NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

Faecal microbiota transplant for recurrent *Clostridioides difficile* infection

How medical technology guidance supports innovation

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice.

If the case for adopting the technology is supported, the specific recommendations are not intended to limit use of other relevant technologies that may offer similar advantages. If the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

1 Recommendations

1.1 Faecal microbiota transplant (FMT) is recommended as a cost saving option to treat recurrent *Clostridioides difficile* infection in adults who have had 2 or more previous episodes.

Why the committee made these recommendations

Clinical trial evidence shows that FMT is significantly better than antibiotics at resolving a *C. difficile* infection in people who have had 2 or more previous infections.

FMT is cheaper than all treatment with antibiotics, regardless of how it is delivered. It is cost saving by at least £1,500 per person.

2 The technology

Technology

2.1 Faecal microbiota transplant (FMT) aims to restore a healthy gut microbiome in people who have recurrent or refractory *Clostridioides difficile* infections. It involves transferring intestinal bacteria and other microorganisms from healthy donor faeces into the gut of the recipient.

2.2 FMT can be used as a fresh or frozen preparation or in capsule form. It can be given via a lower gastrointestinal route (rectal enema, colonoscopy or flexible sigmoidoscopy), upper gastrointestinal route (using a nasogastric tube, nasoduodenal tube or nasojejunal tube) or via oral capsules.

2.3 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. A strict donor screening programme should also be in place for FMT. An FMT service should be delivered by a multidisciplinary team.

Care pathway

2.4 First-line treatment for a *C. difficile* infection involves rehydration and antibiotic therapy. Some people have recurrent, relapsing, or refractory *C. difficile* infections and need further courses of antibiotics. NICE's guideline on antimicrobial prescribing for *C. difficile* infection recommends antibiotics for first and second *C. difficile* infections and recommends considering 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 says 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 normal arrangements are in place for clinical governance, consent and audit. It also says that clinicians should ensure that a confidential record is kept of the donor and recipient of each faecal microbiota transplant.

Innovative aspects

2.5 The aim of the procedure is to treat the infection with transplanted gut microbiota instead of prescribing further courses of antibiotics.

Costs

2.6 The cost of frozen FMT material is £850 per 50 ml or £1,700 for 150 ml. Oral capsules cost between £500 and £600, based on expert opinion. Additional costs include staff time, procedural costs, additional drugs given as part of the procedure and pretreatment short-course antibiotics.

3 Evidence

NICE commissioned an external assessment centre (EAC) to review the evidence. This section summarises that review. Full details of all the evidence are in the project documents on the NICE website.

Clinical evidence

The clinical evidence comprises 5 randomised controlled trials

3.1 The EAC did a literature search to find randomised controlled trials (RCTs) comparing faecal microbiota transplant (FMT), by any route of delivery, with NICE-recommended comparators, to treat a *Clostridioides difficile* infection in people who have had at least 2 previous episodes. It identified and assessed 5 RCTs including 274 adults in total. For full details of the clinical evidence, see section 3 of the assessment report.

More *C. difficile* infections resolved with FMT than antibiotics in 4 RCTs; there was no difference in 1 RCT

3.2 FMT was significantly better at resolving a *C. difficile* infection than:

- vancomycin in 4 RCTs (Cammarota et al. 2015, Hvas et al. 2019, Rode et al. 2021 and van Nood et al. 2013)
- fidaxomicin in 1 RCT (Hvas et al. 2019).

C. difficile infection was resolved in 57% (Rode et al. 2021) to 94% (van Nood et al. 2013) of people having FMT (when any number of infusions was considered). However, Hota et al. (2017) showed less *C. difficile* infection resolution in the FMT group (given via enema) compared with vancomycin taper pulse (VTP; 43.8% compared with 58.3%, respectively), although they did not report statistical significance.

Recurrence rate is comparable to or lower than antibiotics

3.3 Three trials found lower *C. difficile* infection recurrence in the FMT group (range 6% to 10%) compared with the antibiotic group (vancomycin range 62% to 69%, fidaxomicin 46%; Cammarota et al. 2015, Hvas et al. 2019 and van Nood et al. 2013). Hota et al. (2017) reported comparable *C. difficile* infection recurrence after FMT by enema (56.2%) and VTP (41.7%). However, none of the trials reported statistical significance.

