# The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridioides difficile* infection and other potential indications: second edition of joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

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All authors contributed to writing. All authors except AB also provided advice; AB also conducted searches and evidence syntheses.

*"NICE has accredited the process used by the British Society of Gastroenterology and the Healthcare Infection Society to produce: "The use of faecal microbiota transplant as treatment for recurrent or refractory* Clostridioides difficile *infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines." The NICE accreditation of HIS methodology is valid for five years from March 2020. More information on accreditation can be viewed at http://www.nice.org.uk/about/what-we-do/accreditation"*

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# 1. Abstract

The first British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS)-endorsed faecal microbiota transplant (FMT) guidelines were published in 2018. Over the past five years, there has been considerable growth in the evidence base (including publication of outcomes from large national FMT registries), necessitating an updated critical review of the literature and a second edition of the BSG/HIS FMT guidelines. These have been produced in accordance with NICE-accredited methodology, thus have particular relevance for UK-based clinicians, but are intended to be of pertinence internationally. This second edition of the guidelines have been divided into recommendations, good practice points, and recommendations against certain practices. With respect to FMT for *Clostridioides difficile* infection (CDI), key focus areas centred around timing of administration, increasing clinical experience of encapsulated FMT preparations, and optimising donor screening. The latter topic is of particular relevance given the COVID-19 pandemic, and cases of patient morbidity and mortality resulting from FMT-related pathogen transmission. The guidelines also considered emergent literature on the use of FMT in non-CDI settings (including both gastrointestinal and non-gastrointestinal indications), reviewing relevant randomised controlled trials. Recommendations are provided regarding special areas (including compassionate FMT use), and considerations regarding the evolving landscape of FMT and microbiome therapeutics.

## Executive summary of recommendations

### Effectiveness and safety of FMT in treating CDI

**1.1:** Avoid FMT as an initial treatment for *C. difficile* infection (i.e. first episode).

**1.2:** Consider FMT for a first recurrence or for patients with refractory *C. difficile* infection.

**1.3:** Offer FMT to all patients with two or more recurrences of *C. difficile* infection.

**1.4:** Ensure that FMT is preceded by the treatment of *C. difficile* infection with appropriate antimicrobials for at least 10 days.

**1.5:** Offer FMT to all types of patients, regardless of their health status, except in those with anaphylactic food allergy.

**1.6:** Offer one or more FMT after initial clinically assessed FMT failure.

*Good practice points*

**GPP 1.1:** Consider early FMT for patients with severe, fulminant or complicated *C. difficile* infection who are not responding to antimicrobial therapy.

**GPP 1.2:** If FMT was given via endoscopy, ensure that immediate management after administration is in line with any local protocols.

**GPP 1.3:** Inform patients about the short-term adverse events, in particular the possibility of self-limiting gastrointestinal symptoms and that serious adverse events are rare.

**GPP 1.4:** Inform inflammatory bowel disease patients with *C. difficile* infection about a small risk of exacerbation of their condition after FMT.

**GPP 1.5:** Follow-up the FMT recipients for at least eight weeks to establish its efficacy and adverse events.

**GPP 1.6:** Do not test for cure by absence of *C. difficile* toxin after FMT, unless the patient has persistent *C. difficile* infection symptoms or is suspected to have relapsed.

**GPP 1.7:** Consider investigation for alternative causes for symptoms in patients who fail to respond to anti- *C. difficile* infection treatment including FMT. **GPP 1.5:** Follow-up the FMT recipients for at least eight weeks to establish its efficacy and adverse events.

## Recipient factors influencing the outcome of FMT for patients with CDI

**2.1:** Do not refuse or delay FMT therapy due to any recipient risk factors e.g. age over 75 years old.

## Donor factors influencing the outcome of FMT for patients with CDI

**3.1:** Use FMT from universal donors in preference to related donors.

**3.2:** All potential donors must be screened by questionnaire or personal interview to establish risk factors for transmissible diseases and for factors influencing the gut microbiota (Box 1).

**3.3:** Blood and stool of all donors must be tested for transmissible diseases to ensure FMT safety (Box 2 and 3).

**3.4:** Discuss and agree the content of donor health questionnaire and laboratory testing at a local level, following a robust risk assessment.

**3.5:** Undertake ongoing review, revision and updating of the list of pathogens for screening/testing based on local epidemiology and the latest evidence.

**3.6:** Blood and stool of all donors must be re-screened periodically to ensure FMT safety.

**3.7:** Health assessment which captures the donor's ongoing suitability must be completed at each stool donation.

**3.8:** Ensure that FMT manufactured from donors is quarantined pending post-baseline screening and test results.

*Good practice points*

**GPP 3.1:** Follow suggested recommendations in Boxes 1-4 for conditions to be included in screening and health questionnaire.

## Preparation-related factors influencing the outcome of FMT for patients with CDI

**4.1:** Frozen FMT must be offered in preference to freshly processed products.

**4.2:** Start processing stools within 150 minutes of defecation.

**4.3:** Process stools aerobically or anaerobically – both methods are acceptable.

**4.4:** Store prepared FMT products frozen at -70°C for up to 12 months.

**4.5:** Add cryoprotectant such as glycerol for frozen FMT products.

**4.6:** If capsules are used, these can be obtained from frozen or lyophilised faecal slurry.

*Good practice points*

**GPP 4.1:** Follow a standard protocol for stool collection.

**GPP 4.2:** When possible, use at least 50g of stool in each FMT preparation.

**GPP 4.3:** Use sterile 0.9% saline as a diluent for FMT production.

**GPP 4.4:** Mix a minimum of 1:5 stool with diluent to make the initial faecal emulsion.

**GPP 4.5:** Consider homogenisation and filtration of FMT in a closed disposable system.

**GPP 4.6:** Consider thawing frozen FMT at ambient temperature and using it within six hours of thawing.

**GPP 4.7:** Avoid thawing FMT in warm water baths, due to the risks of cross contamination with *Pseudomonas* (and other contaminants) and reduced bacterial viability.

**GPP 4.8:** Where glycerol is used as a cryopreservative, ensure it is at 10-15% final concentration of the prepared faecal material/slurry, with vortexing or other methods used to fully mix the cryopreservative into the material.

## Route of delivery and other administration factors influencing the outcome of FMT for patients with CDI

**5.1:** Choose any route of FMT delivery but, if possible, avoid enema.

**5.2:** When choosing the route of delivery, consider patient preference and acceptability, cost, and the impact on environment.

**5.3:** Consider enema for patients in whom other FMT delivery methods are not feasible.

**5.4:** There is no need to administer proton pump inhibitors or other antisecretory agents as a preparation for FMT.

**5.5:** Do not use antimotility agents as a preparation for FMT.

**5.6:** Use bowel preparation/lavage as a preparation for FMT.

**5.7:** After upper gastrointestinal tract administration is used, remove the tube following the flushing with water.

**5.8:** For patients at risk of regurgitation or those with swallowing disorders, avoid administration via upper gastrointestinal tract and deliver FMT via lower gastrointestinal tract instead.

**5.9:** If colonoscopic administration is used, ensure that the FMT is delivered to a site that will permit its retention.

