National Institute for Health and Care Excellence

Medical technologies evaluation programme

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

Consultation comments table

Final guidance MTAC date: 17th June 2022

There were 70 consultation comments from 3 consultees:

- 1 Professional Organisation (n=18)
- 1 Pharmaceutical Company (n=20)
- 1 NICE medicines optimisation team, NICE Centre for Guidelines (n=32)

The comments are reproduced in full, arranged in the following groups – (list groups used, for example, clinical use, cost considerations and miscellaneous).

#	Consultee ID	Role	Section	Comments	NICE response FINAL
Recommendations					
1	1	Professional Organisation	1.1	Although FMT is cost saving that is not the only reason for recommending its use. Suggest helpful to note it is highly effective in recurrent CDI and avoids potential harmful effects of antibiotics on gut microbiome. The recommendation for FMT is made for adult patients with 2 or more previous episodes and economic	Thank you for your comment. Please see NICE's response to comments 28 to 34 on safety and comment 35 on patient preference.

				assessment suggests a cost benefit for FMT compared to current antibiotic therapies for CDI. There is an increasing understanding of the gut microbiome and its effects on health and disease. While replacing microbiome by FMT does successfully treat CDI, it not yet clear what additional effects may be found in the recipient over time. Infection is screened for to avoid obvious transmission, but the non-infectious effects of the flora transplanted are far harder to gauge and work is ongoing to delineate what flora is important for health and what components of the microbiome might have a deleterious long-term effect on a recipient. Therefore, it is not a simple case of making a cost benefit analysis before recommending FMT for all adults with 2 or more relapses of CDI. The individual circumstances of the patient are relevant, whether they need hospital care or not, what their age and other co-morbidities are could affect how suitable FMT is for them. Certainly, in younger individuals, the potential for long term effects is greater and therefore additional caution would be reasonable. Elderly patients, with significant morbidity already identified from recurrent CDI would seem to be the first group in which to recommend FMT as routine.	
2	2	Pharmaceutical Company	Recommendations	There is limited clinical evidence to suggest that FMT may have a place in the treatment of CDI. This position was established in the July 2021 guidance document NG199 and the present consultation does not appear to add anything new to the conclusions in that assessment. The present document raises some concerns that the potential benefits of FMT in the treatment of recurrent CDI, which are not yet sufficiently well understood, may be given undue prominence.	Thank you for your comment. Please see NICE's response to comment 3.
3	2	Pharmaceutical Company	1.1	The evidence presented is based on the same data considered for NG199, which is described in NICE supporting evidence as being weak. The five studies were largely incomplete, with few participants due to poor recruitment, inconsistent methodology and delivery of treatment. We are therefore concerned that the committee's conclusion that FMT is significantly better than antibiotics is	Thank you for your comment. The committee acknowledged that the evidence base reviewed included small population sizes and were limited by heterogenous trial design, as stated in sections 3.5 and 3.6 of the guidance. However, it still felt the evidence was sufficient to recommend the use of FMT after 2 or more previous episodes of *C. difficile* infection. The committee also acknowledged that the NICE clinical guideline on *C. difficile*