Gastrointestinal side effects can occur in the short term after FMT

3.4 Short-term gastrointestinal side effects were reported in 4 RCTs (Cammarota et al. 2015, Hota et al. 2017, Hvas et al. 2019 and van Nood et al. 2013). The most common effects included diarrhoea, bloating, abdominal pain or cramps. These symptoms lasted (when reported) between 3 hours (van Nood et al. 2013) and 12 hours (Cammarota et al. 2015), or were described as ‘transient’ (Hvas et al. 2019).

Small sample sizes and the relevance of the population to the NHS limit the evidence

3.5 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 was partly because 4 of the trials stopped early; only 1 completed after recruiting the target number of people (Hvas et al. 2019). The evidence is also limited by not being done in the UK and the trial populations having fewer comorbidities and a lower chance of being hospitalised than the eligible UK population.

Heterogeneous study designs limit the evidence

3.6 The included studies used different FMT administration routes:

- 2 used an enema (Hota et al. 2017 and Rode et al. 2021)
- 1 used colonoscopy (Cammarota et al. 2015)
- 1 used a nasoduodenal tube (NDT; van Nood et al. 2013)
- 1 used mixed routes (colonoscopy or nasojejunal tube; Hvas et al. 2019).

None of the included trials evaluated FMT delivered in a capsule, or by nasogastric tube (NGT) or flexible sigmoidoscopy. The number of times FMT was given also varied, from 1 to 4 infusions. Some people in 3 of the trials had a mixed number of recurrences, with some having a first recurrence of *C. difficile* infection (Cammarota et al. 2015, Hota et al. 2017 and van Nood et al. 2013). However, the EAC said that only a minority of cases were first recurrences.

Cost evidence

Of 8 economic studies found, 1 used an NHS perspective

3.7 The EAC found 8 economic evaluation studies relevant to the decision problem. Abdali et al. (2020) was a UK-based cost–utility analysis comparing 4 treatments for recurrent *C. difficile* infection (FMT via NGT, FMT via colonoscopy, oral fidaxomicin, and oral vancomycin). The

analysis used a Markov model with 4 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 were dominated by FMT via NGT and FMT via colonoscopy (that is, FMT was cost saving and more effective).

For full details of the cost evidence, see section 4 of the assessment report and the assessment report appendix.

A Markov model compared FMT with antibiotic treatment

3.8 The EAC created a cohort Markov model that included adults with recurrent *C. difficile* infection who have had 2 or more previous episodes. It had a time horizon of 6 months and cycle length of 2 months. The model included 4 routes of FMT administration (colonoscopy, enema, NDT and oral capsules) and 3 antibiotic comparators (vancomycin, fidaxomicin and VTP). It had 4 health states:

- recurrent *C. difficile* infection
- persistent *C. difficile* infection (recurrent, relapsed or refractory *C. difficile* infection)
- recovered
- dead.

The quality of the clinical evidence limits the economic model

3.9 The EAC said that the quality of the clinical evidence led to uncertainty in the clinical parameters used in the economic model. No eligible RCTs were identified comparing FMT oral capsules with antibiotics in people with a second recurrence of *C. difficile* infection. However, because 2 studies found oral capsules were comparable to FMT colonoscopy (Kao et al. 2017, Ramai et al. 2020) the EAC assumed the transition probabilities to be the same. Other routes of administration were excluded because of a lack of RCT-level data from the clinical evidence review.

The economic model used a number of clinical assumptions

3.10 The economic model used the following clinical assumptions:

- people are treated with the same treatment again if the first treatment does not work
- constant treatment response and recurrence rates in each cycle
- pre-antibiotic treatment is only used for the initial FMT administration
- the same risk of death as the general population for anyone in the recovered group
- initial treatment includes 5 days of hospital stay for FMT and 10 days for antibiotics
- costs of tests and follow up assumed to be the same between groups and so excluded from the model.

FMT by all administration routes evaluated was cost saving in the base case

3.11 The EAC's base case analysis found that all 4 routes of FMT were associated with increased health benefits and reduced costs against all 3 antibiotic comparators, with savings ranging from £3,369 (FMT enema compared with VTP) to £13,134 (FMT oral capsule compared with vancomycin). Health benefits ranged from a quality-adjusted life year (QALY) gain of 0.17 (FMT enema compared with VTP) to 0.66 (FMT via NDT compared with vancomycin).

