-level data from the clinical evidence review. The EAC acknowledged that NGT is one of the most commonly used routes of administration in the NHS, and although this was excluded from the economic model due to a lack RCT evidence, it was assumed the clinical benefits of NDT may be applicable for NGT. No eligible RCTs were identified comparing FMT oral capsules against antibiotics in people with a second recurrence of *C. difficile* infection, however, 2 studies were identified comparing oral capsules to FMT colonoscopy (Kao et al. 2017, Ramai et al. 2020). Both studies found oral capsules to be non-inferior or comparable to colonoscopy and so the transition probabilities for oral capsules were assumed to be the same.

The model has 4 health states: recurrent *C. difficile* infection population, persistent *C. difficile* infection (recurrent/ relapse/ refractory *C. difficile* infection), recovered and dead. The cohort starts in the recurrent *C. difficile* infection population state. Following treatment, the cohort is divided between recovered, persistent, or dead. Individuals can recover at any time from the persistent health state. In subsequent cycles, a proportion of the recovered population may experience another recurrence or relapse of *C. difficile* infection, where the rate of recurrence is assumed to be the same for people who recovered from their third *C. difficile* infection episode or from the persistent state. Individuals can die at any point (from infection or other causes) upon which they will move into the dead state.

A 6-month time horizon was used in the base case. The EAC considered this appropriate given the duration of the follow up reported in the clinical evidence. The EAC used a 2-month cycle length which is consistent with previous *C. difficile* infection models (Abdali et al. 2020 and Luo et al. 2020). This time horizon and cycle length allows for 3 further recurrences of *C. difficile* infection to be modelled in the recurrent *C. difficile* infection population.

Figure 1: Markov model structure



Abbreviations: CDI, *Clostridioides difficile* infection

Model parameters

Clinical Parameters

The values and sources used for the probability of *C. difficile* infection resolution and recurrence are listed in table 3.

The EAC's model used a number of key assumptions:

- If initial treatment failed, people are treated with the same treatment again.
- There are constant response and recurrence rates for the same treatment option in each cycle (for anyone in the recurrent or persistent *C. difficile* infection states).
- Of those who recover from *C. difficile* infection, regardless of which state they recovered from, it is assumed that the risk of death is comparable to the general population.
- Pre-antibiotic treatment is only used for the initial FMT administration.
- Initial treatment is assumed to include 5 days of hospital stay for FMT and 10 days hospital stay for antibiotics, as used in Abdali et al. (2020). Ongoing treatment after this period is assumed to be at home.
- Costs of tests and follow up is assumed to not differ between the intervention and comparators and excluded from the model.

Table 3: Clinical parameters use in the model

Variable	Value used	Source
Probability of *C. difficile* infection resolution		
FMT colonoscopy	92.0%	Hvas et al. (2019)
FMT NDT	94.0%	Van Nood et al. (2013)
FMT oral capsule	92.0%	Assumed same as FMT colonoscopy base on Kao et al. (2017)
FMT enema	57%	Rode et al. (2021)
Vancomycin	19.0%	Hvas et al. (2019)
Fidaxomicin	42.0%	Hvas et al. (2019)
VTP	48.0%	Rode et al. (2021)
Probability of *C. difficile* infection recurrence		
FMT colonoscopy	8.3%	Hvas et al. (2019)
FMT NDT	8.3%	Assumed same as FMT colonoscopy
FMT oral capsule	8.3%	Assumed same as FMT colonoscopy
FMT enema	8.3%	Assumed same as FMT colonoscopy
Vancomycin	69%	Hvas et al. (2019)
Fidaxomicin	46%	Hvas et al. (2019)
VTP	42%	Hota et al. (2017)
Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.		

Mortality was applied in the model for the three different health states. All-cause mortality (2-monthly mortality risk 0.2%; Office for National Statistics (2021) life tables) was applied to people in the recovered health state. Those with *C. difficile* infection are subject to a higher mortality rate with the 6-month mortality risk for non-recurrent *C. difficile* infection being 29.8% (Karas et al. 2010) and the 6-month hazard ratio for mortality in the recurrent *C. difficile* infection population against non-recurrent *C. difficile* infection population being 1.33 (Olsen et al. 2015). From this information a 2-monthly mortality risk of

14.5% was estimated. The model also includes fulminant colitis (FC) as an additional complication of prolonged *C. difficile* infection.

Costs and resource use

The breakdown of costs for the individual treatment options are detailed in Tables 29 to 32 in the EAC's assessment report and amended in the EAC's appendix. The total cost per person is shown in table 4 below. For FMT treatment the cost of FMT material is £850 per 50ml of FMT, which includes the costs of donor screening. For NDT and enema administration 50ml of FMT material is used. For colonoscopy 150ml of FMT material is needed. It is costed as 3 units for the price of 2 at £1700. For FMT oral capsules the price is £550, based on expert assumption of costs ranging from £500 to £600 (costs including donor screening). In addition to this, there are FMT administration costs which include staff time (including a consultation with a gastroenterologist), procedural costs (such as colonoscopy), additional drugs given as part of the procedure (such as proton pump inhibitors) and pre-treatment short course of antibiotics (125mg vancomycin 4 times a day for 4 days). Bowel lavage was included in the economic model for FMT via colonoscopy only at a cost of £3.25 for 2 sachets of sodium picosulfate. For antibiotic treatment, the costs were sourced from the BNF or eMIT and the dosages were based on the Hvas et al. (2019) trial for vancomycin and fidaxomicin (125 mg vancomycin, 4 times daily, for 10 days and 200mg fidaxomicin twice daily for 10 days). For VTP, the EAC used a conservative approach of considering the shorter treatment course for vancomycin taper from Hota et al. (2017) study (14 days of 125 mg 4 times daily, followed by 125 mg 2 times daily for 1 week, 125 mg daily for 1 week, 125 mg every other day for 1 week, and 125 mg every third day for 1 week).

For both intervention and comparator groups, hospitalisation costs are applied for the first treatment. Total cost of hospital stay for first treatment was estimated to be £1,857 (5 day stay) and £3,714 (10 day stay) for those receiving FMT and antibiotic only treatments, respectively. This is not applied for those requiring re-treatment in the persistent state as a separate total

hospital stay cost from recurrent *C. difficile* infection is applied (shown in table 5) to avoid double counting.

Table 4: Summary of total treatment cost

Parameter	Total cost
FMT treatments	
FMT colonoscopy	£6,864
FMT NDT	£5,873
FMT oral capsule	£9,046
FMT enema	£4,032
Antibiotic treatments	
Vancomycin	£17,166
Fidaxomicin	£15,718
VTP	£12,415
Abbreviations: FMT, Faecal microbial transplant; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse	

Additionally, the model assumes that a proportion of the population will develop FC as an additional complication of persistent *C. difficile* infection. A weighted average cost of treating FC was calculated by multiplying the cost of colectomy and medical management by the proportion undergoing each FC treatment, with an assumption of 10% requiring colectomy and 90% requiring medical management (based on the economic model for the NICE guideline on *C. difficile* infection model, NICE 2021a). The weighted cost was multiplied by the prevalence of FC, reported to be 16% by Varier et al. (2015).

Table 5: Additional costs considered in the model

Parameter	Value	Components	Source
Recurrence hospitalisation cost	£7,799	Average number of bed days 21, Unit cost of hospital stay £371 (currency code: SD01A)	Wilcox 2017; National Cost Collection 2021
FC cost			
Colectomy	£13,954*	Reported cost of £12,917.33; inflated to 19/20 prices	NICE 2015b; PSSRU 2020
Medical treatment	£4,240	Average of 4 NHS non-elective spell tariff codes: FZ37K FZ37L FZ37M, and FZ37N	National Cost Collection 2021
Total cost of FC	£834	Colectomy and medical treatment weighted based on 10% requiring colectomy	Assumption
* Inflated using the PSSRU inflation index to 2019/2020 costs Abbreviations: FC, fulminant colitis; NICE, National Institute for Health and Care Excellence; PSSRU, Personal and Social Services Unit.			

Results

Base case results

The EAC's base case analysis found that all 4 routes of FMT are associated with increased health benefits and reduced costs against all three antibiotic comparators (tables 6 and 7). Largest cost savings are observed when FMT via oral capsule is compared against vancomycin whilst largest health benefits are observed for FMT via NDT against vancomycin (additional 0.66 QALYs). All FMT routes of administration are associated with a positive net health benefit.

Table 6: Summary of base case results

	Costs per person	**QALYs per person**
FMT colonoscopy	£6,864	1.83
FMT NDT	£5,873	1.84
FMT enema	£9,046	1.61
FMT oral capsule	£4,032	1.83
Vancomycin	£17,166	1.18
Fidaxomicin	£15,718	1.39
VTP	£12,415	1.44
Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.		

Table 7: Incremental analysis (per person)

	ΔCosts	**ΔQALYs**	**NHB**	**ICER**
FMT vs vancomycin				
FMT colonoscopy	-£10,303	0.65	1.17	Dominant
FMT NDT	-£11,293	0.66	1.22	Dominant
FMT enema	-£8,120	0.43	0.84	Dominant
FMT oral capsule	-£13,134	0.65	1.31	Dominant
FMT vs fidaxomicin				
FMT colonoscopy	-£8,854	0.44	0.88	Dominant
FMT NDT	-£9,844	0.45	0.94	Dominant
FMT enema	-£6,672	0.22	0.55	Dominant
FMT oral capsule	-£11,686	0.44	1.02	Dominant
FMT vs VTP				
FMT colonoscopy	-£5,551	0.39	0.66	Dominant
FMT NDT	-£6,541	0.40	0.72	Dominant
FMT enema	-£3,369	0.17	0.34	Dominant
FMT oral capsule	-£8,382	0.39	0.80	Dominant

Abbreviations: FMT, Faecal Microbiota Transplantation; ICER, Incremental Cost Effectiveness Ratio; NDT, Nasoduodenal tube; NHB, Net health benefit; QALYs, Quality-adjusted life years; VTP, Vancomycin taper pulse.

In addition to the routes of FMT included in the economic model, FMT via NGT was also considered by the EAC. A meta-analysis by Ramai et al. (2020) estimates of the efficacy of FMT via NGT based on data from 6 studies (which included one study that used NDT). It suggested an overall cure rate of 78.1% when compared to antibiotic treatment. The delivery of FMT via NGT is estimated to be cheaper than NDT because it does not need endoscopy guided tube insertion. Abdali (2020) estimated the total cost of NGT delivery to be £740. As the cure rate is estimated to be higher for FMT via NGT compared to via enema (78.1% compared to 57% for NGT and enema respectively), and the costs less than FMT via enema (£740 compared to £999 for NGT and enema, respectively), FMT NGT is likely to be a cost-saving intervention for recurrent *C. difficile* infections, against all three comparators considered.

Sensitivity analysis

The EAC identified uncertainty associated with the inputs used to inform the model, in particular the resolution and recurrence data. It quantified the extent of uncertainty through deterministic sensitivity analyses (DSA), probabilistic sensitivity analyses (PSA), and various scenario analyses.

The DSA (shown in the EAC's assessment report appendix) compared FMT via enema (the least cost saving FMT route) to VTP (the comparator with the lowest cost and highest health benefit of all three comparators). The DSA results found that the largest cost drivers are the resolution probability for FMT via enema and VTP, followed by the hospital stay for any cases of *C. difficile* infection in subsequent cycles. The resolution probability determines the proportion of the cohort in the persistent *C. difficile* infection health state which is associated with large costs. However, FMT enema was still found to be cost

saving when compared with VTP. The results of the PSA showed that FMT colonoscopy is estimated to be cost saving 99% of the time when compared with VTP. When compared to both vancomycin and fidaxomicin, FMT via colonoscopy is found to be cost saving 100% of the time. FMT via NDT and oral capsules were also found to have a 100% likelihood of cost savings when compared with all three comparators. FMT via enema was found to be 100% cost saving when compared with vancomycin but cost saving 99.6% and 96% of the time, when compared with fidaxomicin and VTP, respectively.

Scenario analysis

Five scenarios were considered (shown in full in tables 6 to 9 and figure 6 of the EAC's assessment report appendix with comparison to VTP for scenarios 1, 2, 4 and 5 summarised here in table 8). The first scenario considered the use of pre-antibiotic treatment for subsequent FMT treatments against VTP. It found that, this leads to a small increase in costs in the FMT arm but that all four routes of FMT administration remain cost saving. The second scenario considers that everyone with *C. difficile* infection in subsequent cycles are given VTP instead of a repeat of the starting treatment. This led to reduced cost savings associated with all four FMT routes against antibiotics, but FMT still remained cost saving against all three antibiotics. The third scenario was a threshold analysis around fidaxomicin discount as fidaxomicin was associated with the largest cost of all the antibiotic comparators considered in the model. It found that as the cost of fidaxomicin pack price decreases, cost savings with FMT colonoscopy also decreases. However, FMT remains cost saving at 75% discount in fidaxomicin price. The fourth scenario extended the 6-month time horizon to one year. This longer time horizon is associated with increased cost savings and health benefits for all FMT administration routes considered compared with VTP. The fifth scenario set both treatment arms to a 1-day hospital stay for the index treatment instead of the 5 and 10 days stay for FMT and antibiotic treatment, respectively, used in Abdali et al. (2020). This is associated with a reduction in estimated cost savings for all FMT routes against all three comparators but remained cost-saving.

Table 8: Scenario analyses comparing cost of FMT to VTP

	∆Costs
Base Case	
FMT colonoscopy	-£5,551
FMT NDT	-£6,541
FMT enema	-£3,369
FMT oral capsule	-£8,382
Scenario 1: pre-antibiotic treatment for subsequent FMT treatments	
FMT colonoscopy	-£5,548
FMT NDT	-£6,538
FMT enema	-£3,357
FMT oral capsule	-£8,379
Scenario 2: VTP treatment for subsequent cycles	
FMT colonoscopy	-£2,158
FMT NDT	-£3,002
FMT enema	-£1,338
FMT oral capsule	-£4,645
Scenario 4: 1 year time horizon	
FMT colonoscopy	-£11,214
FMT NDT	-£12,377
FMT enema	-£8,518
FMT oral capsule	-£14,553
Scenario 5: 1 day hospital stay for index treatment	
FMT colonoscopy	-£3,694
FMT NDT	-£4,684
FMT enema	-£1,512
FMT oral capsule	-£6,525
Abbreviations: FMT, Faecal Microbiota Transplantation; NDT, Nasoduodenal tube; VTP, Vancomycin taper pulse.	

5. Ongoing research

The EAC identified 3 ongoing RCTs (Section 8.2 of the EAC's assessment report) comparing FMT (2 trials using oral capsules and 1 using both upper and lower GI routes) to antibiotic treatment in people with recurrent *C. difficile* infection.

6. Issues for consideration by the Committee

Clinical evidence

The EAC found that based on RCT-level evidence, FMT is more effective than comparator antibiotics for resolving *C. difficile* infections in people with recurrent *C. difficile* infection. It considered this treatment effect as large as 4 trials found FMT to be superior to vancomycin with absolute risk differences of 11% to 64% for *C. difficile* infection resolution and 1 trial found FMT to be 42% more effective for this outcome when compared to fidaxomicin.

However, the EAC's analysis highlighted uncertainty in the clinical evidence due to the heterogeneity in study design, small population sizes (due to early termination of 4 studies) and risk of bias in the studies. FMT is already recommended for the treatment of recurrent *C. difficile* infections in those who have had 2 or more previous episodes. Do the committee feel there is sufficient evidence on the clinical effectiveness to support robust cost modelling of FMT?

From a patient perspective, a patient expert and patient organisation highlighted the delays in *C. difficile* diagnosis and the debilitating impact of severe diarrhoea symptoms, leading to weight loss and dehydration. Diarrhoea symptoms also effects patient dignity, especially when it leads to incontinence or when the patient is in a hospital or nursing home. As a result, there is a reduction in quality of life (also reported by a Canadian patient survey, Vent-Schmidt et al. 2020) and patients may need help with day to day living.

Cost evidence

The EAC found that FMT via enema, colonoscopy, oral capsule and NDT is a cost saving and cost-effective treatment compared with vancomycin, fidaxomicin, and VTP for recurrent *C. difficile* infections in those who have had 2 or more previous episodes. However, it highlighted the uncertainty around the clinical evidence used to inform the model and uncertainty around the true costs FMT and comparator treatments. The EAC noted that the clinical evidence for oral capsules used in the economic model assumed equivalent efficacy to colonoscopy. It also was unable to include FMT via NGT in the economic model due to a lack of RCT-level evidence, however, the EAC acknowledged that FMT via NGT was likely to be cost saving as a meta-analysis suggested greater efficacy to FMT via enema and the use of an NGT tube would be cheaper than the use of NDT.

The EAC noted that there is uncertainty in the true costs of both FMT and fidaxomicin. Clinical expert opinion suggests that the estimate for FMT does not fully capture the costs of processing involved in the collection and delivery

of treatment. Therefore, the costs used within the model may be an underestimate. However, the current results estimate large cost savings of over £3,000 per person with FMT (in the base case) which may accommodate any increase in FMT treatment cost.

Despite the uncertainties highlighted in the economic model, the results were robust following sensitivity and scenario analysis, suggesting FMT is likely to be cost saving. Have the scenario analyses adequately detailed the uncertainty in the results?