*Good practice points*

**GPP 5.1:** Use polyethylene glycol preparation as a preferred solution for bowel lavage.

**GPP 5.2:** Consider using prokinetics (such as metoclopramide) prior to FMT via the upper gastrointestinal tract route

**GPP 5.3:** Follow best practice for prevention of further transmission of *C. difficile* when administering FMT to patients.

**GPP 5.4:** Consider a washout period of at least 24 hours between the last dose of antibiotic and treatment with FMT.

**GPP 5.5:** If upper gastrointestinal tract administration is used, nasogastric, nasoduodenal or nasojejunal tube, upper GI endoscopy or a permanent feeding tube may be used for delivery.

**GPP 5.6:** If upper gastrointestinal administration is used, administer no more than 100 mL of FMT to the gastrointestinal tract.

## Post-FMT factors influencing the outcome of FMT for patients with CDI

**6.1:** Wherever possible, avoid using non- *C. difficile* infection antimicrobials for at least eight weeks after FMT.

**6.2:** Consult infectious disease specialists or medical microbiologists for advice whenever FMT recipients have an indication for long term antibiotics or have an indication for non- *C. difficile* infection antibiotics within eight weeks of FMT.

## Prophylactic FMT treatment to prevent *C. difficile* infection

**7.1:** No recommendation

## FMT for non-CDI indications

**8.1:** Do not offer FMT routinely to patients with indications other than *C. difficile* infection.

**8.2:** Consider FMT on case by case basis for patients with ulcerative colitis in whom licenced treatment options have failed or for those who are not suitable for currently available treatments.

### Compassionate use of FMT

**9.1:** Consider offering compassionate use of FMT in non- *C. difficile* infection settings after discussion and approval in a multidisciplinary team setting.

**9.2:** When offering compassionate use of FMT, the following conditions must be met:

- There is a biological rationale to justify consideration.
- Patient is at risk of significant clinical compromise due to a limited alternative range of therapeutic options.
- Patient understands the risks and benefits of FMT compared to other treatment options.

**9.3:** Prior to treatment, define what will be considered as a success or failure of FMT.

**9.4:** Prior to treatment, agree potential strategy for further FMTs based upon initial clinical success.

### Self-banking of stool for potential future autologous FMT

**10.1:** Do not routinely self-bank stool from faecal material donated by patients or healthy people for potential future autologous FMT.

### Regulation and oversight of FMT

**11.1:** Centres that manufacture and dispense FMT must adhere to any regulations applicable to the area in which they are located.

## 2. Patient summary

Faecal microbiota transplant (FMT), sometimes also known as stool or poo transplantation, can be an effective treatment for patients with *Clostridioides difficile* (commonly known as *C. diff*) infection. It is usually given when the infection comes back after antibiotic treatment (relapse), or occasionally if antibiotics do not work (refractory). It is not fully understood how FMT helps patients with *C. diff* infection, but it is thought it is partly to do with restoring beneficial gut microorganisms (e.g. bacteria) and the chemicals (e.g. metabolites) they produce.

The first BSG/HIS guidelines on the use of FMT for *C. diff* were published in 2018, and since this time new evidence has become available. This has prompted this second edition of the guidelines. Key recommendations focus on which patients should be offered FMT, when it should be offered, and the best ways to administer it. The guidelines also describe important considerations for screening of stool donors to ensure the safety and success of FMT. Two further topics are focused on in this second edition. One is the evidence for the use of FMT for conditions other than *C. diff* infection, including irritable bowel syndrome, ulcerative colitis and Crohn's disease, as well as conditions outside of the gut, such as obesity and metabolic syndrome. The second topic considers patients with conditions in which there are no other treatment options available to them, and if they can be offered FMT: this is called compassionate use.

Glossary of terms used is provided in Supplementary Materials file B.

## 3. Introduction

Faecal microbiota transplant (FMT; sometimes referred to by other names, including 'intestinal microbiota transplant/transfer'[1]) describes the transfer of minimally manipulated faeces from a healthy screened donor to a patient for the treatment of disease. FMT is now entering its second decade of use in modern mainstream medicine, with the first randomised trial reporting its utility in recurrent *Clostridioides difficile* infection (rCDI) in 2013.[2] The first BSG/HIS-endorsed FMT guidelines were published in 2018,[2] and interest continues to grow in the use of FMT, both for CDI and for its potential in the management of non-CDI conditions.[3]

Since the first BSG/HIS FMT guidelines in 2018, there has been publication of European and North American CDI-related guidelines[4] that have also addressed FMT, consensus reports relating to aspects of FMT service design and delivery,[5] and other BSG guidelines that have made consideration of a role for FMT in a non-CDI setting, e.g. for inflammatory bowel disease.[6] More recently, National Institute for Health and Care Excellence (NICE) medical technologies guidance summarised the clinical and cost effectiveness of FMT, from a UK National Health Service (NHS) perspective.[7] Despite these publications, the BSG and HIS advocated for a second edition of the UK FMT guidelines for a number of reasons. Firstly, the high levels of clinical interest within this field mean that this has been a fast-moving area with a rapidly-growing literature base. Particular areas of evolution since the last guideline iteration have included randomised trials in both CDI and non-CDI settings, the reporting of data from regional and national FMT registries (with longer periods of follow-up and larger numbers of patients than were previously described), and concerns related to donor screening (relating both to the COVID-19 pandemic, and high profile reports of FMT-related pathogen transmission with adverse patient outcomes). Secondly, while the NICE medical technologies guidance presented a general evaluation of the clinical use of FMT, its remit did not include guidance as to many of the more specific areas related to FMT provision and administration that are of greatest relevance to practising clinicians in this field, including donor selection and screening and material preparation, or consider non-CDI indications. As such, there was a compelling case to apply NICE-accredited methodology to the current evidence base and provide clinicians with the highest quality recommendations and guidance on which to base their practice of FMT use in adults.

The focus of these guidelines was on the use of 'conventional' FMT, to inform use in healthcare settings (primarily the NHS), and in academia. As such, as per the prior guidelines, studies were considered only if they explored the administration of whole stool, and not modified products, such as cultured microorganisms (or their proteins, metabolites or other components), or microbiota suspensions. The guideline development team (referred to as Working Party) are aware of developments in the United States in this space, particularly the recent FDA approval of 'next generation' FMT products, including RBX2660/Rebyota (Ferring; a rectally-administered FMT-type product),[8] and SER-109/ Vowst (Seres/Nestle; a purified spore-based product)[9] for preventing CDI relapses. Clinical trials that contributed to the licensing of these products investigated the performance of these agents compared to standard-of-care anti-CDI antibiotics. None explored efficacy compared to 'conventional' FMT. At the time of writing, no such products were licensed for use within the UK or European Union, and none have been licensed in any region as part of management of a non-CDI indication.

## 3.1 Aims and Scope

The main purpose of this second edition of the guidelines was to set recommendations and best practice for the optimal provision of an effective and safe FMT for recurrent or refractory CDI in adult (≥18 years) patients. The secondary purpose was to provide guidance for using FMT in conditions other than CDI in the adult population. These recommendations focused on the provision of FMT in the UK, although many aspects are also relevant internationally. The focus was on 'minimally manipulated' stool, and not the 'next generation' FMT products (i.e. defined microbial communities 'microbiome therapeutics'). The diagnosis and management of CDI in general were considered outside the scope of these guidelines.