				based on limited data. The antibiotics referred to in this comparison were required to undergo much more rigorous regulatory evaluation and be supported by a substantial weight of clinical data before receiving a marketing authorisation to treat CDI. We are concerned that the potential benefits of FMT are as yet unknown and may be being exaggerated.	infection: antimicrobial prescribing and NICE interventional procedures guidance on faecal microbiota transplant for recurrent *C. difficile* infection suggest considering FMT for a recurrent episode of *C. difficile* infection in adults who have had 2 or more previous episodes or give normal arrangements for the procedure, respectively.
4	3	NICE medicines optimisation team	1.1	i think 'cost-saving option' sounds odd. why is just cost being singled out here in the rec when there are other important issues - efficacy, safety, patient factors... also what strength of recommendation is this meant to be. In the APG it's a 'consider'. this sounds more like an 'offer'	Thank you for your comment. The NICE committee considered this comment and decided not to amend the recommendation wording. This is because the focus of this guidance was to evaluate whether FMT treatment would be cost saving for recurrent *C. difficile* infections. The wording used is in line with the recommendation wording template used by the Medical Technology Evaluation Programme.
5	3	NICE medicines optimisation team	1.1	see also later comments that the evidence for FMT is for antibiotics followed by FMT. FMT was not given alone - it followed an antibiotic course. So it is not strictly FMT vs comparator but FMT + antibiotic vs comparator. This does not seem to be acknowledged.	Thank you for your comment. Please see NICE's response to comment 41.
6	3	NICE medicines optimisation team	4.1	in the APG, FMT is a 'consider' rec. what strength of recommendation is this meant to be? '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.'	Thank you for your comment. Medical technologies guidance aims to promote the adoption of treatments which are clinically non-inferior and resource-releasing. Although a positive recommendation is not mandated for use, positive guidance could be considered for the MedTech Funding Mandate.
Clinical Evidence					
7	1	Professional Organisation	3.1	The quality of evidence is low with only 5 small RCTs and none of them include FMT using capsules. Since capsules are used as an option in the economic analysis it may be helpful to include any studies reporting their use as evidence.	Thank you for your comment. The EAC conducted a systematic review and did identify RCTs that compared the use of FMT by oral capsules to other types of FMT delivery. However, these were not an eligible comparison in the NICE decision problem and so excluded from the clinical evidence review. For the economic model, 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.
8	2	Pharmaceutical Company	3.9	*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* Assumptions such as this, which are based on weak data, do little to support the validity of the economic model.	Thank you for your comment. The EAC provided a response to this comment. It stated that it has been transparent about the uncertainty and have undertaken deterministic and probabilistic sensitivity analysis of the key variables and also run a number of scenarios varying assumptions. The committee acknowledged that the economic model is limited by the assumptions included, however, they felt that the sensitivity analyses were able to consider variations in the key parameters. It decided no change to the guidance was needed in response to this comment.
9	2	Pharmaceutical Company	3.1	The inclusion of only 274 adult patients, in 5 low quality clinical studies, is a far lower standard of evidence that that required for any other medicinal product that is required to undergo regulatory review and approval. This is true even of those treatment options which occupy second or third line positions in care pathways.	Thank you for your comment. The Medical Technologies Evaluation Programme evaluates the cost consequences of introducing innovative technologies to the NHS. It is not intended to limit access to other technologies with similar advantages. Please see the response to comment 3 on the clinical evidence.
Clinical Evidence informing the economic model					
10	2	Pharmaceutical Company	3.6	We are concerned that the studies cited are not applicable to the UK context, nor are they reliable with regard to the safety and efficacy of the intervention. As stated in the Supporting Documentation compiled by NICE for this consultation (p78), ""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."" Given these acknowledged limitations, it is unlikely that the economic model can be considered completely valid until more extensive clinical knowledge is developed.	Thank you for your comment. The EAC provided a response to this comment. They acknowledge that there are data limitations in this analysis and have undertaken sensitivity analysis around all key variables to test the impacts of the uncertainty in this model. The model results should be interpreted in the context of the data limitations and alongside the clinical evidence. The committee acknowledge the limitation in the evidence as discussed in the response to comment 3. Clinical experts stated that the non-UK based evidence would not affect the outcome data used in the economic modelling. The committee decided that no change was needed to the guidance in response to this comment but it welcomes the collection of UK based evidence.

11	3	NICE medicines optimisation team	3	comments [redacted] From table 28 in the supporting document: I am somewhat uncertain about why the outcomes selected have been used for the modelling, from the Hvas et al study it appears that the secondary trial outcome of clinical resolution at week 8 has been selected (giving the probabilities of 92% for FMT, 42% for fidaxomicin and 19% for vancomycin, respectively). However, this was not the trials primary outcome (primary end point was combined clinical resolution and negative CD toxin polymerase chain reaction test result at 8 weeks) which had different estimates of effect (lower for FMT at 71% and fidaxomicin 33% but the same 19% for vancomycin). Similarly, while the outcome of Cure without relapse at 10 weeks in the van Nood study was 94% in the FMT arm, the corresponding vancomycin alone arm (i.e. without bowel lavage) was higher than seen for vancomycin in the Hvas et al study (30.8%). It is interesting that Cure in the van Nood et al study was defined as an absence of diarrhoea or persistent diarrhoea that could be explained by other causes with three consecutive negative stool tests for C. difficile toxin. It is perhaps concerning that the estimate for FMT taken from the van Nood study (94%) is taken from an outcome which closely resembles that defined as the primary outcome in the Hvas et al study, which was not used to inform the model. It does appear, perhaps to the untrained eye, that the model takes the highest estimates across different outcomes for FMT and uses lower estimates for in particular vancomycin. I think perhaps it needs to made clearer where (and for what outcomes) this data is being taken from and the comparable data and outcomes used?	Thank you for your comment. Clinical experts agreed that the primary end point (combined clinical resolution and negative CD toxin polymerase chain reaction test result at 8 weeks) was not an appropriate outcome measure. This is because a CD toxin polymerase chain reaction test result can be positive up to 3 months after the FMT procedure, and so is not used as a marker of infection resolution in clinical practice. Clinical experts agreed that the secondary outcome (clinical resolution at 8 weeks) was the most appropriate outcome to use in the economic model. The EAC notes that the Van Nood study did not have clinical resolution as a stand-alone outcome so clinical resolution with adverse event resolution was used instead. The EAC confirmed that they used a systematic approach to populating outcome figures in the economic model and used the most appropriate outcomes from the best quality studies available. The committee reviewed this information and were happy that the most appropriate outcome measures were used in the economic modelling. They decided that no further amendments were needed to the economic model in response to this comment.
12	3	NICE medicines optimisation team	3.12	*FMT via NGT could also be cost saving, although there is no RCT-level evidence*	Thank you for your comment. The EAC confirm that no direct RCT evidence was identified comparing FMT via NGT to FMT via enema. This is because