7. Authors

Charlotte Pelekanou, Senior Technical Analyst

Peslie Ng'ambi, Technical Analyst

Kimberley Carter, Technical Adviser

NICE Medical Technologies Evaluation Programme

February 2022

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

Ferrante di Ruffano L et al. Faecal microbiota transplant for recurrent *Clostridioides difficile* infection, February 2022

B Related NICE guidance

- Clostridioides difficile infection: antimicrobial prescribing (2021) NICE guideline NG199.
- Faecal microbiota transplant for recurrent Clostridium difficile infection (2014) NICE interventional procedures guidance IPG485.

C References

Abdali ZI, Roberts TE, Barton P, et al. (2020) Economic evaluation of faecal microbiota transplantation compared to antibiotics for the treatment of recurrent clostridioides difficile infection. EClinicalMedicine 24**:** 100420

Baro E, Galperine T, Denies F, et al. (2017) Cost-effectiveness analysis of five competing strategies for the management of multiple recurrent community-onset clostridium difficile infection in France. Plos One [Electronic Resource] 12(1)**:** e0170258

British National Formulary. (2021a). FIDAXOMICIN [online]: National Institute for Health and Care Excellence. Available from: https://bnf.nice.org.uk/medicinal-forms/fidaxomicin.html [Accessed 15.12.2021.

British National Formulary. (2021b). OMEPRAZOLE [online]: National Institute for Health and Care Excellence. Available from: https://bnf.nice.org.uk/drug/omeprazole.html [Accessed 15.12.2021.

British National Formulary. (2021c). DOMPERIDONE [online]: National Institute for Health and Care Excellence. Available from: https://bnf.nice.org.uk/drug/domperidone.html15.12.2021].

British National Formulary. (2021d). LOPERAMIDE HYDROCHLORIDE [online]: National Institute for Health and Care Excellence. Available from: https://bnf.nice.org.uk/drug/loperamide-hydrochloride.html.

Cammarota G, Masucci L, Ianiro G, et al. (2015) Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for

the treatment of recurrent clostridium difficile infection. Alimentary Pharmacology & Therapeutics 41(9): 835-43

Cold F, Baunwall SMD, Dahlerup JF, et al. (2021) Systematic review with meta-analysis: encapsulated faecal microbiota transplantation - evidence for clinical efficacy. Therapeutic Advances In Gastroenterology 14: 1-19

Craven LJ, McIlroy JR, et al. (2020). Letter: intestinal microbiota transfer-updating the nomenclature to increase acceptability. Aliment Pharmacol Ther. 52(10):1622-1623.

(eMIT) Drugs and pharmaceutical electronic market information tool (2021). [online; accessed 8 December 2021] https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

Finn E, Andersson FL, Madin-Warburton M. Burden of Clostridioides difficile infection (CDI) - a systematic review of the epidemiology of primary and recurrent CDI. BMC Infect Dis. 2021;21(1):456

Hota SS, Sales V, Tomlinson G, et al. (2017) Oral vancomycin followed by fecal transplantation versus tapering oral vancomycin treatment for recurrent clostridium difficile infection: an open-label, randomized controlled trial. Clinical Infectious Diseases 64(3): 265-271

Hvas CL, Dahl Jorgensen SM, Jorgensen SP, et al. (2019) Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent clostridium difficile infection. Gastroenterology 156(5): 1324-1332.e3

Kao D, Roach B, Silva M, et al. (2017) Effect of oral capsule–vs colonoscopy-delivered fecal microbiota transplantation on recurrent Clostridium difficile infection: a randomized clinical trial. JAMA 318(20): 1985-1993.

Karas JA, Bradhsaw S, Mahmud W et al. (2010) Mortality in hospitalized older adults associated with Clostridium difficile infection at a district hospital. INFECTIOUS DISEASE REPORTS 2(1).

Konijeti G, Sauk J, Ananthakrishnan A, et al. (2013) Cost-effectiveness of competing strategies for recurrent clostridium difficile infection acg/astrazeneca fellow award. American Journal of Gastroenterology 108(Suppl 1): S473

Lapointe-Shaw L, Tran KL, Coyte PC, et al. (2016) Cost-effectiveness analysis of six strategies to treat recurrent clostridium difficile infection. Plos One [Electronic Resource] 11(2): e0149521

Luo Y, Lucas AL and Grinspan AM (2020) Fecal transplants by colonoscopy and capsules are cost-effective strategies for treating recurrent clostridioides difficile infection. Digestive Diseases & Sciences 65(4): 1125-1133

Merlo G, Graves N, Brain D, et al. (2016) Economic evaluation of fecal microbiota transplantation for the treatment of recurrent clostridium

difficile infection in Australia. Journal of Gastroenterology & Hepatology 31(12): 1927-1932

Mullish B, Mohammed N, Segal J, et al. (2018) The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. London Available from: https://www.bsg.org.uk/wp-content/uploads/2018/09/The-use-of-faecal-microbiota-transplant-as-treatment-for-recurrent-or-refractory-Clostridium-difficile-infection-and-other-potential-indications-1.pdf

National Health Service (2021). 2019/20 National Cost Collection data Version 2. https://www.england.nhs.uk/national-cost-collection/.

National Institute for Health and Care Excellence (2014) Faecal microbiota transplant for recurrent Clostridium difficile infection. Interventional procedures guidance [IPG485]. London Available from: https://www.nice.org.uk/guidance/ipg485

National Institute for Health and Care Excellence (2015) Clostridium difficile infection: risk with broad-spectrum antibiotics. Evidence summary [ESMPB1]. London Available from: https://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence#summary [Accessed: 17 March]

National Institute for Health and Care Excellence (2015b). Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy Available from: https://www.nice.org.uk/guidance/ta329. [Accessed: 15 December]

National Institute for Health and Care Excellence (2021a) Clostridioides difficile infection: antimicrobial prescribing [NG199]. London 1-40. Available from: https://www.nice.org.uk/guidance/ng199 [Accessed: 23 July]

National Institute for Health and Care Excellence (2021b) GID-MT566 Faecal microbiota transplant for recurrent Clostridioides difficile infection. London Available from: https://www.nice.org.uk/guidance/indevelopment/gid-mt566/documents

Office for National Statistics (2021). National life tables: UK. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.

Olsen M, Yan Y, Reseke KA, et al. (2015) Recurrent Clostridium difficile infection is associated with increased mortality. Clinical Microbiology and Infection 21(2) 164-170

Personal Social Services Research Unit (2020). Unit Costs of Health and Social Care 2020 https://www.pssru.ac.uk › pub › 5-sourcesofinfo, University of Kent, Canterbury.

Public Health England (2021a). Clostridioides difficile (C. difficile) infection: annual data. Annual counts and rates of C. difficile infections by acute trust and clinical commissioning group (CCG) in patients aged 2 years and over. London: 15 September 2021. Available from: https://www.gov.uk/government/statistics/clostridium-difficile-infection-annual-data

Public Health England (2021b). Annual epidemiological commentary: Gram-negative bacteraemia, MRSA bacteraemia, MSSA bacteraemia and C. difficile infections, up to and including financial year April 2020 to March 2021. London: 15 September 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1016843/Annual_epidemiology_commentary_April_2020_March_2021.pdf

Ramai D, Zakhia K, Fields P, et al. (2020) Fecal microbiota transplantation (FMT) with colonoscopy is superior to enema and nasogastric tube while comparable to capsule for the treatment of recurrent Clostridioides difficile infection: a systematic review and meta-analysis. Digestive Diseases and Sciences 66(2): 369-380

Rode AA, Chehri M, Krogsgaard LR, et al. (2021) Randomised clinical trial: a 12-strain bacterial mixture versus faecal microbiota transplantation versus vancomycin for recurrent clostridioides difficile infections. Alimentary Pharmacology & Therapeutics 53(9): 999-1009

van Nood E, Vrieze A, Nieuwdorp M, et al. (2013) Duodenal infusion of donor feces for recurrent clostridium difficile. New England Journal of Medicine 368(5): 407-15

Varier RU, Biltaji E, Smith KJ, et al. (2015) Cost-effectiveness analysis of fecal microbiota transplantation for recurrent clostridium difficile infection. Infection Control & Hospital Epidemiology 36(4): 438-44

Vent-Schmidt J, Attara GP, Lisko D, et al. (2020). Patient Experiences with Clostridioides difficile Infection: Results of a Canada-Wide Survey. Patient Prefer Adherence 14:33-43

Wilcox MH, Ahir H, Coia J et al. (2017) Impact of recurrent Clostridium difficile infection: hospitalization and patient quality of life. Journal of Antimicrobial Chemotherapy 72(9) 2647-2656

You JHS, Jiang X, Lee WH, et al. (2020) Cost-effectiveness analysis of fecal microbiota transplantation for recurrent clostridium difficile infection in patients with inflammatory bowel disease. Journal of Gastroenterology & Hepatology 35(9): 1515-1523

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Professor Tariq Iqbal

Consultant Gastroenterologist, University Hospitals Birmingham NHS Foundation Trust and Director of University of Birmingham Microbiome Treatment Centre

Dr Horace Williams

Consultant Gastroenterologist, Imperial College Healthcare NHS Trust

Dr Benjamin Mullish

NIHR Academic Clinical Lecturer, Imperial College London and Specialty Registrar, Gastroenterology and Hepatology, Imperial College Healthcare NHS Trust

Professor Yashwant Mahida

Professor of Medicine, Honorary Consultant Physician and Gastroenterologist, Nottingham University Hospitals NHS Trust

Professor Peter Hawkey

Professor Emeritus of Clinical and Public Health Microbiology, Institute of Microbiology and Infection, University of Birmingham, and Locum Consultant Microbiologist, NHS Grampian, and Director Modus Medica Ltd

Dr Simon Goldenberg

Consultant Microbiologist and Infection Control Doctor, Guy's and St Thomas' NHS Foundation Trust

Dr Tom Lee

Consultant Gastroenterologist, Northumbria Healthcare NHS Foundation Trust and Associate Clinical Lecturer, Population Health Sciences Institute, Newcastle University.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded:

- GUTS UK

Appendix D: decision problem from scope

Population	For adults with a refractory *C. difficile* infection or a recurrent episode of *C. difficile* infection who have had 2 or more previous episodes
Intervention	Faecal microbiota transfer (with or without pre-treatment with bowel lavage and/or a short course of antibiotics) via different administration routes including: • lower gastrointestinal route (rectal enema, colonoscopy or flexible sigmoidoscopy) • upper gastrointestinal route (endoscopy or using a nasogastric tube, nasoduodenal tube or nasojejunal tube) • via oral capsules containing frozen FMT or freeze-dried (lyophilised) faecal material.
Comparator(s)	Appropriate dosage and duration of oral antibiotics. NICE's guideline on *C. difficile* infection: antimicrobial prescribing recommends Vancomycin (up to 500 mg orally four times a day for 10 days) with or without Metronidazole (500 mg intravenously three times a day for 10 days) if first- and second-line antibiotics are ineffective or Vancomycin (125 mg orally four times a day for 10 days) or Fidaxomicin (200 mg orally twice a day for 10 days) for a further episode of *C. difficile* infection more than 12 weeks after symptom resolution (recurrence). Vancomycin taper pulse (125mg Vancomycin every 6 hours for 10 days, then 125mg once every 2 to 3 days for 3 weeks) could also be considered as a third-line treatment option for *C. difficile* infections.

Outcomes	The outcome measures to consider include:
	• measures of treatment effectiveness (outcomes from each administration route may be considered separately, if appropriate), for example:
	  ○ resolution of diarrhoea and/or other symptoms
	  ○ negative stool test for *C. difficile* toxin during follow up period (experts state that this measure may be unreliable for up to 3 months post procedure)
	  ○ reoccurrence of *C. difficile* infection leading to retreatment with antimicrobials and/or repeat FMT procedures
	  ○ lack of resolution of *C. difficile* infection leading further gastrointestinal complications and/or surgical interventions (such as colectomy rates) and/or mortality
	• patient-reported outcomes, for example:
	  ○ patient acceptability of the treatment modalities
	  ○ health related quality of life (preferably EQ-5D)
	• measures of resource use, for example:
	  ○ length of hospital stay
	  ○ follow-up GP, hospital visits or telephone consultations
	  ○ follow up tests such as stool test for *C. difficile* toxin
	  ○ pre, intra and post treatment usage of medicines or procedures including antimicrobials, anti-motility drugs, proton pump inhibitors, bowel lavage

	○ resources associated with collection, preparation, and administration of FMT treatment ○ NHS resource usage such as isolation rooms, barrier nursing, ward closures, theatre or procedure room times, follow up appointments • Procedure related adverse events.	
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	None identified	
Special considerations, including those related to equality	*C. difficile* infections are more likely to occur in people over 65, people with certain underlying health conditions, and people with a weakened immune system. Published guidelines make recommendations for the use of FMT for treating *C. difficile* infections in adults but not children due to limited evidence availability. FMT may not be appropriate for some people with an anaphylactic food allergy. An FMT procedure can be offered with caution to people who are immunocompromised and people with inflammatory bowel disease (IBD) should be warned of the small risk of exacerbating their IBD symptoms. Some of these people may be classed as disabled under the Equality Act. Diet and alcohol consumption of potential donors may also be considered as a barrier of having an FMT procedure for people from some faith groups. Disability, age and religion or belief are protected characteristics under the Equalities Act 2010.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Dedicated laboratory facilities for faecal microbiota transplant (FMT) production would be needed to ensure processes adhere to health and safety requirements, aid standardisation of the production process, aid traceability of donors and reduce the risk of cross contamination. This could be done by establishing centralised stool banks. A national registry of donor and recipients would also be needed.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Faecal microbiota transplant for recurrent *Clostridioides difficile* infection

1 The procedure

1.1 Description of the procedure

Faecal microbiota transplants (FMT) aim to restore a healthy gut microbiome in people who have recurrent or refractory *Clostridioides difficile* (*C. difficile*) infections. FMT is a medical procedure rather than a device that can be purchased.

The treatment involves transferring intestinal bacteria and other microorganisms from healthy donor faeces into the gut of the recipient. Donor faeces are taken and diluted with water or saline, then filtered to remove large particles. FMT can be then used as a fresh preparation, frozen or capsulised. Frozen FMT is considered preferable. To prepare the frozen FMT, the suspension is emulsified with a cryoprotectant and frozen and stored for up to 6 months in aliquots of filtered suspension at -80°C, according to joint British Society of Gastroenterology and Healthcare Infection Society guidelines. Commonly used cryoprotectants are glycerol and trehalose. Frozen FMT is thawed at room temperature prior to use. There are different routes of administration for frozen or fresh FMT:

- lower gastrointestinal route (rectal enema, colonoscopy or flexible sigmoidoscopy)
- upper gastrointestinal route (endoscopy or using a nasogastric tube, nasoduodenal tube or nasojejunal tube).

Alternatively, FMT can be given via oral capsules containing frozen FMT or freeze-dried (lyophilised) faecal material.

FMT administration via nasogastric tube and colonoscopy are the most used procedures. Capsulised FMT is less commonly used. This is because some capsule preparations may require taking a high number of large capsules in a single day, which may be challenging for some people, such as the frail elderly with an existing high pill burden. More advanced preparations, such as lyophilised capsules, could reduce pill numbers needed. However, capsulised FMT options are still limited by being more complicated to prepare than other methods of FMT preparation. People receiving an FMT may also have a short course of antibiotics (vancomycin or fidaxomicin) and/or a bowel lavage before transplantation, to reduce the *C. difficile* load in the intestines. It is also recommended to have a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT to minimise any effects of antimicrobials on the FMT material.

Before the procedure, healthy donors (who can be family members or unrelated) are screened using a questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota. Donors are also restricted by age and body mass index (BMI; aged 18 to 60 years with a BMI between 18 and 30 kg/m^2). Blood and stool screening is also done to check for pathogens to ensure there are no transmissible blood or gut infections. When using frozen FMT, it is recommended that the stool is stored in 'quarantine' until donors have successfully completed a donor health questionnaire and laboratory screening assays both before and after the period of stool donation. When using fresh FMT, it is recommended that a repeat health questionnaire should be assessed at the time of each stool donation, with donor health questionnaires and laboratory screening being repeated regularly. Due to the COVID-19 pandemic, it is also recommended to do PCR testing for SARS-CoV-2 using nasopharyngeal swab testing and checking genetic material in donor stool.

FMT is innovative because it uses transplanted gut microbiota to treat the infection rather than antibiotics. It could help reduce antibiotic use in these patients. However, although there are studies showing clinical effectiveness, the mechanism of action which leads to improved health outcomes has not been fully established (Goldenberg and Merrick, 2021).

1.2 Relevant diseases and conditions

The aim of this evaluation is to review the use of faecal microbiota transplant (FMT) in adults with a refractory *C. difficile* infection or a recurrent episode of *C. difficile* infection who have had 2 or more previous episodes. FMT is primarily being used for this purpose in the NHS currently, however, further research is being done to show its efficacy for other gastrointestinal diseases such as ulcerative colitis.

NICE's evidence summary on *C. difficile* infection: risk with broad-spectrum antibiotics states that a *C. difficile* infection occurs when the other harmless bacteria in the gut are disrupted (for example, by taking antibiotics) or when the immune system is compromised, allowing the numbers of *C. difficile* bacteria to increase to high levels. Aside from broad-spectrum antibiotics, other factors increase the risk of *C. difficile* infection including older age, underlying morbidity, hospitalisation, exposure to other people with the infection, long duration of antibiotic treatment, taking multiple antibiotics concurrently or taking multiple antibiotic courses, use of proton pump inhibitors and inflammatory bowel disease.