## 3.2 Methodology

Topics for these guidelines were derived from the initial discussions of the Working Party during the stakeholder meeting. The included questions (Appendix 1) were adapted from those in the previous version of the guidelines published in 2018.[1] Review questions were designed in accordance with the Population-Intervention-Comparison-Outcomes (PICO) and Population-Prognostic Factor-Outcome (PFO) frameworks (Appendix 1), and systematic searches and systematic reviews of published literature were undertaken. The evidence was assessed for methodological quality and clinical applicability according to National Institute for Health and Care Excellence (NICE) protocols. The Working Party collectively reviewed the evidence and used the GRADE approach for judging its quality and making recommendations. More details on methodology are provided in Supplementary file C.

### Data sources and search strategy

Three electronic databases (MEDLINE, Embase, Cochrane Central Register of Controlled Trials) were searched with the last search date in July 2023. Search terms were constructed using relevant index and free text terms (Appendix 1). Reference lists of identified relevant articles were scanned for additional studies and forward reference searching (identifying articles which cite relevant articles) was performed. The searches were restricted to primary articles published in the English language.

### Study eligibility and selection criteria

Search results were downloaded to Covidence software and screened for relevance. Two reviewers (BHM, BM, MNQ, AB) reviewed the titles, abstracts and full text papers. Two reviewers discussed their disagreements first and the third reviewer was available to arbitrate but was not needed. The results of study selection and the list of excluded studies for all questions are available in Appendix 2.

### Data extraction and quality assessment

Included epidemiological studies were appraised for quality using the following checklists (links available in Appendix 3a):

- Systematic reviews: ROBIS for systematic reviews
- Randomised Controlled trials (RCT): RoB_2.0 for RCT
- Non-Randomised Controlled Trials (n-RCT): ROBINS for non RCTs and cohort studies

- Cohort studies: ROBINS for non RCTs and cohort studies
- Interrupted time series (ITS): EPOC RoB for ITS and before-after studies
- Case control studies: CASP for case control studies
- Cross-sectional studies: JBI checklist for analytical cross-sectional studies
- Uncontrolled before-and-after studies: EPOC RoB for ITS and before-after studies

The results of quality appraisal are available in Appendix 3b.

Data were extracted by one reviewer (AB) and checked by other reviewers (BHM, BM, MNQ). For each question, the data from the included studies were extracted to create the tables of study description and summary of findings tables (Appendix 4). Due to the limited number of studies and the heterogeneity between the studies, meta-analyses were only possible for a limited number of questions.

## Rating of evidence and recommendations

The strength of the evidence was defined by GRADE (Grading of Recommendations Assessment, Development and Evaluation) tables (Appendix 5) and using the ratings 'high', 'moderate', 'low' and 'very low' to construct the evidence statements, which reflected the Working Party's confidence in the evidence. The strength of recommendation was adopted from GRADE and reflects the strength of each evidence statement. In instances where no evidence was identified from searches, the statement 'No evidence was found in studies published so far…' indicates that no studies have assessed this as an outcome. Good Practice Points (GPP) were made by the Woking Party where there was limited or inadequate evidence from studies. All disagreements regarding the strength of the evidence, recommendations and Good Practice Points were resolved by discussions and consensus amongst members of the Working Party during the meetings.

When writing recommendations, the Working Party considered the following:

- Who should act on these recommendations?
- What are the potential harms and benefits of the intervention and any unintended consequences?
- What is the efficacy and the effectiveness of each intervention?
- Is it possible to stop another intervention because it has been superseded by the new recommendation?
- What is the potential effect on health inequalities?
- What is the cost-effectiveness of the intervention, including staff resources and other economic concerns?
- Can the recommended interventions be feasibly put into practice?
- Does the intervention have a negative impact on the environment?

The wording of the evidence statements and the recommendations reflected the strength of the evidence and its classification and are in line with NICE specifications. The following criteria were used:

- 'offer', 'measure', 'advise', 'refer', 'use' or similar wording was used if the Working Party believed that most practitioners/commissioners/service users would choose an intervention

if they were presented with the same evidence: this usually means that the benefits outweigh harms, and that the intervention is likely to be cost-effective. This reflects a strong recommendation for the intervention. If there was a legal duty, or if not following a recommendation may have serious consequences, the word 'must' was used.

- 'do not offer' or similar wording was used if the Working Party believed that harm outweighed the benefits or if an intervention was not likely to be cost-effective. This reflected a strong recommendation against the intervention. If there was a legal duty, or if not following a recommendation may have serious consequences, the words 'must not' were used.
- 'consider' was used if the Working Party believed that the evidence did not support a strong recommendation, but that the intervention may be beneficial in some circumstances. This reflected a conditional recommendation for the intervention.
- The 'do not offer, unless…' or similar recommendation was made if the Working Party believed that the evidence did not support the strong recommendation, and that the intervention was likely not to be beneficial, but could be used in some circumstances, for instance if no other options were available. This reflected a conditional recommendation against the intervention.
- The 'Good Practice Points' were made when there was no evidence to support the recommendation but when the Working Party felt that although they may not have an evidence base, they were considered essential or beneficial to good clinical practice. These were derived from the collective expertise of the Working Party, the experience of the individual members, and were based on biological plausibility.

To explain the rationale for recommendations, each section comprised an introduction, a summary of evidence with levels (known as evidence statements), a summary of Working Party's discussions and the recommendations graded according to the available evidence. As per NICE criteria, evidence statements should be prepared for each outcome of the review question. However, upon the evidence review it has become evident that for the majority of topics explored, there were no outcomes related to the quality of life and adverse events. To avoid unnecessary repetitive statements which reported that no studies were found, the decision was made to remove them. Thus, where evidence existed, evidence statements included information about adverse events and the quality of life; the absence of these statements should be considered as an indicator that no studies were found to fit the inclusion criteria specified in PICO/PFO frameworks.

## Consultation process

Feedback on draft guidelines was received from the participating organisations and through consultation with relevant stakeholders. The draft guideline and standard comments form were placed on the BSG and HIS websites for four weeks. The availability of the draft was advertised via email and social media. Stakeholders were invited to comment on format, content, local applicability, patient acceptability, and recommendations. The Working Party reviewed stakeholder comments, and collectively agreed revisions (Supplementary Materials file D). All reviews received from individuals with a conflict of interest or those who did not provide a declaration were excluded.

