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