C. difficile infection symptoms can range depending on the severity of the infection. Symptoms of mild *C. difficile* infections include watery diarrhoea, abdominal cramps, nausea and dehydration. In more severe cases the infection can cause bloody diarrhoea and fever. In a few people *C. difficile* infection can lead to pseudomembranous colitis, sepsis, toxic megacolon, colonic rupture, and death. The risk of death increases in those with multiple comorbidities.

The rate of *C. difficile* infection declined between 2007/08 and 2012/13 and has subsequently fluctuated around the same rate. The number of *C. difficile*

infections in the NHS in England has been reported as a total of 13,177 cases in 2019/20 (Public Health England annual epidemiological commentary: MRSA, MSSA and E. coli bacteraemia and C. difficile infection data, 2019 to 2020). The rates are highest in people aged 75 and older, with little difference in infection rates between men and women. *C. difficile* infections usually respond well to treatment and most people make a full recovery in a week or 2. But symptoms can return, requiring repeat treatment. It is estimated that around 20% of *C. difficile* infections return after a first infection in those treated with metronidazole or vancomycin (Eyre et al. 2012). From the 2019/20 data on *C. difficile* infections, information on mortality was available for 98% of cases. A total of 1,735 deaths (13.5% of cases) were reported within 30 days of a *C. difficile* infection (Public Health England Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and C. difficile infections).

1.3 Current management

First-line treatment for a *C. difficile* infection involves rehydration and antibiotic therapy. Clinical responses are generally favourable, but some people have recurrent, relapsing, or refractory *C. difficile* infections. For these people, further courses of antibiotics are used.

There is a lack of clear distinction between recurrent, refractory and relapsing *C. difficile* infections. NICE's guideline on *C. difficile* infection: antimicrobial prescribing defines a relapsing infection as more likely to be with the same *C. difficile* strain. A recurrent infection is more likely to be with a with a different *C. difficile* strain. However, the guideline acknowledges that there is no agreement on the precise definition of relapse and recurrence, and it is difficult to distinguish between them in clinical practice. The joint British Society of Gastroenterology and Healthcare Infection Society guidelines also states that there is little consensus on the definition of refractory *C. difficile*, with some studies using the terms refractory and recurrent interchangeably (as well as other terms such as salvage therapy). As a result, the quality of evidence for the utility of FMT in refractory cases of *C. difficile* is lower than for recurrent *C. difficile*.

NICE's guideline on *C. difficile* infection: antimicrobial prescribing recommends reviewing existing antibiotic treatment and stopping it unless essential. If an antibiotic is still essential, consider changing to one with a lower risk of causing *C. difficile* infection.

It also recommends assessing:

- whether it is a first or further episode (relapse or recurrence) of *C. difficile* infection
- the severity of *C. difficile* infection
- individual factors such as age, frailty or comorbidities that may affect the risk of complications or recurrence.

For people with suspected or confirmed *C. difficile* infection, review the need to continue any treatment with:

- proton pump inhibitors
- other medicines with gastrointestinal activity or adverse effects, such as laxatives
- medicines that may cause problems if people are dehydrated, such as non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists and diuretics.

For adults, offer an oral antibiotic to treat suspected or confirmed *C. difficile* infection (oral metronidazole, vancomycin or fidaxomicin based on recommendations in NICE's guideline on *C. difficile* infection: antimicrobial prescribing; see table 1 below). In the community, prompt specialist advice from a microbiologist or infectious diseases specialist should be sought before starting treatment. It is also recommended to manage fluid loss and symptoms associated with suspected or confirmed *C. difficile* infection, but not to offer antimotility medicines such as loperamide.

Table 1: Antibiotics for adults aged 18 years and over (taken from NICE's guideline on *C. difficile* infection: antimicrobial prescribing)

Treatment	**Antibiotic, dosage and course length**

First-line antibiotic for a first episode of mild, moderate or severe *C. difficile* infection	Vancomycin: 125 mg orally four times a day for 10 days
Second-line antibiotic for a first episode of mild, moderate or severe *C. difficile* infection if vancomycin is ineffective	Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for *C. difficile* infection if first- and second-line antibiotics are ineffective	Seek specialist advice. Specialists may initially offer: Vancomycin: Up to 500 mg orally four times a day for 10 days With or without Metronidazole: 500 mg intravenously three times a day for 10 days
Antibiotic for a further episode of *C. difficile* infection within 12 weeks of symptom resolution (relapse)	Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for a further episode of *C. difficile* infection more than 12 weeks after symptom resolution (recurrence)	Vancomycin: 125 mg orally four times a day for 10 days Or Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for life-threatening *C. difficile* infection	Seek urgent specialist advice, which may include surgery. Antibiotics that specialists may initially offer are: Vancomycin: 500 mg orally four times a day for 10 days With Metronidazole: 500 mg intravenously three times a day for 10 days

NICE's guideline on *C. difficile* infection: antimicrobial prescribing recommends considering a faecal microbiota transplant (FMT) for a recurrent episode of *C. difficile* infection in adults who have had 2 or more previous episodes. NICE's interventional procedures guidance on FMT for recurrent *C. difficile* infection states that current evidence on the efficacy and safety of FMT for recurrent *C. difficile* infection is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit.

However, NICE's guideline on *C. difficile* infection states that FMT was not effective as a first-line treatment for *C. difficile* infection compared with Vancomycin. The committee discussion acknowledged that long-term safety data on, and regulations about the use of, FMT are minimal compared with medicines. The guidelines committee were aware of variation in mortality rates associated with FMT use, and that there is almost no evidence for its use in children. In the economic model produced, FMT was placed as a third-line treatment (for people with continuing symptoms after first- and second-line antibiotics) that may help prevent serious complications. The committee agreed that FMT may be useful in adults who have had 2 or more previous episodes of *C. difficile* infection, in addition to the current episode, to prevent recurrence of *C. difficile* infection. They were aware of ongoing developments around the screening of faecal microbiota donors to identify multidrug-resistant organisms.

1.4 Current management of FMT in the NHS

FMT is intended for adults with a refractory *C. difficile* infection or a recurrent episode of *C. difficile* infection who have had 2 or more previous episodes. In the NHS this procedure is currently done in a small number of specialist centres, within secondary care. The University of Birmingham Microbiome Treatment Centre is the first Medicines and Healthcare products Regulatory Agency (MHRA) licensed facility in the UK to provide FMT for people with recurrent and refractory *C. difficile* infection. It is responsible for the largest number of FMT administered in NHS hospitals.

FMT procedures in the NHS are generally carried out as an inpatient procedure or day case procedure in hospital. The setting and hospital department varies depending on the route of delivery. If FMT is delivered using a nasogastric (or other nasoenteric) tube, the procedure is usually done by a healthcare professional in a hospital ward or in a day case unit. If FMT is delivered using endoscopy, a trained endoscopist is required and it is usually done in an endoscopy unit. Capsulised FMT can also be done as a less invasive option and does not need specialist care or the use of an endoscopy unit. It is recommended that multidisciplinary teams are formed to deliver FMT

service. This would likely include gastroenterologists, infectious disease specialists and microbiologists.

1.5 Regulatory status

Faecal microbiota transplant (FMT) must be manufactured in accordance with Medicines and Healthcare products Regulatory Agency (MHRA) guidance for human medicines regulation. When FMT is supplied on a named patient basis, within a single organisation, a pharmacy exemption may be used, subject to ensuring proper governance and traceability. Before establishing an FMT service, NHS centres are legally required to seek advice from the MHRA and, if necessary, obtain licences to process, distribute and carry out FMT.

1.6 Potential benefits

The potential benefits to patients are:

- better cure rates than standard care for people with recurrent or refractory *C. difficile* infection, reducing ill-health and hospital admissions
- reduced hospital stay
- less transfer of *C. difficile* spores in hospitals

The potential benefits to the healthcare system are:

- reduced antibiotic use
- reduction in *C. difficile* infection recurrences and associated GP attendances and hospital admissions
- reduced length of hospital stay

2 Decision problem

The aim of this guidance is to review new clinical and economic evidence alongside the evidence evaluated for NICE's guideline on Clostridioides difficile infection: antimicrobial prescribing. The purpose of the evaluation is to perform a cost consequences analysis for giving FMT to adults with a refractory *C. difficile* infection or a recurrent episode of *C. difficile* infection

who have had 2 or more previous episodes, when compared with current care options.

Population	For adults with a refractory *C. difficile* infection or a recurrent episode of *C. difficile* infection who have had 2 or more previous episodes
Intervention	Faecal microbiota transfer (with or without pre-treatment with bowel lavage and/or a short course of antibiotics) via different administration routes including: • lower gastrointestinal route (rectal enema, colonoscopy or flexible sigmoidoscopy) • upper gastrointestinal route (endoscopy or using a nasogastric tube, nasoduodenal tube or nasojejunal tube) • via oral capsules containing frozen FMT or freeze-dried (lyophilised) faecal material.
Comparator(s)	Appropriate dosage and duration of oral antibiotics. NICE's guideline on *C. difficile* infection: antimicrobial prescribing recommends Vancomycin (up to 500 mg orally four times a day for 10 days) with or without Metronidazole (500 mg intravenously three times a day for 10 days) if first- and second-line antibiotics are ineffective or Vancomycin (125 mg orally four times a day for 10 days) or Fidaxomicin (200 mg orally twice a day for 10 days) for a further episode of *C. difficile* infection more than 12 weeks after symptom resolution (recurrence). Vancomycin taper pulse (125mg Vancomycin every 6 hours for 10 days, then 125mg once every 2 to 3 days for 3 weeks) could also be considered as a third-line treatment option for *C. difficile* infections.

Outcomes	The outcome measures to consider include:
	• measures of treatment effectiveness (outcomes from each administration route may be considered separately, if appropriate), for example:
	  ○ resolution of diarrhoea and/or other symptoms
	  ○ negative stool test for *C. difficile* toxin during follow up period (experts state that this measure may be unreliable for up to 3 months post procedure)
	  ○ reoccurrence of *C. difficile* infection leading to retreatment with antimicrobials and/or repeat FMT procedures
	  ○ lack of resolution of *C. difficile* infection leading further gastrointestinal complications and/or surgical interventions (such as colectomy rates) and/or mortality
	• patient-reported outcomes, for example:
	  ○ patient acceptability of the treatment modalities
	  ○ health related quality of life (preferably EQ-5D)
	• measures of resource use, for example:
	  ○ length of hospital stay
	  ○ follow-up GP, hospital visits or telephone consultations

	○ follow up tests such as stool test for *C. difficile* toxin ○ pre, intra and post treatment usage of medicines or procedures including antimicrobials, anti-motility drugs, proton pump inhibitors, bowel lavage ○ resources associated with collection, preparation, and administration of FMT treatment ○ NHS resource usage such as isolation rooms, barrier nursing, ward closures, theatre or procedure room times, follow up appointments • Procedure related adverse events.	
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	None identified	
Special considerations, including those related to equality	*C. difficile* infections are more likely to occur in people over 65, people with certain underlying health conditions, and people with a weakened immune system. Published guidelines make recommendations for the use of FMT for treating *C. difficile* infections in adults but not children due to limited evidence availability. FMT may not be appropriate for some people with an anaphylactic food allergy. An FMT procedure can be offered with caution to people who are immunocompromised and people with inflammatory bowel disease (IBD) should be warned of the small risk of exacerbating their IBD symptoms. Some of these people may be classed as disabled under the Equality Act. Diet and alcohol consumption of potential donors may also be considered as a barrier of having an FMT procedure for people from some faith groups. Disability, age and religion or belief are protected characteristics under the Equalities Act 2010.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Dedicated laboratory facilities for faecal microbiota transplant (FMT) production would be needed to ensure processes adhere to health and safety requirements, aid standardisation of the production process, aid traceability of donors and reduce the risk	

	of cross contamination. This could be done by establishing centralised stool banks. A national registry of donor and recipients would also be needed.

3 Related NICE guidance

Published

- Clostridioides difficile infection: antimicrobial prescribing (2021) NICE guideline NG199.
- Faecal microbiota transplant for recurrent Clostridium difficile infection (2014) NICE interventional procedures guidance IPG485.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association for Clinical Microbiologists
- Association for Continence Advice
- Association of Clinical Biochemists - Microbiology Section
- Association of Clinical Pathologists
- Association of Clinical Scientists
- Association of Coloproctology of Great Britain and Ireland
- British Dietetics Association
- British Geriatrics Society
- British Infection Association
- British Society of Gastroenterology
- British Society of Gastroenterology Gut Microbiota for Health (GMfH) clinical research group
- British Transplantation Society
- Primary Care Society for Gastroenterology
- Royal College of Pathologists
- Royal Institute of Public Health and Hygiene
- Society for General Microbiology
- The Association of Clinical Pathologists

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- C. diff. Support Site
- Crohn's and Colitis UK (NACC)
- GUTS UK
- Immunodeficiency UK

NICE National Institute for Health and Care Excellence

Adoption report: Faecal Microbiota Transplant (FMT) for recurrent *Clostridioides difficile (C. difficile)* infection GID-MT566

Summary

Adoption considerations

- Adoption levers and barriers vary according to whether FMT is locally produced or ordered via a national sample bank.
- Either a national sample bank (n=1) or regional and national sample banks (n=2) was the preferred model for ongoing FMT supply – to optimise governance and safety, to avoid impeding research and to minimise wider system effort and costs.
- A national FMT registry would enable meaningful clinical outcome data.

Adoption levers identified by contributors

- An alternative to antibiotics that don't always work.
- Can be lifesaving or life changing for patients.
- Can greatly improve patient symptoms, comfort and dignity.
- Additional national funding (such as the previous NHSE Innovation Technology Payment) would incentivise use.

Adoption barriers identified by contributors

- Cost - the previous NHSE funding incentive has expired.
- Numbers of people with recurrent C. difficile are low therefore would be used infrequently.
- It is very costly and effortful to set up a local sample production service.
- Obtaining patient consent can be time consuming.
- Clinician awareness and potential acceptance.
- Distribution - concern about capacity of Blood Bikes who currently provide free courier service for the national sample bank.

1 Introduction

This adoption report has been developed for the medical technology evaluation programme (MTEP) and their advisory committee (MTAC) to provide real world experiences and insights into the potential levers and barriers to the adoption of FMT in routine NHS clinical practice. It does not represent the opinion of NICE or MTAC.

Issue date: [October 2021]

2 Contributors

The adoption team spoke to 7 contributors from 6 NHS trusts - 4 consultant gastroenterologists, 1 clinical microbiologist, 1 consultant colorectal surgeon and 1 deputy director of primary care and medicines. Five contributors have direct experience of FMT.

Infection control, elderly medicine and pharmacy insights were also sought. Twenty-six people were contacted. Four were unable to assist and the remainder did not reply.

3 Current practice in clinical area

C. difficile commonly affects hospital inpatients but recurrences may happen post discharge. First-line treatment for a C. difficile infection involves rehydration and antibiotic therapy. People with recurrent infection may or may not be readmitted to hospital. In hospital the patient is either managed by the responsible clinician with input from pharmacy, infection control, gastroenterology and microbiology, or by a specialist C. difficile or infectious diseases multidisciplinary team (MDT) who manage this aspect of the patient's care.

Standard infection control policies covering the management of C. difficile would apply. For hospital inpatients this would include isolation in a side-room and barrier nursing.

4 Use of FMT in practice

In the NHS FMT is used in a small number of specialist centres, within secondary care. The University of Birmingham Microbiome Treatment Centre (MTC) is the first public sector Medicines and Healthcare products Regulatory Agency (MHRA) licensed facility in the UK to provide FMT for people with recurrent and refractory C. difficile infection. It is responsible for the largest number of FMT administered in NHS hospitals.

In addition to the sample bank, a small number of hospitals have set up local FMT services and produce their own samples using locally recruited donors. Some of these are represented within this report.

Users of the MTC order FMT via an electronic request form. A forty-eight-hour notice period is ideally required. Samples are then transported via Nationwide Association of Blood Bikes to the recipient hospital. Geographic location clearly influences delivery time.

The delivery service is currently free of charge to the NHS. One contributor questioned whether this is sustainable or fair should uptake of FMT increase.

In addition to the sample bank, two other contributing hospitals have set up local FMT services where they process their own samples. In one of these, the FMT service has been temporarily paused due to problems with funding. Multiple specialities provide input to the service but not all are being reimbursed. A resolution is being sought.

FMT can be offered to inpatients or outpatients who meet the eligibility criteria. Four users offer to inpatients only and one to outpatients only. This user orders the samples from the MTC and most often admits the patient the night before the procedure to enable sufficient time to establish an administration route (nasogastric tube) ready for when the sample arrives. It could also be administered as a day-case with adequate co-ordination and timings.

The below table indicates various FMT parameters by contributor.