## 3.3 Guideline development Team and Conflicts of Interest

Members of the Working Party represent professional societies i.e. British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) as well as clinical microbiologists, gastroenterologists, infection prevention and control (IPC) doctors, clinical and academic researchers, FMT production manager, methodologists, and two lay members. Individual members were mostly UK-based but some international experts were also chosen to ensure that the guidelines are also relevant to an international audience. BSG and HIS commissioned the authors to undertake this Working Party report. The authors received no specific funding for this work. Financial support for the time required to obtain the evidence and write the manuscript was provided by the authors' respective employing institutions. B.H.M. was the recipient of an NIHR Academic Clinical Lectureship (CL-2019-21-002). The Division of Digestive Diseases at Imperial College London receives financial and infrastructure support from the NIHR Imperial Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The authors would like to thank Dr Rohma Ghani for her assistance on the topic of donor screening and Dr Bin Gao for reviewing the studies related to FMT given to patients with functional constipation. The views expressed in this publication are those of the authors and have been endorsed by BSG and HIS and approved following a consultation with external stakeholders. Authors declared no substantial conflicts of interest which would prevent them from being the members of the guidelines panel. All conflicts of interest are disclosed in Supplementary Materials file C.

## 3.4 Scheduled Review

The guidelines will be reviewed at least every four years and updated if change(s) are necessary or if evidence emerges that requires a change in practice.

## 3.5 Implementation

The Working Party agreed that there is no anticipated additional cost associated with implementation of these guidelines unless existing practice falls well below currently accepted standards. Assessing the cost-effectiveness of different treatments is not within the scope of this guidance. The practices recommended by these guidelines are currently used in most centres offering FMT in the UK. There is a potential cost saving and other benefits (e.g. reducing the carbon footprint) when certain recommendations are followed (e.g. donor screening or using aerobic processes for FMT preparation).

Regular audit and feedback to healthcare workers is an important part of any guideline implementation. The Working Party suggests specific aspects that could be audited, although they acknowledge that this is not a complete list and that the staff may choose other aspects as appropriate for their organisation.

- Proportion of eligible patients who are offered FMT after second CDI recurrence.
- Proportion of patients who are offered second FMT after an initial failure.
- Proportion of patients who received appropriate post-FMT care for up to eight weeks of follow-up.
- Proportion of procedures prior to which patients received information about the risks and benefits of FMT and any processes used for its administration (e.g. colonoscopy).

- Proportion of procedures in which FMT preparations used were stored for more than 12 months before use.
- Proportion of patients who received bowel preparation before the administration of FMT via lower GI tract.

Lay materials and continuing professional development questions (CPD) are available in the Supplementary Materials (files E and F).

# 4. Rationale for recommendations

## 4.1 Effectiveness and safety of FMT in treating CDI

There is clear evidence of the growing use of FMT globally. With the availability of randomised trial outcome data, FMT has become an accepted treatment for recurrent and refractory CDI. A recent pan-European survey suggested a disparity in access to FMT between countries (or even between regions within countries), suggesting ongoing significant underutilisation in patients who may stand to benefit from FMT.[10] Previous BSG/HIS guidelines[3] recommended that FMT should be offered to patients with recurrent, refractory CDI, or those with risk factors for recurrence, but not as first line treatment. At the time of their publication, there were fewer randomised trials and comparison treatment was limited to vancomycin. Due to a small number of studies conducted before the first the first edition of the guidelines was published, meta-analyses were not possible and the evidence for effectiveness was not well-established. Additionally, effectiveness and, more importantly, safety of FMT for some patient populations including those who were immunocompromised or immunosuppressed, frail and older patients, and patients with certain comorbidities, was unknown.

**General population with CDI**

*Effectiveness of FMT vs standard care or placebo*: There was strong evidence which suggested that FMT is more effective than standard care or placebo for treating CDI in general population. The evidence was obtained from a meta-analysis of six RCTs.[2,11-15] Patients receiving FMT had significantly higher cure rates (defined as symptom resolution following one or more FMT and/or negative *C. difficile* toxin test and no recurrence at minimum eight weeks of follow-up) compared to patients given vancomycin,[2,11,13,14] fidaxomicin,[11] or placebo[12,15] (RR 2.22 [95% CI 1.46-3.37]). There was high heterogeneity ($I^2$ = 70%, $p$ = 0.003), and sensitivity analyses (Appendix 4) did not resolve this issue. One study,[14] which used retention enema for FMT delivery, showed no benefit; one study[15] used autologous FMT as placebo but found that this group also had a low incidence of CDI recurrence; and one study[11] demonstrated that patients given fidaxomicin had a lower recurrence rate than patients who were given vancomycin. Sensitivity analyses showed that excluding one or all of these studies resulted in a greater FMT effect observed.

*Adverse events following FMT vs standard care or placebo:* There was strong evidence which suggested no negative effect of FMT. The evidence was obtained from six RCTs.[2,11-15] Two of these studies reported that there was no difference in the number of patients who experienced adverse events when comparing patients who received FMT via colonoscopy (10/24, 42%)[11] or orally (20/21, 95%)[12] and those who received antibiotics (vancomycin or fidaxomicin, data not reported; *p*-value reported not significant)[11] or oral placebo capsules (21/21, 100%, $p$ = 1.00).[12] This corresponded to two adverse events per person in FMT group (colonoscopy) for one study (data for control group given antibiotics not provided but reported no significant difference),[11] and 5.3 events in FMT group given

oral capsules compared to 4.4 events in control group given placebo capsules, *p* = NS).[12] The adverse events experienced included pain (n = 1), bloating (n = 5), constipation (n = 1), diarrhoea (n = 3) – all self-limiting – in patients given FMT via colonoscopy[11] as well as diarrhoea, nausea, abdominal pain, bloating, malaise, abdominal sounds, urgency, fatigue, fever, vomiting, flank pain, hot flushes and constipation in patients given oral capsules with FMT or placebo (reported incidence not significant for either adverse event).[12] Another study[2] described a similar incidence of adverse events in a group of patients who received FMT via nasoduodenal (ND) tube (data not collected for patients receiving vancomycin) and reported that 94% of patients experienced diarrhoea, 31% experienced cramping, 19% experienced belching, 19% developed constipation, 12.5% experienced abdominal pain, and 6% experienced dizziness, with all occurring shortly after FMT administration and all resolving within 24hrs. They also reported that there were some non-GI events which occurred after 24hrs and were possibly related to FMT, including one urinary tract infection, one fever during haemodialysis, hospital admission for choledocholithiasis. One study[13] reported a high incidence of diarrhoea (19/20, 94%) and abdominal bloating (12/20, 60%) in patients who received FMT via colonoscopy and none of these events occurred in a control group receiving vancomycin (0/19, 0%, *p*-value not reported). Another study[14] reported the incidence of different adverse events, none of which seemed to be associated with either FMT (via retention enema) or vancomycin; the adverse events included fever, nausea or vomiting, abdominal pain or tenderness, abdominal distention, bloating, feeling unwell, mucoid or bloody stools, smelly stools, faecal incontinence, anorexia, fatigue and skin rash. Lastly, one study[15] reported that the incidence of adverse events was similar (data and *p*-value not provided) in groups receiving FMT or autologous faecal transplant via colonoscopy and included diarrhoea, abdominal pain, fatigue, gas, bloating, nausea, flatulence, vomiting, anorexia and constipation. The authors reported that the only almost significant difference was the incidence of chills which occurred more frequently in the autologous transplant group (*p* = 0.053). For severe events, one patient given colonoscopy developed sepsis-like symptoms which resolved without treatment within 24hrs,[11] one patient given oral FMT capsules was hospitalised due to severe abdominal pain,[12] one patient was hospitalised due to vomiting and constipation,[12] and one patient was hospitalised due to bleeding associated with either FMT or CDI.[14] In the control group, one patient given placebo capsules experienced *Bacteroides fragilis* bacteraemia and confusion and another experienced pneumonia,[12] one patient died (but the death was not considered due to vancomycin or CDI),[2] and three patients were hospitalised following autologous FMT due to different conditions (diarrhoea, CDI symptoms and mood disorder).[15]

## Patients with severe, complicated or fulminant CDI

*Effectiveness of FMT in patients with severe CDI*: There was weak evidence which suggested that FMT is beneficial in this patient group. The evidence was from one case series,[16] which reported that five of 15 (33%) patients who received one or more (median 3) FMTs via retention enema experienced symptom improvement and no recurrence within 30 days.