				is there any direct evidence to support this? 'Because the cure rate is estimated to be higher for FMT via NGT than via enema,'	this comparison was outside of the scope of the systematic review as outlined in the NICE decision problem.
Cost of FMT					
13	1	Professional Organisation	2.6	Costs for local donor FMT are not included and these would presumably be much higher in staff time and procedural costs than use of a manufactured product.	Thank you for your comment. The committee acknowledged that the unit cost of FMT was based on the cost to produce the sample at the Birmingham Microbiome Treatment Centre. Clinical experts stated that it is more likely that the FMT product would be sourced from a stool bank over local production. As a result, the committee were happy that appropriate source of costs were used. No changes were made to the guidance in response to this comment.
14	1	Professional Organisation	3.7	The figure of £850 seems low given the regulatory requirements for setting up and maintaining an FMT service. The whole system costs of FMT have likely been much underestimated. The full costs of setting up a FMT service include registering, obtaining and maintaining a medicines production licence. How have the costs been calculated (or not) for faecal donor material to be obtained, screened (after which most donations are rejected), stored, dispatched, received, and consented for administration? Have the specific, full costs of patient admission for FMT administration and follow up visits/monitoring been included? Staff training also required. There are several published costings on FMT with substantially higher costs: 2020=$1695 https://pubmed.ncbi.nlm.nih.gov/33682170/#:~:text=FMT%20material%20in%202020%20was,at%20a%20much%20higher%20cost) 2017 = €3095 https://pubmed.ncbi.nlm.nih.gov/31007720/ £850 per treatment is the cost quoted by The Microbiome Treatment Centre in Birmingham, but this is not peer reviewed or substantiated, therefore should not form the basis of the assessment. It should also be noted that Openbiome in the US, a not-for-profit FMT company, announced in 2021 that it was unable to remain financially viable, while charging several	Thank you for your comment. The £850 cost for FMT is as stated on the Birmingham Microbiome Treatment Centre website. NICE followed up with the director of the centre who states that the reason why this is low is because transport costs are not included nor are costs associated with maintaining the MHRA licence. The cost is in relation to manufacture of the product only and also does not account for more rigorous post-COVID 19 screening. Their centre is currently reviewing the costs and suggests a more realistic cost to take the above factors into account would be around £1,300. As a result, the EAC undertook further economic analysis in which the cost of FMT in the base case was £1,300 as well as 25% of people in the comparator arm being treated in the community in line with comment 22. The new base case found that almost all routes of FMT are cost saving against all three antibiotic comparators considered. The exception is FMT enema which is cost-incurring against VTP with an additional cost per person, over 6 months, of £1,287. The EAC further conducted threshold analyses around the unit cost of FMT. Please see the economic appendix for further information. Administration costs associated with FMT treatment have been considered within the economic model. The committee accepted this new base case and section 4.9 and 4.10 were added to the guidance document as a result.

				hundreds of dollars per procedure, and that it anticipated that the US FDA would discontinue its current guarded support for FMT once regulated alternative (FMT substitute) products became available. A key beneficiary of this NICE advice in the UK could be the Microbiome Treatment Centre and we note that two committee members have links with this organisation.	The committee acknowledged that two clinical expert contributors are the director and previous director of the microbiome treatment centre. These are declared in the assessment report and/or in the expert questionnaires and confirmed within the committee meeting.
15	2	Pharmaceutical Company	1.1	The cost for FMT included in the economic model is based on opinion and is not consistent with other reported values. Material costs represent only a fraction of the actual cost of administering FMT and therefore the economic model is incomplete. For example, recruitment of donors, screening of donor material, preparation of samples and administration costs do not appear to be reflected in the economic model, all of which must be borne by the NHS. In contrast, the costs of oral antibiotics are known, straightforward and only acquisition costs are borne by the NHS.	Thank you for your comment. Please see NICE's response to comment 14 regarding the cost of FMT. The economic model includes the unit cost of FMT (which includes sourcing and preparation of samples) and administration costs of the different administration routes.
16	2	Pharmaceutical Company	2.6	It is very likely that the costs of FMT are underestimated, as is acknowledged in the NICE supporting documentation to this consultation (p104). There is also likely to be considerable variation depending on the method of FMT administration selected. As stated above, donor recruitment and selection, screening of samples, preparation of samples, administration costs and resources (human, facilities and materials), monitoring and follow up costs do not appear to be included in the economic model, which could therefore be considered incomplete.	Thank you for your comment. Please see NICE's response to comments 14 and 15.
17	2	Pharmaceutical Company	3.6	All of the administration routes studied require hospitalisation of the patient, due to their use of liquid material and the relative complexity of administration. This is demanding of NHS facilities, staff and materials and therefore adds to costs. The only route of administration for FMT which can be considered low impact in regards to the points mentioned above is oral capsules, but as acknowledged in the	Thank you for your comment. The committee agrees that FMT administration requires hospitalisation and acknowledges that this has been considered within the economic modelling. The EAC did identify RCTs that compared the use of FMT by oral capsules to other types of FMT delivery. However, these were not an eligible comparator in the NICE decision problem. The committee acknowledged the lack of in scope evidence