Contributor	Date started	Approx numbers per year	Producing locally or sample bank user	Sample type produced	Administration Routes
1	2014	200	Is a sample bank (MTC)	Frozen	Nasogastric tube, colonoscopy, flexi-sigmoidoscopy
2	2014	1-2	Sample bank	Obtain frozen	Nasogastric tube as standard, option for colonoscopy
3	Not used	N/A	Colleague referred patient to MTC in past.	Frozen	Unknown
4	2015	1-2	Locally produced	Fresh	Nasojejunal tube via endoscopy
5 and 6	2015	10/11	Locally produced	Fresh	Nasojejunal tube via endoscopy
7	Not used	N/A	N/A	N/A	N/A

Table 1: FMT parameters by contributor

As per Table 1, FMT usage is low ranging from 1 to 2 to 10 to 11 uses per year for local producers or users of the sample bank. The MTC produces around 200 samples per year. It was estimated that if all patients who meet the eligibility criteria received FMT, this number would increase to approximately 300 per year. It was reported that COVID-19 may increase numbers due to increased use of antibiotics.

Administration routes were most commonly nasogastric or nasojejunal tube. Most contributors also had the option to administer via colonoscopy.

Capsulised FMT is less invasive and requires no tube insertion or endoscopy involvement but is also less commonly used. Additional processes are required to produce capsules, but these are not technically demanding. The MTC are not currently producing capsules but report they could easily do so if funding became available.

The British Society of Gastroenterology and Healthcare Infection Society have produced joint guidelines on use of FMT.

There is no specific formulation of bacterial species or quantities that would be considered optimal therefore Faecal Microbiota Transplant is also not patented and there are no intellectual property rights.

FMT is being evaluated in research studies in other populations such as inflammatory bowel diseases and there are also ambitions to use in myalgic encephalitis (ME) and Parkinson's disease populations.

5 Reported benefits

The potential benefits of adopting FMT, as reported to the adoption team by the healthcare professionals using the technology are:

- Can be lifesaving when nothing else has worked.
- Can reduce need for isolation in side rooms and barrier nursing.
- Improved patient comfort, dignity and quality of life.
- An alternative to antibiotics.

6 Insights from the NHS

Commissioning and procurement

In 2019/20 NHS England funded FMT via their Innovation Technology Payment (ITP) scheme. FMT could be ordered using a zero-cost model. This ended in April 2020. There have been no announcements on further funding.

Three of the contributors had not heard of this and were not aware this had been available.

One contributor reported the gastroenterology service use the endoscopy tariff as a means of income for performing the procedure but microbiology are not directly reimbursed for their input.

All agreed that additional funding would be a major adoption lever for FMT. If further national funding incentives emerge, one contributor felt it would be important to ensure fair local allocation of those funds among all contributing specialities.

Costs and resource impact

Costs per treatment vary according to whether locally producing or using a sample bank and economies of scale apply. The contributor from the MTC reported that the current cost is £850 per 50ml aliquot (up from £650 to allow for additional PCR testing on stool for COVID-19).

Choice of administration route affects costs because dose volumes differ by route. With all upper gastrointestinal routes, 1 aliquot is the usual dose. If administering via colonoscopy 2-3 aliquots are used.

The contributor from the MTC reported that setting up an FMT service involved a lot of effort and estimated the cost to be between £40,000 to £50,000. Once the system is set up, costs per sample reportedly reduce but are subject to fluctuation.

If using endoscopy to pass either a nasoduodenal or nasojejunal tube or for a colonoscopy this increases the procedure cost.

The cost of administration will depend on whether the procedure is done as an outpatient procedure, day case or as an elective inpatient.

Area of application in NHS, care pathway and patient selection

Patients who develop recurrent C. difficile infection could be on any hospital ward or in the community.

Contributors said that while it is easy to identify inpatients who are C. difficile positive from pathology data, it is not easy to identify patients who are experiencing a recurrence or whether they have had 2 or more recurrences because they don't do repeat testing. Having a dedicated C. difficile or infection control MDT helps identify potentially suitable patients, although it is more difficult to do this with out of area patients as their pathology data is held elsewhere.

Most often, gastroenterologists (or microbiologists) would administer the treatment as the clinician responsible for this element of the patient's care, however it was noted that it could be another appropriately qualified staff member.

FMT is administered at ward level (or in a designated out-patient facility) if using nasogastric, nasoduodenal or nasojejunal routes. If colonoscopy or flexi-sigmoidoscopy is the chosen route, FMT is administered in the endoscopy suite.

One contributor was aware of a patient being transferred to the MTC to receive FMT. In this case there was not a large geographical distance involved. Patient transfer was generally discouraged. Contributors said that moving the FMT sample should be preferable.

Clinical governance

Donor recruitment processes were varied and include general or targeted advertising e.g. among academic staff, asking relatives and via the sample bank website. One contributor stated widening the donor pool helps mitigate risks.

All FMT producers had clear donor selection screening questionnaires. Screening tests and all samples are subjected to rigorous pathogen screening and traceability arrangements. All reported they had protocols describing these.

Screening donors for additional dietary factors that may be important to recipients was considered important by 1 contributor.

The MTC is currently the only user that has an MHRA licence as it is the only centre distributing FMT. One local producer is pursuing a licence so they can engage in more research and potentially distribute FMT. The local producers currently operate under a pharmacy exemption as they produce on a named patient basis only. It is reportedly easier to obtain a licence if the trust already processes human tissues. There was variation among contributors around the requirement for an MHRA licence.

Method, route and processes of administration

Administration route and setting varies according to local structures and agreed protocols, patient eligibility and tolerance and in some cases, patient preference. All users use upper gastrointestinal routes. Two administer FMT into the stomach via a nasogastric tube (inserted on the ward or in another clinical facility). The tube tip position is confirmed by testing the pH of an aspirate as per local protocols. The use of proton pump inhibitors (to reduce any effect of stomach acid on the microorganisms) and pro-kinetic medication (for stomach emptying and to reduce the likelihood of vomiting) with gastric administration is variable.

Two users administer into the jejunum via a nasojejunal tube which requires placement in endoscopy to ensure it is correctly positioned. The patient then returns to the clinical area.

The liquid preparation is drawn up into a transparent syringe that is then connected to either tube type and the contents are depressed slowly through the tube. All tubes are flushed with 50mls saline post sample administration. When using this route, the standard dose of FMT is one 50ml aliquot.

Two users also have the option for lower gastrointestinal administration via colonoscopy or flexi-sigmoidoscopy (both undertaken in endoscopy). Colonoscopy enables administration higher up in the large intestine to the transverse colon. The flexi-sigmoidoscope enables enema administration to the sigmoid colon. The latter is less invasive and requires no sedation so is an option for people who cannot tolerate colonoscopy, however it is reportedly harder for the patient to retain the sample and it is more likely to be expelled. With both options, the sample is administered in the endoscopy suite.

All routes requiring endoscopic placement require patient transfer to the endoscopy suite. Infection control procedures require deep cleaning of the suite before another patient can enter. Users try to book slots at the end of the day list to avoid disruption to patient throughput.

Most contributors showed interest in oral capsules (containing frozen FMT or freeze-dried (lyophilised) faecal material) but none were aware of their availability in routine clinical practice. The MTC are currently not producing capsules but could do so with funding. One contributor said they would not be difficult to produce. Two queried the efficacy of capsules. All acknowledged the pill burden associated with the standard capsules given the dosage is 20-30 capsules in one day. The dose of lyophilised capsules is smaller. One contributor commented on aesthetics and why the capsule casing was transparent enabling a visual of the brown-coloured pellets inside. He felt this would affect patient acceptance.

Timeframes from identifying the patient and administering FMT will vary depending on the following factors: patient receptivity, acceptance and consent, donor acquisition, time to establishing an administration route, time to produce/acquire the sample, distance (from sample bank) and potentially obtaining an endoscopy slot. Delays to receiving treatment could be problematic for patients who are severely unwell. It was therefore suggested that having clear local processes and protocols and staff buy-in was important to the successful and timely administration of FMT regardless of sample acquisition method.

Two contributors strongly felt that using a sample bank would make best use of NHS resources, reduce variation in practice, maximise safety and enable faster adoption of FMT. It was suggested that this be either via the current MTC or via this plus specific regional sample banks so that FMT research can continue unimpeded.

Patient factors and acceptance (as reported by contributors)

It was reported that patients are sometimes repulsed by the concept of receiving donor faeces and need time to think about it. One contributor said the name FMT doesn't help with this. In the Gut Microbiota for Health community many clinicians have reportedly moved to using the term 'intestinal microbiota transfer' instead because it avoids reference to faeces and 'transplants', this may help acceptability and is more scientifically accurate. Published dialogue addresses this point.

All contributors have patient information leaflets and discuss the procedure in detail offering time for questions and concerns.

Contributors said some patients may need additional help from family members to understand the procedure and most need time to consider it.

While it can take time to gain consent and initial patient reluctance may occur, no users have had patients refuse treatment. Users advise that people are often so unwell they are desperate to try anything that might help them recover.

None have experienced patient refusal due to unknown dietary factors on behalf of the sample donor. It was identified that this issue may need further consideration.

Some patients who meet eligibility criteria are unable to provide informed consent due to age, frailty, cognitive difficulties or severity of illness. One contributor refuses to use FMT without informed consent. Two users do still treat the patient if it is considered to be in their best interest but would try to do as least invasively as possible, selecting the most appropriate route on a case-by-case basis.

Samples are reportedly odorous. One contributor reported preparing the sample (drawing into a syringe from the sample pot) away from patient bedside to minimise likelihood of the patient smelling it.

Patient outcomes and safety

Users report FMT it is generally well tolerated. Reported side effects were bloating and gas. None reported patient vomiting even with nasogastric administration and without the use of prokinetic medication.

One user reported a recipient had initial improvement and then repeat diarrhoea. Investigation identified Salmonella in the recipient's sample. Isolate was genetically identical to Salmonella isolated from the recipient several years previously.

One user reported 1 patient death from aspiration of the sample. This had reportedly been administered via a nasojejunal tube. Patients with dysphagia may be at higher risk of aspiration.

All users reported treatment success rates of 80-90% in line with published data. The need for repeat FMT treatment occurred in a couple of patients. Avoiding administration into the sigmoid colon or rectum and ensuring adequate sample volume were thought to be the best ways to improve success and avoiding need for repeat treatment.

Maintenance and quality control

Local producers are not currently freezing their samples. This means donor sample matter is wasted and reduces efficiency. One local producer said with hindsight he would freeze samples to increase efficiency but that adequate storage facilities are essential to doing this successfully.

The samples bank dispatches frozen samples. They can either be kept frozen or allowed to thaw in transit. Choice may depend on distance, the ambient temperature and timing intentions of the recipient. It takes between 2-3 hours (summer) and 4-6 hours (winter) to thaw a frozen sample at room temperature. Heating should not be used during thawing.

Governance, including rigorous donor screening and traceability, as well as a national registry, were suggested as means of improving quality control. Two users felt that having a licenced sample bank (national or regional and national) was the best way to maintain high quality and safety.

Clinician confidence and acceptance

The users felt more awareness raising was needed to promote FMT. Some felt clinicians might be reluctant to use FMT and would avoid it. One non-user preferred to consider other forms of bacterial transfer such oral probiotics.

Intellectual property

The microbiologist stated that neither the variety of bacterial species nor corresponding quantities are measured with FMT in each filtered sample, so the optimum sample composition remains unknown. This is the element of FMT that would create intellectual property rights.

Training

Training and development in relation to the safe and secure handling of the FMT can be achieved using standard infection prevention and control policies and effective disposal of bodily waste products.

Consideration to patient comfort and tolerance by minimising sight and smell of the sample was also suggested as important for all staff administering FMT.

7 Comparators

There were no comparators mentioned.

National Institute for Health and Care Excellence

Collated comments table

MTG Medtech Guidance: GID-MT566 FMT

Expert contact details and declarations of interest:

<table>
<tr><td>Expert #1</td><td>Professor Tariq Iqbal, Consultant Gastroenterologist and Chair of Clinical Microbiome, Queen Elizabeth Hospital Birmingham and University of Birmingham</td></tr>
<tr><td></td><td>Nominated by: NICE</td></tr>
<tr><td></td><td>DOI: Yes
<table>
<tr><th rowspan="2">Type of interest *</th><th rowspan="2">Description of interest</th><th colspan="2">Relevant dates</th></tr>
<tr><th>Interest arose</th><th>Interest ceased</th></tr>
<tr><td>Non-financial professional</td><td>FMT lead for UK Gut Microbiome for Health Expert Panel</td><td>2016</td><td></td></tr>
<tr><td>Non-financial professional</td><td>Director University of Birmingham Microbiome Treatment Centre</td><td>2016</td><td></td></tr>
<tr><td>Direct - financial</td><td>I was a member of an advisory board for Ferring who have an FMT product but to prevent rather than treat CDI. Not licenced in Europe or UK</td><td>2019</td><td>2019</td></tr>
</table></td></tr>
<tr><td>Expert #2</td><td>Dr Horace Williams, Consultant Gastroenterologist, St Mary's Hospital, Paddington</td></tr>
<tr><td></td><td>Nominated by: NICE</td></tr>
<tr><td></td><td>DOI: None</td></tr>
<tr><td>Expert #3</td><td>Dr Benjamin Mullish, NIHR Academic Clinical Lecturer, Department of Metabolism, Digestion and Reproduction at Imperial College London</td></tr>
<tr><td></td><td>Nominated by: Expert</td></tr>
<tr><td></td><td>DOI: None</td></tr>
<tr><td>Expert #4</td><td>Professor Yashwant R Mahida, Consultant in gastroenterology, Queen's Medical Centre, Nottingham</td></tr>
<tr><td></td><td>Nominated by: NICE</td></tr>
<tr><td></td><td>DOI: Yes</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><th rowspan="2">Type of interest *</th><th rowspan="2">Description of interest</th><th colspan="2">Relevant dates</th></tr>
<tr><th>Interest arose</th><th>Interest ceased</th></tr>
<tr><td>Non-financial professional</td><td>Currently undertaking a feasibility study to investigate the role of a bile acid supplement in the prevention of recurrence of C. difficile infection.</td><td>A few years ago</td><td>No, continuing</td></tr>
<tr><td>Indirect</td><td>Have obtained approval from my NHS Trust for this procedure (FMT to be obtained from Birmingham stool bank)</td><td>A few years ago</td><td>No, continuing</td></tr>
</table>
</td></tr>
<tr><td>Expert #5</td><td>Prof Peter Hawkey, Prof of Clinical and Public Health Bacteriology & Consultant microbiologist Grampian Health Board, University of Birmingham & Grampian Health Board</td></tr>
<tr><td></td><td>Nominated by: RCPATH</td></tr>
<tr><td></td><td>DOI: None declared</td></tr>
<tr><td>Expert #6</td><td>Simon Goldenberg, Consultant Microbiologist and Infection Control Doctor, Guy’s and St Thomas’ NHS Foundation Trust</td></tr>
<tr><td></td><td>Nominated by: NICE</td></tr>
<tr><td></td><td>DOI: Yes
<table>
<tr><th rowspan="2">Type of interest *</th><th rowspan="2">Description of interest</th><th colspan="2">Relevant dates</th></tr>
<tr><th>Interest arose</th><th>Interest ceased</th></tr>
<tr><td>Direct - financial</td><td>Enterobiotix – advisory board</td><td>2015</td><td>Ongoing</td></tr>
<tr><td>Direct - financial</td><td>Tillotts – advisory board</td><td>2021</td><td>Ongoing</td></tr>
<tr><td>Direct - financial</td><td>Shonogi – research funding</td><td>2019</td><td>2020</td></tr>
</table>
</td></tr>
<tr><td>Expert #7</td><td>Tom Lee, Consultant Gastroenterologist, Northumbria Healthcare NHS Foundation Trust</td></tr>
<tr><td></td><td>Nominated by: NICE</td></tr>
<tr><td></td><td>DOI: none</td></tr>
</table>

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Expert #1: I set up the first MHRA licenced GMP facility to produce FMT as a medicine at the University of Birmingham Microbiome Treatment Centre (MTC). Yes Other than for routine use in my practice for patients with CDI and for use in the NIHR-funded STOP-COLITIS trial of FMT for inflammatory bowel disease, as Director of the MTC I have led the provision of FMT for patients with refractory and recurrent CDI across the UK. This service is currently funded under an NHSE Innovation Tariff and in 2020-2021 (including during the first peak of COVID-19) we have treated in more than 200 patients in the NHS and provided more than 300 FMT samples for use in translational research. FMT is mainly used and/or prescribed by gastroenterologists, Infectious disease physicians and elderly care physicians. However, it is a simple procedure which does not require special training and is within the competency of anyone who can pass a naso-gastric tube. Hospital in-patients with recurrent or refractory CDI may be treated by the team looking after them anywhere in a DGH. With my clinical colleagues in the MTC we have to vet and approve/reject all requests that come in locally or from anywhere else in the UK. In other hospitals the selection of patients for FMT is usually the remit of Infectious Disease specialists or gastroenterologists according to local expertise and interest. Most of these requests come to the MTC.
		Expert #2 Yes.