*Effectiveness of FMT in patients with severe CDI compared to patients with mild/moderate CDI*: There was moderate evidence which suggested there was no difference between these two patient groups. The evidence was from one retrospective cohort[17] and six case control studies,[18-23] which assessed the effect of severity of CDI on the effectiveness of FMT. None of these seven studies reported differences in success rates between patients who had severe or non-severe CDI.

*Effectiveness of FMT in patients with refractory or fulminant CDI vs recurrent CDI:* There was inconsistent evidence which suggested no difference in effect for these patient groups. Evidence was from one retrospective cohort[24] and four case control studies,[25-28] which assessed the effect of recurrent, refractory or fulminant CDI on the effectiveness of FMT. The studies compared refractory

vs recurrent CDI,[24,25,27,28] fulminant vs recurrent CDI[26] and whether patients responded to initial anti-CDI antibiotics or not.[26] From the studies which compared refractory and recurrent CDI, two reported no effect[24,27] and two reported that patients with refractory CDI had a lower rate of FMT success.[25,28] One study[25] reported that, at 60 days follow-up, there was a higher proportion of patients with recurrent CDI to refractory CDI in the group with a successful FMT (109/140, 77.9%) when compared to those in whom FMT failed (12/25, 48.0%; $p$ = 0.006). Another study[28] reported that there was a higher proportion of patients who had symptom resolution within seven days after FMT when patients with refractory CDI were compared to those with recurrent CDI (35/48, 73% vs 64/70, 91% respectively; $p$ = 0.007). Longer-term effects were not reported in this study. For patients with fulminant CDI compared to recurrent CDI, the proportion of patients with successful FMT was lower for fulminant CDI group (5/9, 55.6% vs 10/11, 90.9%).[26] While this was not significant ($p$ = 0.127), this could be due to a small sample size. For patients who partially responded to anti- CDI antibiotics, there was a higher success rate of FMT (13/13, 100%) compared to the patients who did not respond (2/7, 28.6%; $p$ = 0.001).[26]

*Effectiveness of FMT in patients with pseudomembranous colitis compared to other patients:* There was weak evidence, and it is not clear whether in these patients FMT may be less successful. Evidence was from two case control studies.[18,21] One of these studies[18] reported no difference in the number of patients with pseudomembranous colitis when comparing groups with successful and failed FMT at eight-week follow-up (3/27, 11.5% vs 1/3, 33% respectively; $p$ = 0.2611), although it is worth noting that the study sample was very small. Another study[21] reported a significantly higher proportion of patients with pseudomembranous colitis when comparing patients with successful and failed FMT after five years of follow-up and that all three patients who had pseudomembranous colitis eventually failed FMT (0/70, 0% vs 3/70 4.3% respectively; $p$ = 0.03).

*Adverse events in patients with severe, refractory or fulminant CDI*: There was weak evidence which suggested there was no increased risk associated with FMT for these types of patients. The evidence was from two retrospective cohort studies,[17,24] one case series[16] which assessed severe CDI as a risk factor for adverse events following FMT. One study[17] reported that there was only one death which occurred in patients with severe CDI 1/63 (1.6%) and this was not related to FMT or CDI. Another study,[24] reported no adverse events in patients with either recurrent or refractory CDI. The last study[16] which assessed adverse events in patients with severe, complicated or fulminant CDI, reported that eight patients (8/15, 53%) experienced severe adverse events, none of which were deemed due to FMT but four of which were due to unresolved or recurrent CDI. This included two deaths and two hospitalisations.

*Adverse events in patients with pseudomembranous colitis*: There were no studies.

## First episode of CDI

*Effectiveness of FMT:* There was weak evidence which suggested that FMT is effective in these patients. The evidence was from one case series,[29] which used 54 patients who underwent FMT via colonoscopy and another FMT via enema the following day. The study reported that 53 (98%) of patients achieved cure defined as negative culture and negative CDI toxin test at four to eight weeks of follow-up. Additionally, it was reported that all except one patient were given a course of antibiotics before FMT was provided but that the one patient who did not receive any antimicrobial therapy also achieved sustained cure.

*Adverse events*: There were no studies.

## Patients with co-existing Inflammatory Bowel Disease (IBD) and CDI

*Effectiveness of FMT:* There was weak evidence that suggested FMT was effective in treating CDI in patients with IBD. Evidence was from five case series,[30-34]. One study,[30] which was conducted in patients with ulcerative colitis, Crohn's disease or indeterminate colitis, reported that in 116 of 145 patients (80%) one or more FMT via colonoscopy resulted in sustained symptom improvement or achieving a negative *C. difficile* toxin test (median follow-up 9.3 months, min-max 0.1-51.3 months). However, despite the negative *C. difficile* toxin tests, the authors mentioned that only 48 (33.1%) of patients reported improvement in symptoms and overall well-being. Another study,[31] which included 49 ulcerative colitis and Crohn's disease patients reported that 44 (90%) of patients responded to one FMT via colonoscopy and had no recurrence for eight weeks of the follow-up period. The authors reported that of the remaining five patients, one was lost to follow-up (and was considered treatment failure) and further four were offered a second FMT and achieved cure. Another study[32] included 18 patients with Crohn's disease or ulcerative colitis of whom 17 (94%) experienced symptom resolution and no recurrence within eight-week follow-up following one or more FMT delivered via colonoscopy. The authors also reported that of 15 patients who received one FMT only, 9 (60%) were CDI toxin negative at three months follow-up. One study[33] which included only ulcerative colitis patients, reported that 91% (32/35) responded to FMT via colonoscopy and were CDI toxin negative at eight weeks. Additionally, they reported that only 46% of the patients achieved resolution after one FMT and that the majority of the patients required two or more FMT courses to achieve a sustained cure. Lastly, one multi-site study[34] of 105 IBD patients who underwent FMT (different routes of administration) for CDI, reported that 75 (71%) achieved clinical resolution and sustained cure at eight weeks. The authors also stated that they performed a case control study to identify risk factors for FMT failure and that they did not identify any differences between successful and failed group when comparing different demographic, clinical and FMT-related factors.