				evidence review, this has not been studied in a comparative clinical trial alongside antibiotics. Therefore, it does not seem appropriate to recommend the use of a treatment which has not yet been studied.	reviewed for this mode of FMT administration as summarised in section 4.4 of the guidance.
Economic model					
18	1	Professional Organisation	3.8	A markedly different economic analysis has been used here compared with that employed in the recent NICE fidaxomicin economic impact assessment (https://www.nice.org.uk/guidance/ng199/evidence/evidence-review-pdf-9194637853 Appendix p 240). Inconsistency of methodology for therapy evaluations within the same infection is unhelpful / of concern, especially noting that there were issues (including failure to account for the increased mortality associated with recurrent CDI in the fidaxomicin evaluation). Why have different methodologies been used and how is this justifiable? Notable important differences are This analysis uses a 1 stage and not 2 stage method. The chance of death in the earlier model states "Acute mortality from CDI was limited to the 5 first decision tree in the model." This new model does stipulate this. Additionally, the cost of a CDI recurrence is quoted as higher elsewhere in UK research – for example £31 121 (https://pubmed.ncbi.nlm.nih.gov/29982502/). It is not clear why the 2017 study by Wilcox was chosen for the £7,799 cost of a recurrence – this is a relatively low figure compared to others. As a minimum, why has a sensitivity analysis to address the differences in cost of CDI/rCDI been performed? Notably, and discussed elsewhere here, these cost-effectiveness estimates discount/ignore safety concerns, partly as these remain unquantified for such unregulated FMT administrations/procedures. Patients and clinicians need to be aware of these uncertainties and should be documented as part of informed consent.	Thank you for your comment. The EAC were asked to provide comment in relation to the different methodologies used in the clinical guidelines when compared to this guidance. It said that different model structures were used but consistent methodology was followed. This is because these are two very distinct decision problems and different study populations, even though they are in the same clinical area. The economic model developed for the NICE clinical guideline 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 *C. difficile* 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 *C. difficile* 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. In terms of the cost recurrence, the unit cost of hospital stay £371 (currency code: SD01A) is taken from National cost collection 2021. This was applied to the median hospital length of stay (LOS) of 21 days for recurrent *c. difficile*

					infection found in the study by Wilcox (2017). The Tresman (2018) study reports mean recurrent *c. difficile* infection LOS, 33 days. The empirical distribution of LOS is often positively skewed. The median is more robust to high-LOS outliers than the mean and therefore used in the analysis. The EAC note that as FMT has a lower rate of relapse than all comparators, any increase in cost of recurrence will be associated with increased cost-saving for FMT. The committee agreed that the economic model structure was appropriate and covered the relevant costs associated with FMT treatment. No changes were made to the guidance in response to this comment.
19	1	Professional Organisation	3.10	One of the clinical assumptions is 'initial treatment includes 5 days of hospital stay for FMT and 10 days for antibiotics.' This will have a major influence on the cost. Is it likely that patients receiving antibiotics for recurrent CDI would stay in hospital for the complete course duration? Note this was agreed via committee discussion (section 4.9) and a new base case analysis conducted. Should the initial assumption and cost analysis be removed to avoid confusion?	Thank you for your comment. Text was added to the guidance to make it clear that further amendments were made to the economic model following clinical expert feedback.
20	2	Pharmaceutical Company	3.10	*initial treatment includes 5 days of hospital stay for FMT and 10 days for antibiotics* There is no evidence to support this assumption. Administration of oral antibiotics is less complex than administration of FMT and there is no data, nor experiential evidence, to suggest that a hospital stay of twice the length would be needed for antibiotics compared to FMT. For example, there have been no meaningful studies to compare the time to resolution of symptoms or clearance of infection between FMT and antibiotics.	Thank you for your comment. This assumption on the number of days is in line with the recent Abdali et al. (2020) economic evaluation. Based on expert feedback, a second base case was done which had a 1-day length of stay for both groups. This is discussed in section 4.9 and 4.10 of the guidance document.
21	3	NICE medicines optimisation team	3.10	why is hospital stay longer for antibiotics? vancomycin and fidaxomicin are oral medicines. so if the patient is well enough (which I don't think would be any different than from an FMT patient where stay is 5 days) they could go home	Thank you for your comment. Please see NICE's response to comments 19 and 20.
22	1	Professional Organisation	3.11	The cost analysis is heavily in favour of FMT therapy and much of this is due to the presumptive need for repeated	Thank you for your comment.