		- Use of the technique since 2014. - Senior author of National (BSG/HIS) Guidelines.
		Expert #3 I am very familiar with this procedure. I have, with colleagues, been co-ordinating the FMT service at Imperial College London/ Imperial College Healthcare NHS Trust since 2014. I have been an author on previous national and international clinical guidelines regarding this procedure. I have personally performed > 80 FMTs on patients with recurrent *Clostridioides difficile* infection (CDI). The latest evaluation of the use of FMT throughout the UK was performed in 2016: https://core.ac.uk/download/pdf/185498546.pdf . Those who I am aware of who co-ordinate FMT services in the UK are often clinicians with a background of either Gastroenterology or Microbiology/ Infectious Diseases. There are a small number of private FMT services within the UK, with some non-clinicians leading these services.
		Expert #4 I have good awareness of the procedure, which we plan to use in the near future. Have obtained approval from my NHS Trust for this procedure (FMT to be obtained from Birmingham stool bank) but it has not been possible to date to use it. In addition to Gastroenterology, clinicians in Infectious Diseases may also perform/use this procedure
		Expert #5 I gave 2 of the first faecal transplants [FMT] in the UK in 1995 for the treatment of recurrent Clostridiodes difficile infection [rCDI]. Since then I have worked on the use of this technology developing initially a service for patients with PHE and then the University of Birmingham in

		conjunction with NHS England innovation initiative. We have completed over 400 successful transplants. Please see McCune VL et al 2020 EClinical Medicine 20:100301 for full details of the national service. I have also been instrumental in contributing to the specialist society guidelines as well as producing the first UK based economic evaluation of FMT.
		Expert #6 Yes – I set up an FMT donor programme and stool bank at Guys and St Thomas' in 2015. We treat mainly recurrent C. difficile Infection patients and have treated over 200 patients to date. I also treat a small number of patients with Ulcerative Colitis. We were awarded an MHRA MIA(IMP) license which allows us to produce FMT products for use in clinical trials and I am involved in clinical trials for cirrhosis, antimicrobial resistance, ankylosing spondylitis and motor neurone disease. I am an author on the UK and European guidelines on the use of FMT: Gut. 2018 Nov;67(11):1920-1941. doi: 10.1136/gutjnl-2018-316818. United European Gastroenterol J. 2021 Mar;9(2):229-247. doi:10.1177/2050640620967898. The main specialties involved in FMT are microbiology and infectious diseases and gastroenterology. However this is changing – the main reason that gastroenterology had to be involved was because of the route of FMT administration eg nasogastric tube or colonoscopy. Many of my patients now have FMT with capsules – therefore there is no need for gastroenterology involvement. CDI in the UK is usually managed primarily by infectious diseases/microbiology rather than gastroenterology.
		Expert #7 Familiar with the process for FMT. Wrote Trust Guidelines 6 years ago for local acquisition of the transplant. Amending the protocol to reflect obtaining transplant from Birmingham. Aware of constraints on the current model. Not really clear on national activity.

		Locally, I work with microbiology and infectious diseases but the service is led by me and the gastro team. I`ve been asked by colleagues about use of FMT for other indications (eg IBS) but we haven`t done this locally.
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have been involved in developing national guidelines and international consensus position statements regarding FMT
		Expert #2 **I have done bibliographic research on this procedure.** **I have done research on this procedure in laboratory settings (e.g. device-related research).** **I have done clinical research on this procedure involving patients or healthy volunteers.** **I have published this research.**
		Expert #3 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research).

		I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. Other (please comment)
		Expert #4 I have done bibliographic research on this procedure. I have had no involvement in research on this procedure.
		Expert #5 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research.
		Expert #6 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. Yes – all of the above. I have >18 peer reviewed papers on FMT/gut microbiome. I am involved in multiple randomised controlled trials of FMT for various indications and have written national/international guidelines on FMT.

		Expert #7 I have done bibliographic research on this procedure. I have had no involvement in clinical research on this procedure. Other (please comment)- previous involvement with c diff vaccination trial.

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1 As the standard of care is the use of broad spectrum antibiotics to treat CDI, the use of FMT to 're-seed' the abnormal microbiome in cases of CDI can be seen as a novel concept and approach. Established practice and no longer new
		Expert #2 **This is difficult to answer: the technique should be available to the majority of trusts in the UK at the moment.**
		Expert #3 Very hard to pick one option, but best fits with - Established practice and no longer new. (However – given the relative novelty on this procedure, potential long term sequelae have not been established. Furthermore, there is a growing area of 'next generation' FMT products, including defined microbiota therapeutics, that remain very novel and with ongoing uncertainties).
		Expert #4 FMT represents a novel concept in the management of patients with recurrent C. difficile infection. Definitely novel and of uncertain long-term safety. Efficacy has been reported in a number of studies.
		Expert #5 The first in a new class of procedure.
		Expert #6 Current standard of care for CDI is evolving. Although fidaxomicin has now been available for around 10 years, extended-pulsed administration regimens appear to be more effective at

		preventing recurrence. We also have access to bezlotoxumab. FMT has a different mechanism of action to these treatment, so it is a novel concept Definitely novel and of uncertain safety and efficacy. Is more widely accepted as a valid treatment for CDI but there are still access issues and theoretical problems with safety. The main issue is that it is largely uncharacterised product with a high degree of variability / lack of standardisation
		Expert #7 Established practice and no longer new.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1 As there are many unanswered questions regarding mechanism of action and long term safety and given the fact that not all patients with CDI fail to respond to standard care, in my opinion this should be considered an addition to standard care at this time.
		Expert #2 N/A
		Expert #3 Will likely become embedded in 'patient pathway' alongside option of antimicrobials as appropriate, rather than fully replacing.
		Expert #4 Likely to replace current standard of care in the management of patients with recurrent C. difficile infection.
		Expert #5 Yes this is recognised by the MHRA as a novel therapeutic
		Expert #6

		In addition to standard care. FMT is not used as a solitary treatment – it requires standard of care antibiotics (fidaxomicin or vancomycin) initially. It is also not appropriate as a first line therapy and should be reserved for patients who have had 3 episodes or more.
		Expert #7 Need is to standardise practise and access.

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1 Standard of care for first episode of CDI in the NHS is antibiotic therapy with either metronidazole or vancomycin (both iv metronidazole plus oral vancomycin if the episode is considered clinically severe). Those patients who develop recurrent/refractory CDI receive vancomycin which may be given as an extended pulsed regimen for those with more than one recurrence. Fidaxomicin is also used for recurrent/refractory CDI
		Expert #2 Antibiotics +/- FMT, if appropriate.
		Expert #3 UK guidelines currently recommend that FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI. FMT is also recommended for appropriate patients with refractory CDI. At present, FMT is not recommended for use in a non-CDI setting outside of a clinical trial.
		Expert #4 Currently, courses of antibiotics (Vancomycin or Fidaxomicin) are used to treat episodes of recurrent C. difficile infection.
		Expert #5

		Patchy adoption of the FMT service results in inappropriate and expensive use of fidaxomicin. .FMT should be the standard of care for recurrent CDI
		Expert #6 Metronidazole no longer recommended. 1st and 2nd episodes should be treated with fidaxomicin or vancomycin, FMT should be offered at 3rd episode. Bezlotoxumab can be considered but cost is prohibitive.
		Expert #7 Locally, FMT is standard of care. Replacing recurrent antibiotics or surgery.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1 No
		Expert #2 N/A
		Expert #3 No
		Expert #4 Currently, there is no alternative or competing procedure with similar mechanism of action. Research is ongoing to identify such alternatives.
		Expert #5 No
		Expert #6 Bezlotoxumab. Ridinilazole (under development) is similar to fidaxomicin. Also be aware of ribaxamase and DAV132, both under development.

		More directly competitors are products from Seres and Rebiotix
		Expert #7 No
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1 FMT is a highly effective and cost effective treatment for patients with recurrent and refractory CDI and widely used around the world for this indication. It is associated with very few immediate side effects and there are no signals of medium term harm. FMT cures CDI, reduces hospital stay and effectively reduces transfer of spores in hospitals
		Expert #2 Please see the BSG/HIS (and subsequent) guidelines: the technique results in excellent cure rates in recurrent/refractory CDI.
		Expert #3 Improved efficacy compared to potential alternative treatment options.
		Expert #4 Cure of recurrent C. difficile infection. Thereby avoiding ill-health and need for hospital admissions.
		Expert #5 Reduced morbidity and mortality from recurrent CDI [rCDI]
		Expert #6 Reduced rate of recurrence, could also be used following antibiotics to PREVENT CDI.
		Expert #7 Avoiding surgery

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1 All patients with recurrent and refractory CDI
		Expert #2 Those with recurrent/refractory CDI.
		Expert #3 Nothing additional to add to patients described in Box 5.
		Expert #4 Susceptible patients are predominantly the elderly, often with comorbidities and therefore more likely to require hospital admission if there is recurrence of C. difficile infection.
		Expert #5 rCDI
		Expert #6 Those with risk factors for CDI Patients over age 65 years Those with comorbidities Those who have been exposed to significant amount of antimicrobials Those who are immunosuppressed Those who are frequent hospital attenders
		Expert #7 Recurrent or refractory C diff
9		Expert #1

	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	FMT is paradigm-changing for the treatment of CDI as it represents a move away from the over-use of broad spectrum antibiotics towards a correction of the microbial ecology in the gut. It has been shown to be the most cost-effective treatment for recurrent CDI and to reduce length of hospital stay. Although not yet adopted as an ambulatory treatment in the UK there is no reason why this could not be developed in the near future. Barriers to this are cultural rather than rational. Certainly in the US and in parts of Western Europe a lot of CDI treatment with FMT is undertaken in an out-patient setting, in many cases removing the need for admission to secondary care.
		Expert #2 Please see the BSG/HIS (and subsequent) guidelines.
		Expert #3 Yes – more widespread use of FMT would be expected to reduce burden of disease with recurrent CDI, with impact upon GP attendances, hospital admissions, antibiotic prescriptions, etc.
		Expert #4 Yes – please see above.
		Expert #5 Huge potential for reducing morbidity/mortality from rCDI as well as reducing cross-infection and releasing beds
		Expert #6 It has already been adopted and recommended in national guidance but if adopted more extensively could lead to reduced hospital admission rate and lower cases of CDI
		Expert #7 Improved outcomes
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the	Expert #1 It has been shown in studies from the UK, Europe and the US that FMT is by far more cost effective than the use of protracted and repeated courses of antibiotics for the treatment of

	procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	recurrent and refractory CDI. Compared to a standard course of vancomycin or fidaxomicin, FMT costs at least 10 to 12 fold less when total length of in hospital stay is taken into account.
		Expert #2 About the same
		Expert #3 Likely about the same, or potential savings – initial outlay in establishing FMT services likely recouped by savings to NHS by fewer hospital readmissions with further CDI episodes. There have been previously published studies confirming the cost effectiveness of FMT vs further courses of antibiotics.
		Expert #4 Likely to cost less than current standard of care in the management of patients with recurrent C. difficile infection.
		Expert #5 See Abdali ZI et al 2020 EClinical Medicine 24:100420
		Expert #6 Depends on formulation of CDI and method of administration. It is probably similar or slightly cheaper than fidaxomicin
		Expert #7 About the same
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1 FMT costs much less than standard of care for the treatment of recurrent and refractory CDI
		Expert #2 About the same
		Expert #3

		As in question 10: -Safe and effective donor recruitment/ screening, FMT laboratory set-up and maintenance, freezing of material, transport of material, etc are resource-intensive/ expensive to establish. -However, established stool banks are likely to overall result in cost savings to a healthcare service, given the efficacy of this treatment vs alternative options.
		Expert #4 Likely to cost less than current standard of care in the management of patients with recurrent C. difficile infection.
		Expert #5 See above
		Expert #6 Quite a bit of resource and infrastructure required in order to set up a donor programme and FMT bank. This would be beyond most hospitals capabilities and resourcing. A distributed models with a small umber of national providers would be best. There may be a time limit to FMT as it is currently being produced – there are several commercial companies (Seres, Rebiotix etc etc) who may have a licensed FMT product that comes to market in the next 5-10 years.
		Expert #7 About same
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1 FMT is undertaken easily on any hospital ward as it usually requires only the placement of a naso-gastric tube temporarily. Certain patients may need FMT to be delivered by the rectal route and this requires a flexible sigmoidoscopy which is a common, very safe procedure universally available in secondary care facilities in the NHS
		Expert #2 Please see the BSG/HIS (and subsequent) guidelines. A clinical setting for the upper or lower GI administration of FMT is required.

		Expert #3 For the stool bank/ FMT service itself – facilities for donor recruitment; laboratory space (including deep freeze freezers) of defined standards for the processing of material and freezing as storage. For the administration of material – defined clean clinical areas (e.g. endoscopy suite) for final preparation of material and safe and administration. Appropriate areas needed for monitoring of patients pre- and post-administration.
		Expert #4 If FMT continues to be available from an authorised stool bank (as is currently the case), it will not be necessary for individual NHS Trusts to establish their own facilities to undertake this procedure.
		Expert #5 See McCune et al
		Expert #6 Depends on route and method of administration Donor recruitment and manufacture of FMT needs a lot of resource.
		Expert #7 Access to national FMT bank. Clarify transport costs . Ensure national bank is adequately resourced.

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1 For FMT by the upper GI route no specific training is needed as the placement of a fine bore naso-gastric feeding tube is within the competency of all qualified nurses. Delivery of FMT to the colon requires training in flexible sigmoidoscopy which is a core competency for all gastroenterologists and lower GI surgeons
		Expert #2 Nothing above or beyond usual clinical practices.
		Expert #3 Yes – training needed for healthcare professionals for all aspects of the process to maximise safety and efficacy, including regarding donor screening, material collection and preparation, and administration of material.
		Expert #4 If administered via endoscopy / colonoscopy, a trained endoscopist would be required – this expertise is expected to be available in almost all NHS Trusts. As regards FMT administration via nasogastric tube, expect there to be many doctors and nurses already trained in the insertion of nasogastric tubes.
		Expert #5 Yes but not complex
		Expert #6 Just very basic training
		Expert #7 no

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: The main potential harm is the risk of unwitting transmission of pathogens. This is mitigated by careful donor screening and testing of FMT prior to release under an MHRA specials licence. Acute side effects are transient abdominal bloating, flatulence, diarrhoea and nausea. These are not common (less than 20% cases) and transient. SAEs from RCTs are uncommon and mortality rate is 1.4% related to aspiration (Marcella C et al Alim.Pharmacol. Therap. Nov 2020 online https://doi.org/10.1111/apt.16148) There was a fatality reported in the literature due to transmission of multi-resistant E.coli to a patient in the US as a result of inadequately screened FMT (DeFilipp Z et al. New.Eng.J.Med 2019;381:2043-2050). There has been an FDA alert in relation to infections and consequently two deaths caused by enteropathogenic Escherichia coli (EPEC) and Shigatoxin-producing Escherichia coli (STEC) that have occurred following investigational use of FMT in the US. There has been one case of aspiration pneumonia-related death following FMT following sedation for colonoscopic delivery of FMT (Lee CH et a; JAMA 2016;315:142-149) and three cases of aspiration following treatment via the foregut (Cohen NA et al. Israel.Med.Assoc.J 2016;18:594-599). FMT doesn't involve only the transfer of bacteria but also fungi, viruses, metabolites, immunoglobulins etc and our understanding of the potential long-term consequences of this is incomplete. It is not possible to understand the theoretical adverse events without knowledge of the interaction between human physiology and the gut microbiome. There is has been a suggestion of transmission or new auto-immune or rheumatological disease following FMT (Brandt LJ et al Am.J.Gastroenterol 2012;107:1079-1087)
		Expert #2 Potential adverse events/risks are documented in detail in the BSG/HIS (and subsequent) guidelines
		Expert #3

		Gastrointestinal and constitutional symptoms: The most widely recognised harms; typically mild and self-limiting. These include (but are not limited to) diarrhoea, abdominal discomfort, nausea and fever. • Potential risk of transmission of infective agents: This has included documented transmission of multi-drug resistant bacteria (ESBL E. coli), ETEC, and other pathogens. • Risks relayed to route of administration – e.g. perforation after colonoscopy; aspiration after upper GI route administration. • Potential theoretical long term risks: Theoretical risk of transmitting gut microbiota 'traits' (e.g. a 'vulnerability' to diabetes from donor to recipient), although no clinical evidence for this in practice.
		Expert #4 Short-term effects of FMT are predominantly mild and involve gastrointestinal symptoms (belching, nausea, abdominal pain /discomfort) – Gut 2018;67:1920-41. Adverse events may occur in relation to the mode of delivery of FMT. For colonoscopy these would usually be mild and self-limiting and mostly related to sedation. Rarely, the serious adverse event of colonic perforation may occur. For FMT administration via nasogastric tube or upper endoscopy (gastroscopy), aspiration may occur (Clin Infect Dis 2015; 61: 136-7; Clin Infect Dis 2014; 59: 319). Procedure-related adverse event are unlikely to occur if / when FMT is available in capsules Serious adverse events related to the FMT may also occur. Transmission of drug-resistant *E. coli* bacteremia by faecal microbiota transplant has been reported in two patients (one of the patients died) - N Engl J Med 2019 Nov 21;381(21):2043-2050. (doi: 10.1056/NEJMoa1910437). Following the above and other reports of infection following FMT the US Food and Drug Administration has issues a safety alert (https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission)

		Expert #5 See the review we wrote McCune et al We were the first to issued with a MHRA specials manufacturing licience [see UoB web site]
		Expert #6 Transmission of infection – see recent FDA warnings about transmission of antibiotic resistant infections. Also SARS-CoV-2 now a concern. Risk of 'transmitting' non-infectious issues – eg increasing risk of cancer, autoimmune, neuro-psychiatric conditions etc Most common AEs are mild and self limiting – nausea, diarrhoea, bloating, flatulence. Occasionally more sever e.g. aspiration pneumonia etc
		Expert #7 Risks of the administration procedure (NG insertion, OGD, aspiration, colonoscopy). risk of infection, transient GI symptoms such as gurgling or abdominal cramping after administration (2-3%). Risk of autoimmune condition (RA, Sjogrens, ITP) during follow up though the temporal association between FMT and onset of disease was not clear and the wider literature suggests this risk is <1%.
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1 The key efficacy outcome would be CDI cure which is defined as resolution of symptoms and assessed at 1 week and 8-12 weeks.
		Expert #2 These are documented in established guidelines such as those of the BSG/HIS.
		Expert #3 Improved rates of remission from recurrent CDI (principally measured through resolution of diarrhoea) in comparison to the alternative of antimicrobials.
		Expert #4

		Subsequent recurrence of C. difficile infection.
		Expert #5 See Abdali et al
		Expert #6 CDI recurrence rate e.g. at 12 weeks post FMT
		Expert #7 Further c diff episodes Death Need for surgery
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1 There is extensive worldwide experience of using FMT to treat CDI and it appears very effective and safe in the short-medium term. However, as discussed in [14] above this is very new science and long term safety has not been assessed
		Expert #2 These are documented in established guidelines such as those of the BSG/HIS.
		Expert #3 Uncertainties regarding potential efficacy for patients with primary CDI, and/or whether should be recommended earlier in the clinical course for patients with recurrent CDI. Ongoing uncertainties about whether more novel routes of administration (e.g. capsulised FMT) have comparable rates of efficacy to 'conventional' faecal slurries. Clinical trial data only just starting to emerge regarding potential efficacy of 'next generation' FMT products in treating recurrent CDI (i.e. defined microbial communities).