*Effectiveness of FMT in IBD patients with CDI compared to patients without IBD:* There was moderate evidence which suggested that FMT for CDI is equally successful in patients who have IBD and those who do not. Evidence was from two retrospective cohort studies,[27,35] seven case control studies[18,21,22,25,36-38] and two cross-sectional studies.[39,40] Ten of 11 studies reported that the success rates were similar in patients with and without IBD. This also included one study[27] which reported no significant difference in outcomes when comparing patients with Crohn's disease to patients with ulcerative colitis at six-month follow-up (3/13, 23.1% vs 9/18, 50%; $p$ = 0.13) or when comparing patients with active IBD to those in remission (1/25, 20% vs 10/25, 40%; $p$ = 0.63 at six-month follow-up). One study[21] which observed a significant effect reported that there was a higher proportion of patients with IBD in a group which failed FMT (11/70, 15.7% in successful vs 24/70, 34.3% in failed FMT; $p$ = 0.01), a factor which remained significant after multivariate analysis was performed (OR for failure 4.34 [95% CI 1.24-15.15]). However, it is also worth noting that success in this study was defined as initial improvement and no recurrence up to five years after FMT.

*Effect on adverse events:* There was weak evidence, but it suggested that FMT is safe in patients with IBD treated for CDI. Evidence was from two retrospective cohort studies[27,35] and three case series.[30,32,33] In one study,[30] the authors reported that, from the total of 145 patients, 11 (7.6%) experienced a flare in IBD while further 32 (22%) continued to have a flare which started before FMT. A total of three patients (2%) also experienced severe adverse events which included two cases with severe abdominal pain which required visit to the Emergency Department (both confirmed due to IBD flare) and one case of severe hypotension which resulted in hospitalisation and required administration of intravenous fluids. Another study[35] reported that eight of 21 (38%) IBD patients experienced adverse events, which included two patients requiring colectomy and six patients experiencing IBD flare-up. Three studies[27,32,33] reported that no adverse events occurred.

## Immunocompromised or immunosuppressed patients with CDI

*Effectiveness of FMT:* There was weak evidence which suggested that FMT is effective in treating CDI in patients who are immunocompromised or immunosuppressed. Evidence was from two case series.[41,42] One of these studies[41] reported that of 17 patients who received FMT via retention enema, 14 (82%) achieved symptom resolution and/or negative *C. difficile* toxin test and had no recurrence within 12 weeks after one treatment. A further two patients responded to a second FMT bringing the total number of patients responding to FMT to 16 (94%). Another study[42] reported that all 11 patients who received one dose of FMT delivered via oral capsules responded to the therapy and had no recurrence for at least three months. The authors reported that there was one patient who experienced a new episode of CDI (> 3 months) which was provoked by administration of antibiotics. This patient was given another dose of FMT and experienced no recurrence during four months of follow-up.

*Effectiveness in immunocompromised/immunosuppressed patients compared to immunocompetent patients:* There was moderate evidence which suggested that there was no difference in effectiveness between these two patient groups. Evidence was from nine case control studies,[18,20-22,25,36-38,43] and three cross-sectional studies.[27,39,40] From 12 studies, eight reported no difference in outcomes and four reported that immunocompromised/ immunosuppressed patients were less likely to respond to FMT. One study[25] reported there was a higher proportion of immunosuppressed/ immunocompromised patients in a group who failed FMT (9/25, 36%) when compared to a group who did not (23/140, 16.4; $p = 0.03$). Another study[36] reported that there were two patients who did not respond to FMT and that both patients were immunosuppressed/immunocompromised while among those who had an initial response, there were four (22%) immunosuppressed/immunocompromised patients. However, at one-month follow-up, the proportion of those who were immunosuppressed/immunocompromised was similar in both groups (3/6, 50% in failed and 6/14, 43% in successful FMT, *p*-value not reported). Another study[22] stratified patients into three groups and reported that of 13 who failed eight (61%) were immunocompetent, three (23%) were immunosuppressed/immunocompromised and two (15%) were severely immunosuppressed/immunocompromised. In a group of 114 patients who had a successful FMT, 93 (82%) were immunocompetent, 20 (17%) were immunosuppressed/immunocompromised and 1 (1%) was severely immunosuppressed/immunocompromised. The difference between the two groups was significant ($p = 0.01$) and it was likely due to the proportion of severely immunosuppressed/immunocompromised patients. Lastly, in one study,[38] the multivariate analysis showed that being immunosuppressed/immunocompromised reduced the odds of FMT success (OR 0.124 [95% CI 0.024–0.642], $p = 0.013$).

*Adverse events:* There was weak evidence which suggested that FMT is safe in this patient group. Evidence was from two case series.[41,42] Both studies reported that none of the patients experienced any adverse events.

## Cancer patients with CDI

*Effectiveness of FMT:* There was weak evidence which suggested that FMT is effective in this patient group. Evidence was from two case series.[44,45] One study[44] reported that of 10 patients with solid tumours who received FMT via colonoscopy or upper endoscopy, eight (80%) recovered and experienced no CDI recurrence during the six month follow-up period. Another study,[45] which included a total of 19 patients with haematological and solid cancers, reported that 16 (84%) responded to FMT via colonoscopy and had no CDI recurrence over an eight-week follow-up. The authors also reported that 14 (74%) patients had no recurrence at one year follow-up and that the success rates at both eight weeks and one year were similar in patients with solid and haematological cancers. The median

duration of CDI symptoms after FMT was 1.0 day (IQR 1.0-1.5d) in patients with solid tumours and 1.5 days (IQR 1.5-2d) in patients with haematological malignancies.

*Effectiveness in cancer patients compared to patients with no cancer:* There was weak evidence, but it suggested that there was no difference in the effectiveness between these two patient groups. Evidence was from two case control studies,[18,20] and one cross-sectional study.[39] None of the studies reported that cancer had any effect on the outcome of FMT for treatment of CDI.

*Adverse events:* There was weak evidence that suggested that FMT was safe in this patient group. Evidence was from two case series.[44,45] One study[44] reported that of a total of 10 patients receiving FMT, four (40%) experienced fever and two (20%) experienced a range of mild, self-limiting events which included abdominal pain/cramping, constipation, diarrhoea, back ache, malaise, toothache (related to upper endoscopy) and gas. None of the 10 patients had any infections following FMT. Another study[45] reported that three (3/19, 16%) experienced adverse events which included abdominal pain and/or nausea. They also reported that two patients died, although not as a result of FMT. One patient died due to CDI after FMT failed and underlying malignancy, and another due to liver failure.

## Post solid organ-transplant patients with CDI

*Effectiveness of FMT:* There was weak evidence which FMT is effective in this patient group. Evidence was from one case series.[46] The authors reported that a primary cure following one administration of FMT (different delivery methods), defined as symptom resolution and/or negative *C. difficile* toxin test and no need for further treatment at one month, was achieved in 60 of 94 (64%) patients. The primary cure at three months follow-up was achieved in 54 of 92 patients (58.7%, two patients were lost to follow-up). The authors also reported that those who failed the initial FMT were offered additional courses and that a total of 82 of 92 patients (91.3%) achieved sustained cure at three months follow-up with one or more FMT.

*Effectiveness in solid organ transplant patients compared to patients with no solid organ transplant:* There were no studies.