				hospital admissions of 21 days in patients who fail to respond to antibiotic therapy. It is not true that all patients with CDI require readmission and particularly patients who are diagnosed in community settings may not accrue the costs predicted in this assessment when they have relapses of CDI. If all patients with recurrent CDI are to be recommended to have FMT, then perhaps a cost assessment that incorporates community management costs, rather than just those for hospital cases would be reasonable.	Clinical experts agreed that a proportion of people in the antibiotic treatment group would be treated in the community instead of in hospital. Therefore, a new base case was created to account for 25% of people in the comparator group being treated in the community instead of in hospital. As discussed in comment 14, the new base case found that almost all routes of FMT are cost saving against all three antibiotic comparators considered. The exception is FMT enema which is cost-incurring against VTP with an additional cost per person, over 6 months, of £1,287. The EAC further conducted threshold analyses around proportion of people in the comparator arm being treated in the community. Please see the economic appendix for further information. The committee accepted this new base case and section 4.9 and 4.10 were added to the guidance document as a result.
23	2	Pharmaceutical Company	3.10	*people are treated with the same treatment again if the first treatment does not work* This is inconsistent with NICE own guidance on the treatment of CDI (NG199), which recommends a second antibiotic when the first choice fails, or recurrence or relapse of infection occur.	Thank you for your comment. The committee acknowledges that this is an assumption used in the economic model. Clinical experts agreed that there is no consistent treatment approach if antibiotics fail in those with a *C. difficile* infection in those who have been treated for 2 or more episodes previously. Experts also agreed that if the index FMT treatment failed, people would have a second FMT treatment, in line with the economic model. The committee overall agreed with the assumptions used in the economic model. No changes were made to the guidance in response to this comment.
24	2	Pharmaceutical Company	3.12	*FMT via NGT could also be cost saving, although there is no RCT-level evidence* As stated previously, the recommendations in this document appear often to be based on assumptions and estimations. It may be better to wait for the findings of more robust studies before drawing such definitive conclusions.	Thank you for your comment. The committee acknowledge that assumptions have been used in the economic model and that sensitivity analysis of the key variables has been run to accommodate for the uncertainty.
25	3	NICE medicines optimisation team	3.11	*FMT by all administration routes evaluated was cost saving in the base case* i am surprised by these findings - what is driving the main cost savings vs antibiotics?	Thank you for your comment. The economic model shows that treatment with FMT is generally costlier than antibiotics alone, cost savings from reduced hospitalisations due to recurrence compensates for the high initial treatment costs.

Comparator					
26	2	Pharmaceutical Company	4.1	The replacement of the gut microflora by FMT may not be required if broad spectrum antibiotics were not used as a first line therapy for CDI. Were a narrow spectrum, microbiota-preserving antibiotic treatment used instead, FMT not be required at all, or less often, and associated costs, numbers of recurrences and patient outcomes may be considerably improved.	Thank you for your comment. The comparators used in this evaluation were based on the NICE clinical guideline on *C. difficile* infection: antimicrobial prescribing. This guideline recommends vancomycin as a first-line antibiotic for a first episode of mild, moderate or severe *C. difficile* infection. According to the NICE clinical guideline, narrow spectrum antibiotics, such as fidaxomicin, would be used for a further infection episode, prior to FMT treatment being considered.
27	2	Pharmaceutical Company	4.5	There is increasing and compelling evidence that the gut microbiome plays a vital role in human development and health and disruption of the microbiome should be minimised wherever possible. This is further support for the use of narrow spectrum antibiotics as first line therapy in CDI.	Thank you for your comment. Please see NICE's response to comment 26.
Safety/Regulation					
28	1	Professional Organisation	2.3	A strict donor screening programme should also be in place for FMT. Suggest more detail on this would be helpful. The governance issues are substantial around what is/is not screened for and how robustly this is performed. There is a long and increasing list of potential pathogens for which donor faecal samples must be screened. Notably, there is no CE marked test available to screen faeces for the presence of SARS-CoV-2 and with the ongoing worldwide outbreak of hepatitis cases likely due to an adenovirus we do not know implications of this for screening.	Thank you for your comment. A link to the British Society of Gastroenterology and Healthcare Infection Society guidelines has been added to section 2.3 of the guidance as it provides more detail on best practice for the donor screen programme. Clinical experts confirmed that these guidelines are reviewed every 3 years. Clinical experts acknowledge that there is no CE marked test to screen for SARS-CoV-2 but confirm that the Birmingham microbiome treatment centre use a MHRA approved test for the stool samples and also take nasopharyngeal swabs at the start and end of the donation period.
29	1	Professional Organisation	4.5	The potential problem of cross-acquisition of antibiotic resistance traits from donor microbiome to transplant recipients may be challenging to address. It should, however, be considered. In this connection, definitions of	Thank you for your comment. Section 4.5 of the guidance acknowledges the safety aspects of the FMT procedure and states that only healthy participants are chosen as donors using screening to establish risk factors