		Expert #4 Currently there are no long-term studies of the safety or efficacy of FMT.
		Expert #5 Licensed by MHRA we have not experienced any serious AE's
		Expert #6 As the product is unstandardized and variable there will always be concerns about safety
		Expert #7 Need for repeat FMT.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1 No
		Expert #2 These are documented in established guidelines such as those of the BSG/HIS.
		Expert #3 As per 16, and also regarding potential risks as outlined in 14. Risk of infection transmission has becoming particular pertinent in the era of COVID-19, with ongoing discussion regarding optimal screening of donors to minimise risk of transmission.
		Expert #4 Long-term safety of FMT.
		Expert #5 There are concerns about changing the microbiomes of individuals. However the administration of antibiotics in CDI has caused gross perturbation and FMT restores a more normal flora. There have been as yet no proven cases of transmission of traits to the recipients. The faecal microbiome is a dynamic community influenced by the daily intake of minute amounts of faecal material during life.

		Expert #6 What is the underlying mechanism of action? Does FMT need to be manufactured anerobically? What is the minimum amount of stool needed to treat patients effectively? What is the best route of administration e.g colonoscopy, nasogastric tube, enema, capsule etc
		Expert #7 Clarify advice on antibiotic management before and after.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1 Most or all district general hospitals but sourced from one or several central licenced stool banks.
		Expert #2 **Most or all district general and teaching hospitals in the UK.** ~~A minority of hospitals, but at least 10 in the UK.~~ ~~Fewer than 10 specialist centres in the UK.~~
		Expert #3 A minority of hospitals, but at least 10 in the UK.
		Expert #4 Most or all district general hospitals.
		Expert #5 Most or all district general hospitals.
		Expert #6 Most or all district general hospitals.
		Expert #7

		Most or all district general hospitals.
19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1 Recent international consensus regarding FMT practice during the SARS-CoV-2 pandemic: Ianiaro G et al Gut 2020 Sep;69(9):1555-1563 Most comprehensive recent international guideline (IDSA 2018): McDonald LC et al Clin.Infect.Dis 2018;66:e1-e48 Kelly CR, Yen EF, et al. Fecal Microbiota Transplant is Highly Effective in Real-World Practice: Initial Results from the FMT National Registry. Gastroenterology. 2020 Sep 30:S0016-5085(20)35221-5. doi: 10.1053/j.gastro.2020.09.038. Epub ahead of print. PMID: 33011173.
		Expert #2 N/A
		Expert #3 Key relevant publications all listed on PubMed etc. I have just had a systematic review/ meta-analysis regarding FMT for rCDI accepted for publication, and can make this available after embargo prior to publication.
		Expert #4 A recent publication reports on the efficacy and adverse events of FMT in real-world practice (https://doi.org/10.1053/j.gastro.2020.09.038)
		Expert #5 -
		Expert #6 Too many to list
		Expert #7 -

20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1 US registry recently set up but practice in US currently stalled pending SARS-CoV-2 screening of donors
		Expert #2 There are many. Though most have been impacted by the COVID-19 pandemic.
		Expert #3 Over 300 trials related to FMT listed on clinicaltrials.gov.
		Expert #4 FMT National Registry has been established in USA (https://doi.org/10.1053/j.gastro.2020.09.038
		Expert #5 UoB registry
		Expert #6 -
		Expert #7 -
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1 About 300-400 in UK. There are approximately 1500 cases of CDI reported on the government website every year. Of these about 30% would be recurrent and therefore eligible for FMT. 400 is a conservative estimate.
		Expert #2 Blank
		Expert #3

		~14000 patients with recurrent CDI each year. Theoretically, could be that all would be considered for treatment.
		Expert #4 5 – 10 per year in a NHS Trust
		Expert #5 1000-2000
		Expert #6 There were 13,177 cases reported in English NHS Trusts in 2019/20. If 15-20% of these had a recurrence (=1977-2635) and 20-25% of these had a further recurrence = 395-659 patients per year would be eligible, assuming only patients with 3 episodes or more would be treated.
		Expert #7 Not known

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1 No
		Expert#2 There are inherent issues with the use of faeces or faeces-derived products as a therapeutic modality.
		Expert#3 As described above – considerable resources required for establishment and maintenance of safe and effective FMT services.
		Expert #4 If obtained from a stool back, is delivered frozen and has to be used (administered) the same day. Suggest consider including guidance for NHS Trusts wishing to establish their own FMT provision.
		Expert #5 See McCune et al
		Expert #6 Capsules are much easier to administer and preferred by patients and are more cost effective, although they are not widely available. Administration by colonoscopy requires additional resource and the input of a gastroenterologist
		Expert #7 Acceptibilty to patients. Cultural issues.
23	Are you aware of any issues which would prevent (or have prevented) this	Expert#1 No

	procedure/technology being adopted in your organisation or across the wider NHS?	Expert#2 No
		Expert#3 As per 22/ other answers above.
		Expert #4 Provision of FMT from an authorised and regulated stool bank will probably be the most convenient option for most of the NHS Trusts. In the absence of stool bank support, recruitment of suitable donors and ability to undertake the recommended screening would be a significant challenge for individual NHS Trusts.
		Expert #5 No we are doing it
		Expert #6 Availability of FMT material. Most Trusts do not have the resources to recruit and screen donors and manufacture the FMT
		Expert #7 no
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Expert#1 It would be very valuable to establish a robust UK registry of patients who have received FMT for long term follow up
		Expert#2 No
		Expert#3 Nil in addition to that already described.

		Expert #4 Long-term safety Delivery of FMT via capsules Safety and efficacy of FMT provision established locally vs that obtained via a regulated stool bank.
		Expert #5 -
		Expert #6 What is best route of administration? What makes a good donor?
		Expert #7 Role in non- c diff indications.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post	Expert#1 Beneficial outcome measures: Resolution of symptoms at 1 week post procedure Maintenance of benefit at 8-12 weeks post FMT Maintenance of remission at 1 year QOL using standard QOL scoring system at 1 week, 8-12 weeks and 1 year post FMT Need for recurrent administration of FMT Change in microbiome and metabolites following FMT (increased diversity) Adverse outcome measures: Immediate complications at 1 week Delayed complications at 8-12 weeks and 1 year post procedure

	procedure timescales over which these should be measured	Expert#2 Beneficial outcome measures: - Cure rate for recurrent/refractory CDI is the most important measure. - Other outcome measures are as documented in the BSG/HIS (and subsequent) guidelines. Adverse outcome measures: - Any adverse events should be reported, as advocated in the BSG/HIS (and subsequent) guidelines.
		Expert#3 Beneficial outcome measures: Rates of efficacy in treating rCDI symptoms (normally measured at eight weeks post-procedure); impact on quality of life. A previous published study (https://www.acpjournals.org/doi/pdf/10.7326/M18-3635) has also suggested that FMT for rCDI may also result in fewer bloodstream infections and/or lower all cause mortality, but this has not been confirmed prospectively. Adverse outcome measures: Failure rates (typically measured at eight weeks post-procedure); incidence of donor-to-recipient infection.
		Expert #4 Beneficial outcome measures: Recurrence of C. difficile infection over the subsequent 90 days and long-term (10 year), via patient follow-up and confirmation of any recurrence via review of diagnostic stool tests. Adverse outcome measures: Related to procedure for delivery FMT – usually occurs within a few days

		Adverse events from FMT – short term (within 30 days) and long-term (10 years)
		Expert #5 Happy to discuss in a meeting
		Expert #6 -
		Expert #7 -
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology	Expert#1 MTC in Birmingham continued to supply FMT from 'pre-COVID' donors until these stocks ran out in approximately April 2020. We have recently developed a novel stool SARS-CoV-2 stool assay and donor screening pathway which has been submitted to MHRA for approval. One this is received we will continue to supply around the UK according to need. The our quoted price (£650 per aliquot) will need adjusting in light of the new arrangements in light of COVID-19. We have recently completed a pilot trial of FMT for patients with ulcerative colitis. The procedure was well tolerated and effected a beneficial response in 75% patients treated with FMT delivered to the colon. IBD is likely to be the next treatment area for FMT as there are already three positive RCTs published.

		Expert# 2 Blank
		Expert#3 As above
		Expert #4 Consider including information on regulatory and procedural issues for NHS Trusts wishing to establish their own FMT provision on a named-patient basis, with consideration of advantages / disadvantages of FMT material provided by a regulated stool bank.
		Expert #5 See my published work
		Expert #6 -
		Expert #7 -

NICE National Institute for Health and Care Excellence

Patient expert statement

GID-MT566 Faecal microbiota transplant for recurrent Clostridioides difficile infection

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Olivia Anderson**

NICE National Institute for Health and Care Excellence

2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	NHS
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	C-diff puts people in a miserable situation; it's soul destroying, debilitating, you're not able to function. While isolated on a ward during covid I could only speak to my kids on the phone but I didn't want to, I felt so destroyed. I felt on edge as I had to be near a toilet, during a bout you feel like you're dying. Clinicians need to super aware of c-diff for diagnosis, listen to patients who have experience of C-diff, they know what's happening to them. There is a massive shame attached to soiling yourself, yet this is completely involuntary. This is mortifying and distressing. Elderly people or people who cannot vocalise or shout loud enough could feel this but not be able to vocalise their distress. The impact of this stays with you for a long time.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I found FMT easier than having IV antibiotics. I would rather have this treatment than have to have any more antibiotics!!
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Slightly more than 2 weeks since treatment, I have not had diarrhoea. I took one oral tablet, that was it, no pain from a procedure.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I struggled to drink the bowel clearing solution which needs to be done before the procedure; it was such a lot of liquid (2 x 2 litres)
Patient population	
13. Are there any groups of patients who might benefit	

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Elderly, people not able to vocalise their thoughts or distress.**
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For	

example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Need for responsive, understanding clinical team who can use humour as well as compassion.

- Acceptability: I was not squeamish about it but I could understand people's reticence. For me this was an oral tablet which changed my frenetic desperation to complete relief. My gut has made me mentally feel better. The idea behind the treatment made such sense to me.
- Elderly – could find it a massive relief, it would be beneficial after their 1st incidence of C-Diff as, in most cases, they are getting more co-morbidities that increase the risk of life threatening/severe illness with C-Diff and reduce ability to recover/have quality of life.
- Treat with FMT sooner - knowing that C-Diff sits in the bowel awaiting your next weak point, it should be part of the treatment after antibiotics have been completed for the first bout. Why we would wait for someone to be so weakened after multiple bouts of C-Diff?
- People close to the end of life are more inclined to suffer but people at my age can feel such shame; the soiling is mortifying and shaming, no control over it. Upsetting to hear other people in the same situation on a ward. Could people be treated with it sooner rather later?
- Based on my experience, it was a game changer for how I felt despite other health issues and I have been able to maintain working full time. I would think that it would not be difficult to include it as part of the recovery process, especially where a patient is admitted to hospital and would put them in a stronger position going forward. It's just so simple and the results/benefits are huge.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

NICE National Institute for Health and Care Excellence

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

NICE Medical Technologies Advisory Committee
Faecal microbiota transplant for recurrent Clostridioides difficile infection

Please read the guide to completing a submission fully before completing this template.

Information about your organisation	
Organisation name	Guts UK Charity
Contact person's name	Julie Thompson
Role or job title	Information Manager
Email	[redacted]
Telephone	[redacted]
Organisation type	Patient/carer organisation (e.g. a registered charity) ☒ Informal self-help group ☐ Unincorporated organisation ☐ Other, please state:
Organisation purpose (tick all that apply)	Advocacy ☒ Education ☒ Campaigning ☐ Service provider ☐ Research ☒ Other, please specify:
What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)? It is not a membership based organisation therefore this question is not applicable	

Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to medtech@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place. Up to 20 places will be available, depending on the size of the venue. Where meetings are oversubscribed NICE may need to limit the number of places we can offer.

Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

As a charity that supports people with digestive diseases, we are approached by people with lived experience of gastrointestinal infection including *Clostridium Difficile (C Difficile)*. I am the charities Information Manager and I handle any calls for information and support to the charity. I have also in my role as a health care professional have treated people for nutrition support in the past when they have been acutely unwell in hospital with *C. Difficile*. I am a member of the Gut Microbiota for health expert group for the British Society of Gastroenterology and as such I am a link for public awareness of the gut microbiota for this group. I also used a quality-of-life study for this submission published in Canada, not the UK, but this gave good insight into experiences of people diagnosed with *C. Difficile*. Jens Vent-Schmidt, Gail P Attara, Daniel Lisko, Theodore S Steiner (2020) Patient Experiences with Clostridioides difficile Infection: Results of a Canada-Wide Survey Patient Preference and Adherence 2020:14 33–4.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

Impact of the symptoms, condition or disease

1. How do symptoms and/or the condition or disease affect people's lives or experiences?

Hospital episode statistics from 2020-2021 reported 3,950 emergency hospital admissions hospital emergency admissions for C Difficile and these were mainly in older individuals. 72% of people in hospital reported severe watery diarrhoea (Vent-Schmidt et al, 2020), 63% fatigue (Vent-Schmidt et al, 2020), 53% experienced loss of appetite (Vent-Schmidt et al, 2020) and most of those who responded had two or more of these symptoms.

Having a diagnosis of *C difficile* and experiencing the severe diarrhoea symptoms that results have impact on patients' dignity. Patients who need hospital or nursing home care with *C Diff* may experience distress over symptoms with respect to privacy and dignity (Vent-Schmidt et al 2020). This is particularly the case with diarrhoea if this results in incontinence and frequent linen changes. Severe diarrhoea can prevent patients eating as they may feel that if they don't eat the symptoms will stop. This may exacerbate the symptoms of weight loss and dehydration experienced in hospital and in the community. Nutritional implications may mean longer hospital stay and slower recovery. A survey published by Vent-Schmidt et al, (2020) of people from Canada who have experience of *C Difficile* reported that 6% of patients experienced poor attitudes of hospital staff because of symptoms "I had a nurse berate me in emerge because I 'contaminated' the bathroom, screaming that in front of all the patients". In community living symptoms may prevent people from going out because they may be afraid of incontinence episodes in public and social stigma. In older population being able to go out and maintain activity levels is important for social interaction as well as maintaining strength and mobility.

167 survey responders' reported infection with *C Difficile* had a median quality of life score of 4 (needing some assistance with normal activities). 34% felt unable to care for themselves (QOL score 1 and 2), 35% unable to work or needing some assistance with normal activities (QOL of life score 3 or 4).

Frequently hospitalised patients have more than one diagnosed condition (*C Difficile* plus another diagnosis) this occurred in 73% of participants (Vent-Schmidt et al, 2020) this can really impact on functional status will affect how long people need to stay in hospital and impact on their recovery.

The highest priority reported for patients was improving time to diagnosis.

Little is known about the acceptability of this treatment in the public and knowledge of this treatment appears to be low, but this is a comment from personal experience not from survey results.

2. How do symptoms and/or the condition or disease affect carers and family?

Carers report a worse quality of life than those people with a diagnosis of *C Difficile*.

During the worse stage of infection 30% of carers reported a QoL score of 6 (needing institutional or hospital care) compared with only 10% of patients Vent-Schmidt et al, (2020). This might reflect the study population as the median age was 50-59 whereas this condition can occur in older individuals who may be less mobile and have higher degree of care needs. The fact that people with *C Difficile* can also have other co-morbidities, may put an additional burden on carers who might already have significant responsibilities.

3. Are there groups of people that have particular issues in managing their condition?

People who have lower level of mobility may not be able to reach a toilet quickly and have more episodes of incontinent and loss of dignity.

Experiences with currently available technologies

4. How well do currently available technologies work?

The current technology works well at least as effective if not more than antibiotics depending on the research reviewed. 7 to 9 out of ten people who have treatment will have benefit, with small number of transient side effects for most people.

5. Are there groups of people that have particular issues using the currently available technologies?

Depending on the mode of delivery there may be issues around religion and lifestyle if transplants are delivered by animal-based gelatine capsules.