*Adverse events:* There was weak evidence which suggested that FMT is safe in this patient group. Evidence was from one case series.[46] The authors reported that 22.3% (21/94) patients reported adverse events following FMT. Most of these events included nausea, abdominal pain, abdominal cramping, and/or loose stools which resolved within one week; three patients also experienced reactivation of cytomegalovirus (CMV). However, three (3.2%) patients experienced severe adverse events which included severe diarrhoea requiring hospitalisation, fever and acute kidney injury. There were also three deaths in this cohort of patients but none were due to FMT or CDI. Additionally, the authors reported that of 94 these post-transplant patients, 16 also had underlying IBD and four (25%) of whom experienced worsening in IBD symptoms following FMT. There were no reported bacteraemia cases in this cohort.

## Patients with liver disease and CDI

*Effectiveness of FMT:* There was weak evidence which suggested FMT is effective in this patient group. Evidence was from one case series.[47] The study, which included 63 patients who underwent FMT mostly delivered via colonoscopy, reported that 54 (68%) patients achieved symptom improvement and no CDI recurrence within eight weeks of follow-up after one administration of FMT. The authors also reported that those patients in whom one FMT was not successful, were offered additional FMT and that the total number of patients who experienced symptom improvement and no recurrence within eight weeks was 62 (98.4%).

*Effectiveness in patients with liver disease compared to patients without liver disease:* There was weak evidence which suggested no difference in the effectiveness of FMT between these two groups of patients. Evidence was from one retrospective cohort,[48] one case control study,[37] and one cross-sectional study.[39] None of the studies reported that liver disease had any effect on the success of FMT for CDI. However, one study[39] reported that cirrhotic patients were more likely to require two or three FMT doses instead of one to achieve cure (multivariate analysis OR 18.24 [95% CI 3.18-104.89], p < 0.001).

*Adverse events:* There was weak evidence which suggested that FMT was safe in this patient group. Evidence was from one case series.[47] The study reported that from a total of 63 patients, 30 (47.6%) experienced at least one adverse event, although only in 19 (30.2%) patients the event was considered related to FMT. The adverse events included abdominal pain and cramping in 10 (15.9%) patients and diarrhoea in 9 (14.3%) patients. There were also five serious FMT-related adverse events, which included hospitalization for a Crohn's disease flare, faecal urgency, dehydration resulting in acute kidney injury, hepatic encephalopathy and portal hypertensive bleed.

### Patients with kidney disease and CDI

*Effectiveness of FMT:* There were no studies.

*Effectiveness in patients with kidney disease compared to patients without kidney disease:* There was weak evidence which suggested that there is no difference in the effectiveness of FMT between these patient groups. Evidence was from three case control studies,[18,22,37] and one cross-sectional study.[39] Three of these studies reported that reported that kidney disease had no effect on the outcome of FMT. The remaining study[37] reported that there was a higher proportion of patients with kidney disease in a group which failed FMT (12%) compared to the group in whom FMT was successful (1.3%). In multivariate analysis, kidney disease increased the odds of failure significantly (OR 9.4 [95% CI 2.0-43.8] $p = 0.02$).

*Adverse events:* There were no studies.

### Patients with diabetes mellitus (DM) and CDI

*Effectiveness of FMT:* There were no studies.

*Effectiveness in patients with DM compared to patients without DM:* There was weak evidence which suggested that there is no difference in the effectiveness of FMT between these patient groups. Evidence was from two case control studies,[18,38] and one cross-sectional study.[39] None of the studies reported that DM had any effect on the success of FMT.

*Adverse events:* There were no studies.

### Patients with cardiovascular disease (CVD) and CDI

*Effectiveness of FMT:* There were no studies.

*Effectiveness in patients with CVD compared to patients without CVD:* There was weak evidence, which suggested that there is no difference in the effectiveness of FMT between these patient groups. Evidence was from one case control study.[38] In multivariate analysis the odds of successful FMT for patients with cardiovascular disease were the same as for patients without the disease (OR 1.616 [95% CI 0.384–6.807], $p = 0.513$).

*Adverse events:* There were no studies.

### Patients with urinary tract infections (UTI) and CDI

*Effectiveness of FMT:* There were no studies.

*Effectiveness in patients with UTI compared to patients without UTI:* There was weak evidence, which suggested that there is no difference in the effectiveness of FMT between these patient groups. Evidence was from one case control study.[22] It was reported that there were no patients with recurrent UTIs who relapsed and there were nine r-UTI patients (8%) in the group which had a successful FMT ($p$ = 0.60).

*Adverse events:* There were no studies.

### Patients with COVID-19 infection and CDI

*Effectiveness of FMT:* There was weak evidence which suggested that FMT is effective in this patient group. Evidence was from one retrospective cohort study.[49] The study included patients with moderate to severe COVID-19 infection who were given antibiotics for CDI with or without FMT infused via colonoscopy. The authors reported a significant difference in the number of patients who experienced symptom improvement following one infusion of FMT (45/46, 98%), compared to those who received only antibiotics (23/40, 58%; $p$ = 0.0001).

*Effectiveness in patients with COVID-19 compared to patients without COVID-19:* There were no studies.

*Adverse events:* There was weak evidence which suggested FMT is safe in this patient group. Evidence was from one retrospective cohort study,[49] which reported no adverse events (reported for FMT group only).

### Patients with CDI and other conditions

*Effectiveness of FMT:* There were no studies.

*Effectiveness in patients with other conditions compared to patients without these conditions:* There was weak evidence, which suggested that there is no difference in the effectiveness of FMT between these patient groups. Two case control studies[18,21] reported no difference in a proportion of patients who had diverticular disease when comparing groups who had a successful and failed FMT. Another case control study[38] reported that in the multivariate analysis, the odds for success were lower in patients with gastrointestinal disease (OR 0.124 [95% CI 0.026–0.589], $p$ = 0.009; the type of disease was not specified) at six-months follow-up, although the type of the disease was not specified. One case study[38] reported higher odds of success for patients with neurological conditions compared to those without (multi-logistic analysis OR 8.012 [95% CI 1.041–61.684], $p$ = 0.046). For other conditions, including cognitive impairment,[37] neuromuscular impairment,[37] and mood disorders,[38] the studies reported that there was no effect.

*Adverse events:* There were no studies.

### Patients with CDI and multiple comorbidities

*Effectiveness of FMT:* There were no studies.

*Effectiveness in patients with multiple comorbidities compared to patients without comorbidities:* There was weak evidence which suggested that FMT may be less successful in patients with multiple comorbidities. Evidence was from one retrospective cohort,[50] four case control,[19,26,36,43] and one cross-sectional study,[51] which assessed the effect of Charlson comorbidity index (CCI) or the number of comorbidities on the effectiveness of FMT. Two studies reported that a higher CCI score was a significant risk factor for FMT failure (multivariate OR for CCI > 7 was 7.0 [95% CI 1.5–30.6], p < 0.05

in one case control study[19] and aHR = 1.4, [95% CI 1.1–1.9], $p$ = 0.011).[50] The remaining studies reported no effect when comparing CCI > 5 ($p$-value not reported but stated insignificant),[36] CCI > 3 (64.3% responded in CCI > 3 vs 100% in CCI < 3; $p$ = 0.26),[26] and when counting the number of comorbidities.[43,51]

*Adverse events:* There were no studies.