FMT via NGT could also be cost saving, although there is no RCT-level evidence

3.12 The EAC identified a meta-analysis by Ramai et al. (2020), which suggested an overall cure rate of 78.1% when FMT is given via NGT, when compared with antibiotic treatment. The cost of delivering FMT via NGT is estimated to be £740 (Abdali et al. 2020). Because the cure rate is estimated to be higher for FMT via NGT than via enema, and costs less, the EAC said that FMT via NGT is likely to be cost saving for recurrent *C. difficile* infections, against all 3 comparators considered.

FMT remained cost saving in the sensitivity and scenario analyses

3.13 The EAC did deterministic and probabilistic sensitivity analyses, and scenario analyses. The deterministic sensitivity analysis compared FMT via enema (the least cost saving FMT route) with VTP (the comparator with the lowest cost and highest health benefit). It found that the largest cost drivers were 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 results of the probabilistic sensitivity analysis showed that FMT is estimated to be cost saving 96% to 100% of the time compared with antibiotic treatment. The EAC also did 5 scenario analyses. FMT remained cost saving in all of them:

1. Pre-antibiotic treatment for all subsequent FMT treatments instead of for index treatment only (FMT was compared with the VTP treatment group only).
2. Subsequent treatment with VTP for all treatment arms for those in the persistent *C. difficile* infection state.
3. Threshold analysis on fidaxomicin cost discounting.
4. Extending the time horizon from 6 months to 1 year.
5. All treatment arms having a 1-day hospital stay for the index treatment instead of 5 or 10 days stay in the FMT and antibiotic groups, respectively.

4 Committee discussion

Clinical-effectiveness overview

FMT is an effective treatment for recurrent *C. difficile* infection for people who have had 2 or more previous episodes

4.1 The randomised controlled trial (RCT) evidence showed that faecal microbiota transplant (FMT) was significantly better at resolving a recurrent *Clostridioides difficile* infection than vancomycin in 4 RCTs, and better than fidaxomicin in 1 RCT. Only 1 RCT found no statistical

difference in the efficacy of FMT compared with antibiotics. The committee acknowledged that there are limitations to the evidence base. However, it said that there is an unmet need in this population and FMT is likely to be an effective alternative to continued antibiotic use. It also acknowledged that FMT is already being used in the NHS for recurrent *C. difficile* infections and is recommended in NICE's guideline on antimicrobial prescribing for *C. difficile* infection. Therefore, the committee agreed that FMT should be recommended to treat a recurrent episode of *C. difficile* infection if people have had 2 or more previous episodes.

The use of FMT for refractory *C. difficile* infections is uncertain because the definition of refractory is not clear

4.2 The external assessment centre (EAC) did not identify in-scope RCTs comparing FMT with antibiotics for refractory *C. difficile* infections. The clinical experts said that there is no consensus on the definition of refractory *C. difficile* infections, meaning that there is less available evidence. The committee acknowledged that FMT could benefit this population, but there was too much uncertainty in the definition of refractory infections to make a recommendation in this population.

FMT via enema is likely to be less effective but is a clinically appropriate option in some cases

4.3 The clinical evidence showed that FMT given via enema had less efficacy than that of the other administration routes evaluated. Clinical experts said that FMT is usually done by NGT or colonoscopy, depending on patient preference and suitability of the procedure. However, they said that it was important to have the option of enema available for people who could not have other routes of administration. The committee acknowledged that, although enema was a less effective route of administration, it should be available as an option for people who cannot have FMT by another route.

There is no evidence in scope comparing FMT via oral capsules and antibiotics

4.4 The EAC did not identify any RCTs comparing FMT given in oral capsules with antibiotics in people with a second recurrence of *C. difficile* infection. As a result, no evidence was presented for the clinical efficacy of oral capsules. However, the EAC did identify 2 studies for its economic evaluation (1 RCT and 1 systematic review and meta-analysis), which showed that oral capsules were as effective as FMT via colonoscopy. It also said 2 ongoing RCTs are comparing the oral capsules with antibiotic treatment. Clinical experts said that, if oral capsules were more widely available, they would be preferred because of safety and patient acceptability, especially because newer capsules containing lyophilised FMT material can be given in fewer pills than older versions. The committee acknowledged that, although the comparative evidence presented was limited, oral capsules are a promising option for FMT treatment.