				threshold limits of antibiotic resistance for donor microbiome may be helpful. FMT is generally safe (in the short term), but there needs to be careful consideration of the circumstances in which it is used, with a particular emphasis on long-term safety. However, even in the short term, there have been reported deaths (at least 5 reported in the literature) – and this should be at least mentioned https://pubmed.ncbi.nlm.nih.gov/34992678/ https://pubmed.ncbi.nlm.nih.gov/32011405/ https://pubmed.ncbi.nlm.nih.gov/33159374/ The deaths include from administered pathogens and from aspiration pneumonia/sepsis. The long-term safety of FMT remains unknown. There is an increasing body of evidence surrounding diseases/conditions that are associated with but microbiome dysbiosis, including obesity, diabetes, hypertension, and cancers. Of course, such issues may be of modest concern for a very elderly recipient of an FMT. However, informed consent is a key issue considering the unknowns around long term safety since the regulatory constraints around FMT reflect these.	for transmissible diseases and factors that could affect the gut microbiome. Further comment on the lack of long-term safety data has been added to section 4.5 of the guidance alongside a recommendation for further information to be collected via a registry. The committee acknowledges that of the references provided in this comment, one is a systematic review which reports 5 deaths due to FMT (Marcella et al. 2020), all of which were in people with mucosal barrier injury. It also recognised that NICE's interventional procedures guidance on FMT for recurrent C. difficile infection has reviewed the safety of FMT and given this procedure normal arrangements. The EAC also reviewed all safety information (including alerts and recalls) from the MHRA and FDA websites and summarised the result in their report.
30	2	Pharmaceutical Company	2.3	There are important regulatory considerations which need to be addressed before wider use and scaling up of FMT should be considered. The MHRA has issued guidance on FMT, which it considers to be a medicinal product and therefore is subject to the requirements of Good Manufacturing Practice. Despite this, FMT has not been assessed according to the usual quality, safety and efficacy criteria applied by the MHRA to other medicinal products. At the time of writing, it remains an unlicensed medicinal product. It is perhaps surprising that this point is not more clearly acknowledged by NICE here and in guidance NG199, especially when licensed medicinal products with proven quality, safety and efficacy are available.	Thank you for your comment. Section 2.3 of the guidance outlines the MHRA regulations associated with FMT production.

31	2	Pharmaceutical Company	4.5	Furthermore, the long term safety of FMT has not been studied and this should be acknowledged by NICE when recommending FMT as a treatment option.	Thank you for your comment. Please see NICE's response to comment 28 and 29.
32	3	NICE medicines optimisation team	3.3	what about long term safety - this is lacking. this is a limitation too	Thank you for your comment. Please see NICE's response to comment 28 and 29.
33	3	NICE medicines optimisation team	4.5	the committee for the C. diff APG had real concerns about the safety of FMT. particularly lack of long term safety data, minimal regulations compared with medicines and risks of multidrug resistant organisms from donor faeces. These safety issues don't seen to be acknowledged here. The trials are all short term so long term safety data is limited.	Thank you for your comment. Please see NICE's response to comment 28 and 29.
34	1	Professional Organisation	2.4	It is important to separate out use of commercially manufactured FMT treatments from locally produced donor treatments as requirements for governance and record keeping will vary. Given the complexities of using the local donor approach and inequitable access to such a service would use of manufactured FMT treatments be the preferred option?	Thank you for your comment. The committee acknowledged that the use of stool banks would be the most common option for FMT and the cost of this has been used to inform the economic model.
Patient Involvement					
35	2	Pharmaceutical Company	4.6	As well as informing the patient about FMT as a third line option for treating CDI, patients should also be made aware of the details of FMT. There is likely to be a patient acceptability issue for many people being considered for treatment with FMT, were the basis for the therapy fully understood. Public knowledge of FMT is minimal and rejection of the concept should not be underestimated. NICE guideline NG197 on shared decision making makes clear that patients should be informed and engaged in the selection of their treatment options. It is very likely that some patients, fully informed about the source of FMT material, would be resistant to its use.	Thank you for your comment. Further information has been added to section 4.6 of the guidance on shared decision making and exploring treatment options with patients.
Further research					
36	1	Professional Organisation	3.5	Although the characteristics of the RCT-test populations upon which the recommendations are based are not reflective of the average UK population (as stated), it could	Thank you for your comment.