About the medical technology being assessed

6. For those with experience of this technology, what difference did it make to their lives?

Unable to answer this question as we have not been able to discuss this with someone who has had the treatment.

7. For those without experience of the technology being assessed, what are the expectations of using it?

There may be more preferred means of delivery of faecal microbiota transplantation (FMT), people may feel it is more appropriate to deliver this by colonoscopy that via a feeding tube as this may be perceived as a more appropriate route. Others may not be able to have a colonoscopy and need an enteral feeding tube for delivery.

8. Which groups of people might benefit most from this technology?

People who have recurrent episodes of C Difficile and those at risk of severe disease and complications.

Additional information

9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

Key messages

10. In up to five statements, please list the most important points of your submission.

- ***C Difficile* results in severe diarrhoea and this can lead to loss of dignity and increased stigma. It is a severe infection and can lead to complications.**
- **A third of people with *C difficile* feel unable to work and need assistance with normal everyday activities.**
- **FMT works in about 7 to 10 people who have treatment depending on which research is viewed and is generally well tolerated.**
- **Treatment can improve quality of life, maintain independent living, and prevent complications.**
- **FMT is not widely available in the NHS and people should have better access to treatment.**

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

Thank you for your time. Please return your completed submission to helen.crosbie@nice.org.uk and medtech@nice.org.uk

Using your personal information: The personal data submitted on this form will be used by the National Institute for Health and Care Excellence for work on Medical Technologies (including reviews) and will be held on the Institute's databases for future reference in line with our privacy notice.

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

GID-MT566 Faecal microbiota transplant for recurrent Clostridioides difficile infection

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	4.11.2021	Expert engagement meeting with Tariq Iqbal, Horace Williams, Benjamin Mullish, Yashwant Mahida, Peter Hawkey, Simon Goldenberg, Tom Lee	Questions documented in Appendix 1	Meeting minutes in Appendix 1.
2.	11/11/2021	Prof Giovanni Cammarota (author of included trial Cammarota 2015)	1. You report following-up vancomycin-arm patients who had a C. difficile recurrence, to determine their clinical status. Could you confirm that of the 9 whom you could contact, 7 received 1 to 3 further courses of antibiotics for further recurrences?	1. Yes, confirmed 2. Yes, all patients underwent a follow-up after FMT 3. Patients were followed up the day after FMT, and 1, 2, 5, 10 weeks after FMT

#	Date	Who / Purpose	Question/request	Response received
			2. Could you clarify whether patients in the FMT arm were similarly followed-up for use of further antibiotics for further C. difficile infection recurrence? 3. Could you confirm the timepoint during patient follow-up at which this check was performed?	
2.	16/11/2021	Prof Giovanni Cammarota (author of included trial Cammarota 2015) To clarify response received.	I was wondering whether you could clarify at what month/week of follow-up you performed your check of further antibiotic use in the relapsed vancomycin patients? In your paper you state October 2014, but it would be helpful for us if we could write down a time of follow-up for both arms. Secondly, your paper reports that 2 FMT patients received antibiotics for further recurrence (both were PMC patients). In October 2014, did you also follow-up on all FMT patients for further antibiotic use, or were your records for the FMT group limited to your trial follow-up period (10 weeks)?	No response received.
3.	8/12/2021	Professor Simon Goldberg (Clinical expert)	As part of this we have been trying to accurately capture costs associated with FMT, in particular the total cost associated with providing FMT via an oral capsule. From our internal discussions it was suggested that you might have an insight into this. Any guidance you could provide would be appreciated.	It's actually quite difficult to be confident about the costs but I estimate this to be £500-600, assuming we are manufacturing to GMP standards

#	Date	Who / Purpose	Question/request	Response received
4.	13/01/2022	Professor Tariq Iqbal (Clinical expert)	In the NICE expert meeting last November, I remember you mentioning an estimate for the annual number of UK patients presenting with a second or higher CDI recurrence. Unfortunately this was not recorded. Would you be able to provide us with this estimate again for the MTAC report?	At the MTC we treat about 250-300 patients with FMT annually. As there are about 1500 CDI cases we are probably missing about 200. To clarify, 450-500 cases treated annually with FMT across the UK due to multiple CDI recurrences or refractory CDI. If we move to prophylaxis to prevent a recurrence then we should be looking at 1000-1500 a year.
5.	19/01/2022	Clinical experts: Tariq Iqbal, Horace Williams, Benjamin Mullish, Yashwant Mahida, Peter Hawkey, Simon Goldenberg, Tom Lee	Currently costs for providing FMT via NGT is sourced from the Abdali 2020 study. Is it reasonable to assume that those costs would be applicable for administering FMT via NDT? We currently assume that pre-antibiotic treatment is only provided for the initial FMT treatment in the model and not for any subsequent FMT treatment, if the CDI is unresolved or reoccurs. Is this reasonable?	Peter Hawkey- delivery costs for NGT in Abdali are ok and are based on the Birmingham service costs. We have never recommended Naso-duodenal delivery and it does not appear to offer any clear benefit. It is however more expensive as flexible endoscopy is required. The pre-treatment is part of the patient journey in acquiring recurrent CDI so should not be part of the cost of FMT. Benjamin Mullish- Not necessarily reasonable to assume costs for nasoduodenal tube would be similar, since these might require a gastroscopy or interventional radiology procedure to inset. If an FMT for C diff fails, my personal practice has been to give a further short course of vancomycin (3-5 days) before the next FMT. Lee Thomas- The only slight difference in practice to the NGT costings in the Abdali paper is that a CXR isn`t always needed. If the NG tube position can be confirmed with pH testing, a CXR isn`t

#	Date	Who / Purpose	Question/request	Response received
				performed. If a CXR is performed, staff time for checking the CXR has not considered. Horace Williams- I would factor in the cost of a CXR after NG tube insertion, and a clinical review of the CXR.
6.	22/02/2022	Clinical experts: Tariq Iqbal, Horace Williams, Benjamin Mullish, Yashwant Mahida, Peter Hawkey, Simon Goldenberg, Tom Lee	**General questions:** 1. We note that the FMT sample preparation process may include ingredients derived from animals. Could you confirm whether you use animal-derived products during your preparation of FMT product? This could include: • animal-derived gelatin for oral capsule preparation • animal-derived glycerol in the production of frozen FMT • or any other process involving animal product (please specify the product and animal of origin) 2. If you do use any animal product, have you tried to source or use any non-animal alternatives? **Modelling specific questions:** 3. We have assumed that for the index treatment people will spend 5 days in hospital if on FMT and 10 days if on antibiotics alone (following the same approach applied in Abdali (2020)). Is this reasonable, and if not please could you provide an	1&2. Benjamin Mullish: "Have looked up about glycerol we use (which comes from a major chemical supplier) and I can't see details on its source. On a bit of online research, it looks like that most supplied by major chemical suppliers is a byproduct of soap production or petroleum processes and animal-derived is rarer? But don't think I can confirm this." 3. Benjamin Mullish: "I think reasonable to use that source, so that sounds OK." 4. Benjamin Mullish "I don't fully understand this but... everyone gets antibiotics for CDI but only some people are considered for/ given the option of FMT/IMT. For those patients where it may be appropriate, patients will have an extra consultation with a doctor (gastroenterology/ microbiology/ infectious diseases) and/or specialist nurse to discuss/ consent for FMT/IMT. We also hold a 'virtual MDT' for referrals (i.e. case discussion via email of all stakeholders) where we have been asked to do an FMT/IMT to seek approval; I think others may have a similar process. However - are you saying that you have

#	Date	Who / Purpose	Question/request	Response received
			indication of the length of stay you would expect to see for this population? 4. We have received feedback suggesting factoring in gastroenterologist consultation to account for discussion with patient and consent for FMT treatment. We have assumed this discussion on treatment would be applicable to people regardless of whether they end up having FMT or antibiotics alone. Therefore, there would be no impact incrementally. Is this assumption correct?	already accounted for a discussion, but this cost/ resource is the same whether patients end up receiving FMT/IMT or whether they end up continuing with antibiotics? I might have not understood this right so apologies if so."

Appendix 1.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from question 1:

See Appendix 1

File attachments/additional information from question 2:

No attachments or additional information

File attachments/additional information from question 3:

No attachments or additional information

File attachments/additional information from question 4:

No attachments or additional information

File attachments/additional information from question 5:

No attachments or additional information

File attachments/additional information from question 6:

No attachments or additional information

Appendix 1

GID-MT566 Faecal microbiota transplant - Expert Engagement Meeting

4th November 2021

1. PRESENT

External experts: Tariq Iqbal (TI), Horace Williams (HW), Benjamin Mullish (BM), Yashwant Mahida (YM), Peter Hawkey (PH), Simon Goldenberg (SG), Tom Lee (TL)

NICE: Cheryl Hookway (CH), Kim Carter (KC), Charlotte Pelekanou (CP), Anastasia Chalkidou (AC), Chris Chesters (CC), Helen Crosbie (HC)

York Health Economic Consortium (YHEC): Katy Wilson (KW), Lavinia Ferrante di Ruffano (LF), Laura Coote (LC), Laura Kelly (LK)

2. INTRODUCTIONS

- KC introduced the purpose of the expert engagement meeting. The aim of the project is to evaluate FMT for recurrent CDI through systematic reviews of the clinical effects and safety and economic evaluation data with cost saving assessed by a health economic model.

QUESTIONS FOR EXPERTS

Question 1 (NICE): Can you explain the difference between recurrent, refractory and relapsed C. difficile infections? Is this something that can be clearly distinguished within NHS practice?

- YM commented that there may be microbiological differences between recurrence and relapse of CDI, however this does not translate into clinical practice.

- SG commented that recurrence is a broad category which encompasses both relapse and reinfection), relapse is infection with the same strain whilst reinfection is infection with a different strain. Another episode within 12 weeks is often defined as a relapse, and as a reinfection after 12 weeks, although different cut-off values are used. Refractory CDI is when the patient doesn't adequately respond to current treatment.

- PH agreed with these definitions and commented that in clinic it is hard to distinguish between recurrence and relapse.

- Agreement from all experts that in clinical practice all patients representing are managed as recurrences. Further agreement on definition of refractory.

Question 2 (NICE): NICE's guideline on Clostridioides difficile infection: antimicrobial prescribing recommends considering FMT for a recurrent episode of C. difficile infection in adults who have had 2 or more previous episodes. In practice, would FMT be the first treatment option for the third episode of C. difficile infection or would antibiotics be tried first?

- TI commented that the treatment depends on the patient.

- PH stated that it also depends on local practice. The paper from Birmingham (Abdali et al., 2020) demonstrates potential comparators than can be used for FMT, FMT via NGT, FMT via colonoscopy, oral fidaxomicin, oral vancomycin.

- SG commented that first line treatment is often vancomycin with a few centres still using metronidazole in mild cases, recurrent patients would receive vancomycin or fidaxomicin and patients with repeated recurrences should receive FMT.

- YM and IT discussed the need to take into account patient preferences for receiving FMT. Variation amongst experts regarding personal experience of patients declining, with the majority stating very high acceptance at their clinics.

Question 3 (NICE): What would you consider to be the comparator for FMT (when used as a third line treatment)? Are the recommendations on antibiotic use described in the NICE guideline on Clostridioides difficile infection: antimicrobial prescribing appropriate for all patients?

- TL stated that tapered vancomycin could be a comparator for FMT.

- SG stated that extended pulse vancomycin can be used in practice if standard dosing of vancomycin has failed. Also added that extended pulse fidaxomicin would be considered in some clinics.

- HW stated that in Europe Bezlotoxumab is an accepted clinical comparator.

Question 4 (NICE): Should any of the following doses/regimens for Vancomycin and Vancomycin Taper Pulse not be compared to FMT?

- SG commented that 500mg of vancomycin is not appropriate, as the antibiotic is non-absorbing and so can achieve high concentrations in the bowel with 125mg dose. The evidence for higher dosing is scarce and only realistically used in patients with gut motility issues/ileus (where there is doubt about sufficient amounts of the agent reaching the large bowel) who may need a higher dose.

- TI stated that dose 250mg four times a day is also used in clinic.

- For taper pulse: expert agreement that there is variability in dose, pulse and taper length. YM commented that 125mg 4 times a day for a week, then reducing doses every week to end with 1 week of 125mg every 2-3 days is standard. TL reports using a 6 week taper (250mg or 125mg 4 times a day for 14 days, twice a day for 7 days, daily for 7 days, every other day for last 7 days).

- KC commented that the model can explore the impact of different dosages of vancomycin through sensitivity analysis.

Question 5 (NICE): How does sample processing work in centralised banks and in-house usage? What specialisms are involved? Are special facilities needed? Is there a reason for in-house processing over the use of a centralised bank? If FMT usage increased in this population, would changes need to be made to how samples are processed?

- PH stated that in Birmingham samples are processed through a stool bank rather than in-house. Processing could easily be scaled up in the circumstance of higher demand. Due to MHRA licencing pharmacy exemptions, quality control and sterile conditions in house sample preparation is not viable.

- PH stated the FMT product from Birmingham stool bank is currently transported using Blood Bikes and did not think there would be capacity issues if this process was scaled up. Use of a courier service would increase the cost per sample.

- TI commented that FMT is now being considered as a prophylactic in C.diff patients who respond to antibiotics, noting that this may change the conversation regarding adoption into the NHS including the development of stool sample banks.

Question 6 (NICE): Are the rules for quality assurance, pathogen screening, and donor selection outlined by BSG guidelines routinely used in the NHS for FMT production? Are samples now routinely screened for SARS-CoV-2 (COVID-19)? Is this Is this likely to be common practice going forward?

- BM stated that screening of samples is required.

- TI confirmed that all donors and samples are now screened for SARS-CoV-2, and that this includes donor naso-pharyngeal swabbing, completion of self-reported social distancing during the donation cycle and stool testing. Donor screening is performed at the beginning and end of a donation cycle and a 2 week quarantine period is employed .

- CP commented that due to adding SARS-CoV-2 screening, the cost of sampling has gone up by approximately £200. Is this cost likely to continue and how many samples can be taken from a donor?

- TI confirmed that the cost for an FMT sample has gone from approximately £650 to £850.

- PH commented that the testing for COVID is likely to continue into the foreseeable future.

- TI commented that from one donor there can be a maximum of 70 donations taken over a 10 day period.

- Experts agreed requirement for extensive donor screening for very immune comprised patients is a bit contentious

Question 7 (NICE): Can you explain how the MHRA regulations work in practice for FMT for centralised banks and for in-house FMT processing?

- There were no further comments from the clinical experts as this was deemed already to have been covered.

Question 8 (NICE): What factors determine the route of FMT administration used? Do you know what proportion of patients have different FMT administration options?

- TI commented that the most common form of FMT from the MTC is via nasogastric tube (NGT). A small proportion receive colonic, approximately 5 to 10%. Their rationale is the population is elderly and NGT is less invasive than colonoscopy.

- SG stated that in his clinic the use of capsules are increasing. Approximately half get capsules and half get a colonoscopy. Advantage of capsules is no bowel prep needed, fewer resources needed overall, and not at all invasive and well accepted/preferred by patients.

- HW/BM commented that in their clinic administration is mostly via NGT but believes that the use of pills will increase. The administration route is down to local experience. An advantage of capsules is that centres don't need procedural expertise.

- The patient population in the UK are elderly, with several comorbidities, and frail.

- BM stated that the route depends on the patient and their preference.

- TL commented that it is majority colonoscopy in his clinic, because they have a specialist centre.

- YM commented that delivery via flexible sigmoidoscopy can also be successful.

- PH summarised procedural risks: the main risk for NGT is incorrect tube placement, for which a chest x-ray is needed. The main risk of colonoscopy is perforation.

Question 9 (NICE): What is current practice for preparing patients for FMT? Is bowel lavage and/or short course antibiotics routinely used? Is there a rationale for these additional steps being used or not used? Are there differences depending on administration route?

- PH stated that in his clinic bowel lavage is never used and this hasn't ever been a problem. They also do not use preceding short-course of antibiotics.

- TI commented that many patients are hospitalised and so will have had a preceding course of antibiotics for CDI.

- CH enquired about use of proton pump inhibitors and prokinetics with administration by NGT vs naso jejunal tube and in particular for people at higher risk of aspiration.

- PH added (BM and HW agreed) that for patients at risk of aspiration a prokinetic is used in advance of NJT administration. PH further noted the complication rate for NGT delivery is virtually zero.

- BM commented that he has used bowel lavage but there is no clear evidence on efficacy.

- HW commented that patients stop antibiotics 24 to 48 hours before their procedure.

- HW noted that all patients receiving an NGT FMT need a chest x-ray.

- SG stated that in patients with swallowing difficulties they will give an empty capsule to test that the patient can swallow without biting or chewing the capsule

Question 10 (NICE): Within each of the 3 modes of delivery (Upper GI, Lower GI, Oral Capsule), are procedural differences between different methods likely to influence treatment effects (such as between enema and colonoscopy, or flexible sigmoidoscopy and colonoscopy)?

- BM commented that upper or lower GI are quite involved processes.
- SG stated that the procedure is often trial and error.
- BM/HW commented that for capsules, finding the right dose and a prep that works is more complicated than other methods of administration.
- TI commented that 1 FMT aliquot is needed for NGT FMT and 3 aliquots are needed for colonic administration.