Safety

A strict donor screening programme should be followed

4.5 The joint British Society of Gastroenterology and Healthcare Infection Society guidelines say that donor screening should be done for all potential stool donors. This includes a questionnaire and personal interview, to establish risk factors for transmissible diseases and factors that could affect the gut microbiome. Blood and stool screening for transmissible disease must also be done. Clinical experts said that only a small proportion of donors pass screening, and they are generally young and healthy adults. The committee acknowledged that there is still a risk of disease transmission because screening tests are not 100% sensitive. However, it acknowledged that the strict donor screen programme used currently makes FMT relatively safe. The committee also acknowledged that NICE's interventional procedures guidance on FMT for recurrent *C. difficile* infection has reviewed the safety of FMT.

Other patient benefits or issues

People with a recurrent *C. difficile* infection need to be informed about FMT

4.6 Patient experts said that recurrent *C. difficile* infections reduce quality of life. Pain and diarrhoea symptoms mean people can need help with day to day living and may not be able to work so lose income. Diarrhoea symptoms can also affect people's dignity, especially when it leads to incontinence or when the person is in a hospital or nursing home. The patient experts said patients and clinicians need to be made more aware that FMT is a treatment option for recurrent *C. difficile* infection.

Donor diet may need to be considered when offering FMT

4.7 The committee acknowledged that FMT may not be appropriate for some people with an anaphylactic food allergy. It also recognised that the diet and alcohol consumption of potential donors may be a barrier to having FMT for people from some faith groups or people with dietary preferences. The clinical experts said they had not experienced problems relating to religious beliefs but acknowledged that this is a valid consideration.

Cost modelling overview

FMT is cost saving compared with antibiotics in the EAC's original economic model

4.8 The base case showed that FMT is likely to be cost saving by at least £3,300 per person, compared with antibiotics. The committee acknowledged that the clinical evidence was very heterogeneous. But the cost savings were robust enough to recommend FMT for recurrent *C. difficile* infections for people who have had 2 or more previous episodes.

FMT remains cost saving in all scenarios in the EAC's original scenario analyses

4.9 FMT remained cost saving in all 5 scenarios presented by the EAC (see section 3.13). Clinical experts said that a short course of antibiotics is

used before most FMT treatments and that the length of stay for treatment with FMT or antibiotics is likely to be short. So the committee felt that the 2 scenarios analyses done by the EAC that assumed a 1-day hospital stay and pre-antibiotic treatment for all FMT rounds best reflected the care pathway for FMT, and reduced uncertainties in the modelling. Overall, the committee acknowledged that FMT remained cost saving in all scenarios but requested a new base case analysis to include these assumptions.

FMT remains cost saving compared with antibiotic treatment in the EAC's updated economic model

4.10 The updated base case found that FMT remained cost saving by at least £1,500 compared with antibiotic treatment. The lowest cost savings were for FMT given via enema, because it is a less effective administration route. FMT via colonoscopy, NDT and oral capsule saved between £3,691 (FMT via colonoscopy compared with VTP) and £11,274 (FMT via oral capsule compared with vancomycin). The updated probabilistic sensitivity analysis showed FMT was estimated to be cost saving 80% (FMT via enema compared with VTP) to 100% of the time (FMT via oral capsule compared with all antibiotics, and FMT via NDT compared with vancomycin or fidaxomicin) compared with antibiotic treatment. The EAC also updated scenarios 2, 3 and 4 of the original model (see section 3.13). FMT was found to remain cost saving in almost all scenarios. The only scenario in which FMT was cost incurring was for FMT via enema compared with VTP, and VTP was given as the repeat treatment for everyone in the persistent *C. difficile* infection state. In this scenario FMT was cost incurring by £518. But overall the committee concluded that FMT was highly likely to be cost saving compared with antibiotic treatment.

5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technologies advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of the medical technologies advisory committee, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more health technology assessment analysts (who act as technical leads for the topic), a health technology assessment adviser and a project manager.

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