				be nice, before or in the process leading to wide adoption of the new therapy, to have data from RCTs performed in the UK. Importantly, such RCTs should also be calibrated for statistical power in order to strengthen the recommendations of significant findings there from, also for approximate quantifications of risks involved with wide adoption of the new therapy in the UK population.	A further research section has been added to the guidance (section 4.11) encouraging further evidence collection, including the establishment of a UK based registry.
37	2	Pharmaceutical Company	3.9	There are ongoing clinical studies which should provide more robust evidence to define the appropriate use of FMT. It may be considered appropriate to wait for more data to become available before drawing conclusions based on limited economic evidence.	Thank you for your comment. The committee acknowledged that there are on-going clinical studies as outlined in the EAC's assessment report. NICE periodically reviews medical technology guidance and any new in scope evidence published would be considered within this review process.
Wording					
38	3	NICE medicines optimisation team	2.4	antibiotic treatment rather than antibiotic therapy	Thank you for your comment. The wording in the guidance was amended in response to this comment.
39	3	NICE medicines optimisation team	2.4	say first and further C. difficile infections rather than first and second	Thank you for your comment. The wording in the guidance was amended in response to this comment.
40	3	NICE medicines optimisation team	2.4	TYPO: C. difficile infectionNICE's interventional procedures guidance on FMT for recurrent	Thank you for your comment. This typo was corrected in response to this comment.
41	3	NICE medicines optimisation team	2.5	isn't FMT given following antibiotics? so you still give the antibiotic course too (sometimes a shorter course) just before the FMT. So it's not instead of?	Thank you for your comment. The wording in the guidance was amended to clarify use the use of antibiotics prior to FMT treatment.
42	3	NICE medicines optimisation team	3.1	should it be FMT + antibiotic vs antibiotic? In Cammarota it was 3 day vanc + FMT vs standard/pulse vanc In Hvas it was 4 to 10 day vanc + FMT vs 10 day vanc or 10 day fidax	Thank you for your comment. Please see NICE's response to comment 41.

				In Rode it was 7-14 day vanc + FMT vs 14 day vanc then taper In van nood it was 4 to 5 day vanc plus FMT vs 14 day vanc in Hota it was 14 day vanc + FMT vs 6 week taper vanc	
43	3	NICE medicines optimisation team	3.2	*Recurrence rate is comparable to or lower than antibiotics* recurrence rate with FMT (plus antibiotics) is comparable to or lower than with antibiotics	Thank you for your comment. Please see NICE's response to comment 41.
44	3	NICE medicines optimisation team	3.2	*Recurrence rate is comparable to or lower than antibiotics* same comment that the trials are antibiotic +FMT vs antibiotic	Thank you for your comment. Please see NICE's response to comment 41.
45	3	NICE medicines optimisation team	3.4	*Gastrointestinal side effects can occur in the short term after FMT* do you mean with FMT? in the FMT arm? which is actually antibiotics + FMT	Thank you for your comment. Please see NICE's response to comment 41.
46	3	NICE medicines optimisation team	4.1	*C. difficileFMT is an effective treatment for recurrent infection for people who have had 2 or more previous episodes* same comment about antibiotic + FMT. also do you need to explain vancomycin is different in different studies (10 or 14 day course or taper/pulse etc	Thank you for your comment. Please see NICE's response to comment 41.
47	3	NICE medicines optimisation team	3.2	i don't think I'd use VTP as an abbreviation in recs because it's not well known enough	Thank you for your comment. As vancomycin taper pulse was defined prior to the abbreviation and the abbreviation was used multiple times throughout the document, no change was made to the wording in response to this comment.
48	3	NICE medicines optimisation team	3.2	for the positive trials – Cammarota, Hvas, Rode and van Nood you have only given FMT resolution rates not the comparator group resolution rates	Thank you for your comment. Additional information has been added to section 3.2 of the guidance in response to this comment.
49	3	NICE medicines optimisation team	3.5	'not being done in the UK' sounds a bit odd	Thank you for your comment. No change was made to the wording as the NICE style guide recommends using the simplest and plainest words possible.
50	3	NICE medicines	3.6	'However, the EAC said that only a minority of cases were first recurrences.' sounds a bit odd for NICE guidance.	Thank you for your comment.

		optimisation team		Either we should stand by this fact or not, rather than saying 'they said'?	The wording in the guidance was amended in response to this comment.
51	3	NICE medicines optimisation team	3.9	same comment about EAC said	Thank you for your comment. Please see NICE's response to comment 50.
52	3	NICE medicines optimisation team	3.9	should ' in people with a second recurrence of C. difficile infection.' say in people who have had 2 or more previous episodes	Thank you for your comment. The wording in the guidance was amended in response to this comment.
53	3	NICE medicines optimisation team	4.3	this says 'The clinical evidence showed that FMT given via enema had less efficacy than that of the other administration routes evaluated.' but is there direct evidence comparing different routes of FMT?	Thank you for your comment. RCTs comparing different routes of FMT administration were outside of the scope of clinical evidence review. The wording in section 4.3 has been amended to reflect this.
54	3	NICE medicines optimisation team	4.4	should 'people with a second recurrence of C. difficile infection' say people with 2 previous episodes of C. diff?	Thank you for your comment. The wording in the guidance was amended in response to this comment.
General					
55	1	Professional Organisation	General	*Has all of the relevant evidence been taken into account?* While NICE prefers to only use RCTs, given the low number of these some other less robust quality studies on gaps would be useful addition. E.g., studies on capsule delivered FMT. Note comments below on some important omissions and inconsistencies around costs used and economic modelling.	Thank you for your comment. As the focus of the evaluation was 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, the systematic clinical evidence review was restricted to the review of in scope RCT-level evidence only. This was then considered alongside the evidence evaluated for NICE's guideline on *C. difficile* infection: antimicrobial prescribing and NICE's interventional procedures guidance on FMT for recurrent *C. difficile* infection.
56	3	NICE medicines optimisation team	General	*Has all of the relevant evidence been taken into account?* N/A	Thank you for your comment.
57	1	Professional Organisation	General	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?*	Thank you for your comment.