Question 11 (NICE): What is the resource use associated with recurrent or refractory C. difficile infections? (i.e. isolation rooms, procedure rooms times, follow-up appointments or hospital visits). How does FMT treatment affect this?

- SG stated that there is a costing resource from Guys and St Thomas. In comparison a first episode of CDI is approximately £12,000 to treat whilst recurrent is approximately £30,000. These costs are from their full hospital episode as it is hard to separate out costs of before and after getting CDI. The cost of hospitalisation is the biggest difference.
- PH commented that the nasogastric route requires an x-ray.
- TI stated that the cost was approximately £850/50ml aliquot, or three aliquots for the price of two.
- SG commented that the requirement is five lyophilised FMT capsules, if not lyophilised then will require 10 to 20 capsules.
- TI commented that another potential benefit of FMT is reducing onward transmission in hospitals by reducing C.difficile spores.

Question (CH): The current distribution method of samples is through a voluntary service, is this sustainable?

- PH commented that the voluntary service is a reliable distribution method and to continue into the future. Couriers are more expensive £200 to £250.
- SG stated that at Guys and St Thomas there aren't any transport costs as referrals come to the hospital as their approval is for Investigational Medicinal Product, different to the system at Birmingham.

Question (CH): What is done to make the procedure more attractive to patients?

- TI stated that the capsules could be coloured rather than be transparent and to be mindful of the language used in describing the treatment and administration.

Question (HC): NICE support public involvement for all guidance and are interested in recruiting a patient expert.

- TI stated that they are likely to be able to find a patient, although the general patient demographic will be elderly with comorbidities and likely limited mobility.
- BM commented that carers may be another demographic to ask.
- PH commented that women post pregnancy may be another target population to ask.
- HC stated that the meeting is scheduled for the 18th March and that she will send the experts a follow up email.

3. ANY OTHER BUISNESS

YHEC will circulate the meeting minutes. The committee meeting in March will be the next formal step, where only three external experts will be needed.

NICE National Institute for Health and Care Excellence

Assessment Report Fact Check

GID-MT566 Faecal microbiota transplant for recurrent *Clostridioides difficile* infection

There were 6 consultees who responded to the factual inaccuracy and key assumptions check of the external assessment centre's assessment report. This included:

- 5 Clinical experts
- 1 Patient organisation
- 1 NHS organisation

The 1 NHS organisation did not have any comments and so were excluded from the below table.

The technology

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response
1	Are there any factual inaccuracies in the way the technology has been described? (pages 14-15)	1	Patient Organisation	I wonder if it is worth stating in the document technology description an alternative way of describing FMT as intestinal microbiota transplantation (IMT).	IMT would be perhaps a more acceptable means of describing the technology for patients who might have treatment than faecal microbiota transplantation.	The EAC defers to MTAC as the project title is declared by NICE. The EAC notes that changing the nomenclature to IMT to increase acceptability has been suggested in published letter form.
		2	Clinical Expert	Relatively minor point (page 14): perhaps indicate that in majority of the studies, faecal matter was diluted using 0.9% saline	In the RCTs that compared FMT with antibiotics, the faecal matter was diluted using 0.9% saline	We thank the expert for highlighting this, and have amended the following report sections:

						Section 2 Overview of the technology describes FMT as a procedure rather than the evidence identified in the systematic review, so we have amended wording to reflect the predominance of saline as the diluting agent. Section 5.1 Overview of methodologies of included studies – we have added a sentence that all trials used saline as the mixing agent (Hota 2017 did not specify concentration).
		3	Clinical Expert	'…implants a sample of gut microorganisms from a healthy donor…'	We think it is not just the microorganisms that provide efficacy of FMT but also, for instance, the metabolites produced by those chemicals. Consider rewording to something like: '…implants a sample of gut microorganisms (and of the	We thank the expert for this information and have clarified this point in the report.

					surrounding environment in which they are found) from a screened healthy donor…'.	
		4	Clinical Expert	P9/203 (and similarly P14/203). Suggested opening sentence for P9 (with similar alteration to the sentence on P14): 'Faecal microbiota transplant (FMT) for Clostridiodes difficile infection involves the transfer of faecal matter from a healthy donor into the gastrointestinal (GI) tract of an infected individual.' P9/203. Bowel lavage or preparation, rather than wash.	I would suggest changing these opening sentences to improve clarity. The verb 'implant' is not usually used in this context. This is the usual terminology.	We have amended our terminology as suggested.
		5	Clinical Expert	Page 14, final paragraph "Each transplant of a faecal sample is referred to as an infusion". Infusions are instillations of a liquid, so this term would not cover capsules (which are ingested). Page 14, final paragraph "All 3 methods of delivery use the same mechanism of action". The underlying mechanism(s) of action is poorly understood, so difficult to state this is the case with certainty.		We thank the expert for this information and have clarified both these points in the report.
2	Have all appropriate equality considerations been	1	Patient Organisation	As current treatment is application by endoscopy or enteral tube this might not be applicable, but if FMT is given by	Gelatine components are avoided by certain religious or cultural	We thank the organisation for this important

	considered? (page 16)			capsule there might be religious considerations to be made depending on the capsule components.	groups if it is derived from pork.	information. Although we did not include any trials evaluating oral capsules, we have examined excluded studies and can confirm that gelatine has been used in oral capsule preparation, so we have added this to the special considerations section. We have also checked the reported sampling processes in included trials and note that glycerol (which can be made using animal product, generally beef) was used for producing the frozen product in one trial (Hvas 2019). We have inserted this knowledge into the special considerations section.
		2	Clinical Expert	Appear appropriate	-	-

		3	Clinical Expert	-	-	-
		4	Clinical Expert	I think the current statement is appropriate.		
		5	Clinical Expert	No additional considerations identified		

Clinical evidence

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response
3	The included evidence focused on published RCTs in which FMT was compared to antibiotic treatment (in line with the scope of the assessment). Has any key clinical evidence been missed from this report? (pages 18-40)	1	Patient Organisation	-	-	-
		2	Clinical Expert	Not aware of additional key evidence with the specified scope		
		3	Clinical Expert	Was this study considered? https://www.acpjournals.org/doi/full/10.7326/M16-0271 - in this study, patients randomised to the placebo arm received their own stool. I think this study would not qualify on the definition of FMT – but was this study considered? https://www.nejm.org/doi/full/10.1056/NEJMoa2106516	I think would reach the criteria of 'comparator' set in Table 2. I would expect that Firmicutes spore from human donor stool is too far removed to be considered as 'FMT', but perhaps this merits a comment?	These two RCTs were identified during searching, but were excluded on the following grounds: Kelly 2020: This trial was ineligible for inclusion in the systematic review as it compared FMT vs FMT. Only trials comparing FMT to a comparator arm receiving antibiotics

						only were eligible for inclusion based on the NICE scope. All RCTs comparing FMT to FMT, or FMT to placebo, were therefore excluded. Feuerstadt 2022: we did not identify the full text as it was published after our searches were conducted. However, we did identify the NCT record (NCT03183128). We excluded this trial on the basis that the intervention is not an FMT product, and that the comparator is placebo and not antibiotics. Antibiotics were used prior to the interventions, but as a study eligibility criterion for patients entering the trial. Placebo is not an eligible comparator

						for the systematic review.
		4	Clinical Expert	Not as far as I am aware.		
		5	Clinical Expert	None identified		
4	Are there any factual inaccuracies in the results presented from the evidence base? (pages 35-57)	1	Patient Organisation	-	-	-
		2	Clinical Expert	Not identified	-	
		3	Clinical Expert	-	-	-
		4	Clinical Expert	No. But on P60, 'No trials reported on the effectiveness of FMT to treat patients with refractory CDI', I think it is worth commenting on the looseness of the terms 'recurrent / refractory' in this context, as per our discussion during the video conference.	This is contentious, as we discussed in the video conference.	Thank you for reminding us of the important discussion around terminology, we have added a paragraph of explanatory text at the beginning of section 8 (Interpretation of the clinical evidence) to draw attention to this. The EAC would like to emphasise that although the patient eligibility criteria of the 5

						included RCTs may have included some refractory patients, the focus of these trials was very much relapse/recurrence.
		5	Clinical Expert	None identified		
5	Do you know of any UK-based adverse events not listed in pages 62 to 64?	1	Patient Organisation	No		
		2	Clinical Expert	Aware of US-based adverse events		
		3	Clinical Expert	An often quoted case report from the UK of a serious adverse event after FMT is: https://academic.oup.com/cid/article/61/1/136/340816	I am not aware of any literature from UK experience reporting FMT-related adverse events other than this	Thank you for highlighting this reference. As the scope was limited to RCTs, case report evidence has not been systematically searched for and identified as part of the safety review and therefore the EAC does not consider it appropriate to include one specific report as evidence. However, considering this case is referred to often, we have inserted a

						justification of our findings of no serious harm in section 8.
		4	Clinical Expert	I recall publication of a case of aspiration pneumonia in the UK.		Thank you for highlighting this case report. As the scope was limited to RCTs, case report evidence has not been systematically searched for and identified as part of the safety review and therefore the EAC does not consider it appropriate to include one specific report as evidence. However, considering this case is referred to often, we have inserted a justification of our findings of no serious harm in section 8.
		5	Clinical Expert	None identified		
6	Do you know of any ongoing studies not listed on page 74?	1	Patient Organisation	No		
		2	Clinical Expert	Not aware of additional involving FMT		

		3	Clinical Expert	-	-	-
		4	Clinical Expert	No.		
		5	Clinical Expert	None identified		

Economic evidence

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response
7	Eight economic evaluation studies were included that were relevant to the decision problem, are there any additional studies that should be included that are not reported here? (pages 75-79)	1	Patient Organisation	-	-	-
		2	Clinical Expert	Not aware of relevant additional		
		3	Clinical Expert	-	-	-
		4	Clinical Expert	No.		
		5	Clinical Expert	None identified		
8	Are the interventions and comparators used in the economic model appropriate for the NHS population needing FMT?	1	Patient Organisation	-	-	-
		2	Clinical Expert	Appear appropriate to me. Page 98, second paragraph, suggest change “pathogen” to “strain of *C. difficile*”		Thank you, the wording has been amended in the report.
		3	Clinical Expert	Should the intervention be ‘nasogastric tube’ rather than nasoduodenal?	As discussed before, NG tube is used much more	Whilst the EAC acknowledges that NGT FMT delivery is

					frequently than ND tube for FMT administration in the UK. However, note that page 96 says that no RCTs identified with NG tube to inform results of economic model.	commonly used in the UK it has not been included in the model due to insufficient RCT evidence within this population to inform parameters. Additional context has been added to the methods section and conclusion to reflect the potential benefits of NGT based on results for the other routes of administering FMT included in the model.
		4	Clinical Expert	The points made about NG versus ND and NJ tube administration on P96 are valid and correct. However, the conclusion of this section should be clarified.		Thank you for the feedback. Additional text has been added to page 96 to conclude how the gaps in evidence regarding NGT is addressed in the report.
		5	Clinical Expert	Yes, although fidaxomicin as an extended-pulsed dose regimen is not included as a comparator and may result in less recurrence than the standard dosing regimen.		Thank you for the feedback. The comparators included were based on those reported in the NICE scope and for which data could be obtained for the

						selected population for this assessment (third episode of CDI) from RCTs.
9	Is the rationale for the model design listed on page 98 to 99 appropriate for using FMT in this population?	1	Patient Organisation	-	-	-
		2	Clinical Expert	Believe appropriate based on the identified clinical trials.		
		3	Clinical Expert	-	-	-
		4	Clinical Expert	Yes.		
		5	Clinical Expert	Yes		
10	Are the key assumptions listed on page 99 to 100 appropriate for using FMT in this population?	1	Patient Organisation	-	-	-
		2	Clinical Expert	"…it is assumed that the risk of death is comparable to the general population, once recovered." Clinical experience suggests this may not be the case. There may be publications that have addressed this issue. "..include 5 days of hospital stay for FMT and 10 days hospital stay for antibiotics.." Based on clinical experience, is likely to be shorter.		Thank you for the feedback, we acknowledge this is a limitation of the model. However, no quantitative evidence was found to inform parameters to inform increased mortality in this population following a targeted literature search. A multi-centre cohort study (Hensgens 2013)

						stated that the long-term excess mortality associated with CDI may be higher, but small. Therefore, the impact on results are likely marginal. However, this will be addressed qualitatively in the report. The impact of this assumption is also described in the results section. The impact of the length of stay of assumption on the results has been included in the report.
		3	Clinical Expert	-	-	-
		4	Clinical Expert	I appreciate the discussions about NG/ND/NJ tubes on P96 and the lack of RCT evidence for NG. But NG tube administration remains one of the most common routes for administration in the UK and so the use of ND data (P100 onwards) makes for difficult reading from a UK perspective. I think a further comment about this is necessary on P100.	See comments in the box on the left.	Thank you for the feedback. Additional text has been added to the clinical parameters section for context on what evidence is available for NGT. This is discussed further in the conclusion section to provide an

						indication of the economic impact of FMT via NGT against the comparators considered.
		5	Clinical Expert	Table 28 – clinical parameters used for the model. Is the rate of CDI resolution used for vancomycin (19%) and fidaxomicin (42%) on the low side, and what is the rationale for using Hvas 2019 to populate this parameter? Louie 2011 found a clinical cure rate of 85.8% for vanclomycin and 88.2% for fidaxomicin (NJEM 2011;364:422-31). In a similar RCT Cornely found clinical cure rates of 90.6% and 91.7% respectively (Lancet Infect Dis 2012;12:281-9. Similarly for recurrence rates, the Hvas reference has high recurrence rates for fidaxomicin (46%) compared with Louie (15.4%).		Thank you for providing the additional studies. We identified 5 randomised clinical trials based on the evidence review criteria. Of those, van Nood 2013 and Hvas 2019 included vancomycin treatments. van Nood included people with 1st CDI recurrence cases as well and had a smaller sample size. For this reason, the Hvas RCT was used to inform effectiveness data for vancomycin. Of the 5 eligible studies, Hvas 2019 was also the only study which reported outcomes for fidaxomicin. Whilst there are limitations with all of the evidence, we

						considered Hvas 2019, the most appropriate to inform model parameters. We note that in Cornely 2012 and Louie 2011 more than 80% of the populations were not recurrent CDI cases. Therefore, we considered these data should not be applied to the recurrent population.
11	Are the cost parameters used in the model appropriate (tables 29-32)? Are there any costs to the NHS missed in the total calculation of treatment costs?	1	Patient Organisation	-	-	-
		2	Clinical Expert	Suggest consider additional time of Consultant Gastroenterologist for initial consultation and consent for the procedure. Page 96: "…, it was assumed that any conclusions regarding the clinical benefits of NDT, as sourced from van Nood, may be applicable for NGT." Should Table 30 therefore consider cost of NGT, instead of NDT?		Assuming that treatment options will be discussed with the patient and that this would be applicable for both arms, suggest not updating the costs currently applied in the model. Regarding NDT/NGT cost, additional text has been added outlining the total cost of administering FMT via NGT.

		3	Clinical Expert	-	-	
		4	Clinical Expert	An NG tube insertion would not involve the £1000 ND insertion cost.		Additional text has been added to the cost section to clarify that the cost of providing NGT is lower than for NDT. Cost reported in Abdali (2020) is included for context.
		5	Clinical Expert	These are reasonable estimates, however real costs are likely to be subject to significant variation.		Thank you for this feedback.
12	Are there any areas of key uncertainty in which additional scenario analysis would be warranted? (pages 110-111)	1	Patient Organisation	-	-	
		2	Clinical Expert	-	-	
		3	Clinical Expert	-	-	
		4	Clinical Expert	No.		
		5	Clinical Expert	None identified		

Further comments

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response

13	Please add any further comments relating to factual inaccuracies on the assessment report.	1	Patient Organisation	-	-	-
		2	Clinical Expert	-	-	-
		3	Clinical Expert	Page 12 - Negative stool test for CD toxin during follow up period (experts state that this measure may be unreliable for up to 3 months post procedure).	I think most expert authorities would say positivity lasts typically for up to 30 days, I am not aware of evidence saying up to 3 months but I may be incorrect.	This comment is in relation to the wording of the NICE scope .
		4	Clinical Expert	P120: I acknowledge these sentences: 'Previous analyses have combined NDT and NGT data when pooling results. Therefore, based on the assumption that NDT efficacy data is comparable to NGT, FMT via NGT is also likely to be a cost saving treatment option for this population against all three comparators considered. Particularly, since the cost of NGT (Abdali (2020)) is approximately 50% cheaper than NDT.' This is a vitally important point for UK users. I think that (brief) statements to this effect should be included each time NDT is mentioned and referenced in the economic modelling section, to ensure	See comments in the box on the left.	The conclusion section has been updated to provide more clear application of the model results to the NGT context. This includes comparing what evidence is available to indicate the cost and effectiveness of NGT to other forms of FMT administration included in the model.

				that this work remains relevant to the UK and to a UK audience.		
		5	Clinical Expert	None identified		

Economic model comments (if requested to review the model)

		Consultee ID	Consultee Role	Description of proposed amendment	Justification for amendment	EAC response
14	Please add comments relating to errors or omissions within the economic model.	1	Patient Organisation	-	-	-
		2	Clinical Expert	-	-	-
		3	Clinical Expert	-	-	-
		4	Clinical Expert	-	-	-
		5	Clinical Expert	NA		