				For the reasons stated below, there are clear concerns about the validity of the cost-effectiveness calculations.	Please see NICE's response to comments 10 to 25 on the economic modelling.
58	2	Pharmaceutical Company	General	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?* We believe that the evidence is insufficiently complete to draw some of the conclusions made in the summaries	Thank you for your comment. Please see NICE's response to comment 3.
59	3	NICE medicines optimisation team	General	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?* see comments	Thank you for your comment.
60	1	Professional Organisation	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* Given the uncertainties around the safety of what remains an unregulated, experimental medicine, guidance to the NHS should be more measured. It would be helpful to include a recommendation aimed at commissioners around use of FMT as a treatment option as currently not available in all locations across the UK. In parallel, a recommendation around engagement with patients to provide information about FMT as an option would be helpful, as identified as a gap by patient reps on the group.	Thank you for your comment. Please see NICE's response to comments 28 to 34 on safety and comment 35 on patient involvement. Commissioners are included in the target audience for NICE's recommendations, as are patients.
61	2	Pharmaceutical Company	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* We believe the recommendations are based on weak evidence and this is not made sufficiently clear in the guidance	Thank you for your comment. Please see NICE's response to comment 3.
62	3	NICE medicines optimisation team	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* see comments	Thank you for your comment.
63	1	Professional Organisation	General	*Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* As in the question 3 above, regional variation in access to FMT.	Thank you for your comment. Section 4.6 of the guidance discusses the need for awareness of FMT as a treatment option. Clinical experts confirmed a lack of awareness was one of the causes of regional variation in access.

64	2	Pharmaceutical Company	General	*Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* None that we are aware of	Thank you for your comment.
65	3	NICE medicines optimisation team	General	*Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* what about access generally - only a small number of centres have FMT	Thank you for your comment. Please see NICE's response to comment 63.
66	1	Professional Organisation	2.5	This is a welcome innovation that could help achieve the global, public health goal of avoiding overuse of, or preserving the efficacy of available antibiotics. Would autologous faecal microbiota transplants, using a sample of one's own faeces stored in advance be a suggestion for future consideration.	Thank you for your comment. This comment is outside of the scope for this medical technology guidance evaluation.
67	1	Professional Organisation	4.8	FMT is judged to be cost saving compared to antibiotics. This is using the current systems to screen donors and obtain donations for transplant. As we learn more about the human gut microbiome, it is likely to become important to analyse in much greater detail not only whether an infection is present, so that transmission can be prevented, but also to document the precise composition of the donor flora so that specific groups of organisms can either be included or excluded, depending what we find out through research about what long term effects on health the different groups of organisms have. Therefore, I believe that there is significant scope for a lot more molecular cataloguing of the precise components of stool transplant material to be required in future.	Thank you for your comment. This comment is outside of the scope for this medical technology guidance evaluation.
68	3	NICE medicines optimisation team	General	were gastroenterologist/microbiologist/infectious disease specialists included on the committee? these were included in the C. diff APG committee, and their views seemed more cautious about FMT use than here. Prof Mark Wilcox was the specialist on the APG	Thank you for your comment. Yes, NICE confirms that the clinical experts present at the committee meeting were a: • Consultant Microbiologist and Infection Control Doctor • Consultant Gastroenterologist • Professor of Medicine and Honorary Consultant Physician and Gastroenterologist A further 4 experts involved in using FMT in the NHS were also consulted for advice throughout the process.

69	3	NICE medicines optimisation team	4.5	what about access though? the APG committee said that FMT is only currently done in a small number of specialist centres	Thank you for your comment. Please see NICE's response to comment 60 on access.
70	1	Professional Organisation	3.4	Adverse outcomes are to be expected for any new therapy and in this context, FMT failures may also occur. Therefore, advice on the next line of therapy (or management) in cases of adverse outcomes or treatment failure would be useful.	Thank you for your comment. The scope of this evaluation is to review the clinical and cost evidence for the use of FMT for adults with a refractory *C. difficile* infection or a recurrent episode of *C. difficile* infection who have had 2 or more previous episodes. Although next line therapies have been considered in the economic model (repeat FMT or subsequent VTP administration), providing advice on next line therapy or management is outside of the scope for this review.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."