## Additional data from excluded studies

### *Quality of life*

One study,[52] which was a follow-up of the RCT included in the meta-analysis,[11] reported the quality of life before and after the patients underwent FMT for CDI. Patients included were those who originally participated in the study and had a recurrence (13 treated with vancomycin, 12 treated with fidaxomicin and three treated with FMT) and, as per protocol, were offered rescue FMT as well as an additional 36 patients who were enrolled into study but due to the trial's early termination (FMT shown to be superior and it was deemed unethical to continue the trial treating patients with antibiotics) were subsequently treated with FMT. Health related quality of life (HrQoL) was measured using EQ-5D-3L scale ranging from 0 to 1. At the time of recurrence, HrQoL for untreated patients (n = 64) was 0.675. At week 8, the value increased to 0.813 (p < 0.001) and at week 26, the value slightly decreased but was still significantly higher than at baseline 0.773 ($p$ = 0.003).

### *Mortality*

Two retrospective cohort studies[53,54] of patients with recurrent or refractory CDI who were given bacterial therapy[53] or antibiotic treatment[54] vs FMT reported no differences in mortality (data not reported;[53] OR 1.07 [95% CI, 0.02–56.3], $p$ = 0.97[54]). However, when including patients with severe CDI, three studies reported a benefit. The above-mentioned retrospective cohort study[22] with nested case control reported that early FMT reduced mortality in severe cases (OR 0.08 [95% CI 0.016–0.34], $p$ = 0.001). A before-after study,[55] which investigated the effect of introducing an FMT programme for treatment of CDI in their facility, reported that the incidence of CDI-related mortality decreased from 21.3% to 9.1% ($p$ = 0.015) for patients with fulminant CDI and from 43.2% to 12.1% (p < 0.001) for patients with refractory CDI. It was also reported that FMT reduced the need for CDI-related colectomy. Lastly, a retrospective study[56] with matched controls, which included 48 patients with severe or fulminant CDI who required care in ICU, reported that patients who received FMT (n = 16) had a 77% decrease in odds for mortality (OR 0.23 [95% CI 0.06-0.97], $p$-value not reported) compared to those who received antibiotic treatment.

### *Long-term effectiveness*

There were six studies[22,57-61] which reported the long-term effectiveness of FMT for CDI. One case series[57] included 374 patients who underwent FMT via colonoscopy. After a one year follow-up, 321 (78.1%) did not experience a recurrence of CDI. Of 53 patients who did, the median time until CDI was 119 days (min-max 7-338 days). The only significant factor which predicted CDI recurrence was the use of non-CD antibiotics (HR 0.27 [95% CI 0.15–0.48], p < 0.001). Another study[58] reported that the proportion of the patients without recurrence slowly declined with time but remained relatively high. There were 96% patients with no recurrence at one month, 93.8% at six months and 90.5% at one year follow-up. Once case study[59] investigated a cure at 6-month follow-up and reported that of 207 patients, 177 (85.5%) had not experienced a recurrence. Of the 30 who did, 20 (67%) were successfully retreated with further FMT. In this cohort of 207 patients, 100 (48%) reported using antibiotics for non-CDI related infections, of whom only 11 (5% of the entire cohort) subsequently developed CDI. One further study[60] reported one-year follow-up of the patients who did or did not receive FMT. After 12 months, for patients where data were available, 87.5% still did not experience recurrence

compared to 70.8% in patients in a non-FMT group. The authors also reported that six of 25 (24%) who were not treated with FMT eventually underwent the therapy and that the self-reported symptom improvement at one, three and 12 months was higher in FMT than the non-FMT group. Similarly, another study[22] of 84 patients who were available for follow-up for a minimum of 57 and up to 143 weeks post-FMT, 61 (73%) had a sustained cure. In this study, self-reported defecation pattern in long-term post FMT improved in 38% (25/65), remained similar in 46% (30/65), and deteriorated in 15% (10/65) of the patients when compared to their baseline CDI episode. Lastly, one case series[61] of 23 patients who underwent FMT and were available for follow-up six to 24 months after FMT reported that none of them experienced recurrence or a new episode of CDI. Of this cohort, 12 (52%) patients received antibiotics for various non-CDI related infections and nine (39%) received probiotics.

### *Asymptomatic carriage after FMT*

There was one case series[62] which reported that asymptomatic carriage of *C. difficile* after FMT is rare. From a total of 167 patients, one week after FMT, 144 were asymptomatic and 97.9% (141/144) were negative for CDI. At four weeks post-FMT, 129 were asymptomatic and 125 (96.9%) still tested negative. Thus, the absence of symptoms in post-FMT patients may be seen not only as a clinical cure, but also a likely indication of a microbiological cure with the absence of *C. difficile* and/or its toxins.

### *New or worsening symptoms following FMT*

A total of eight studies reported the onset of new symptoms or a worsening of pre-existing conditions at long-term follow-up.[22,35,53,58,59,61,63,64] One study[22] of 84 patients reported that one year after follow-up nausea was present in 18% (13/73) of the patients, abdominal pain in 21% (15/71) and diarrhoea in 33%, but that no serious events related to FMT occurred. Another study[58] reported that within a year after FMT, the prevalence of constipation increased: 19% at one-week post-FMT to 33% at one year, but that most of the cases did not need treatment. Other symptoms included urgency (approx. 46% rate throughout the year), cramping (50% patients reported to experience this at least once up to one year) and an increased incidence of IBS (16.9%). Two years after FMT, new conditions included weight gain (median 30lb in 10.3% patients), diabetes mellitus (3%), dyslipidaemia (3%), thyroid problems (2.3%), GI problems (13.4%), serious infections (11.8% including CDI, pneumonia, sepsis and UTI). These conditions were not considered directly linked to FMT. Nine patients also reported life threatening diseases but at approximately 20 months after FMT and these were not considered to be a consequence of FMT. Other studies reported the onset of the following new issues: weight gain (n = 21),[61] cancers (n = 17), [35,53, 61] IBS (n = 12),[59, 61] infections with multi-drug resistant microorganisms (investigated up to six months post-FMT, n = 7),[53] hypertension (n = 5), [53, 59, 61] diabetes mellitus (n = 4), [53] IBD (n = 2), [53, 59] myocardial infarction (n = 2), [59] osteoarthritis (n = 1), [61] stage 4 osteoporosis (n = 1), [61] transient ischaemic attack (n = 1), [61] rheumatoid arthritis (n = 1), [61] weight loss (n = 2), [61] pancreatic insufficiency (n = 1), [59] intestinal overgrowth (n = 1), [59] gastroesophageal reflux disease (n = 1), [59] IBD requiring colon resection (n = 1), [59] congestive heart failure (n = 1), [59] atrial fibrillation (n = 1), [59] hyperlipidaemia (n = 1), [59] valve replacement (n = 1), [59] dysphagia (n = 1), [35] Schatzki ring (n = 1), [35] community acquired pneumonia (n = 1), [35] partial large bowel obstruction (n = 1), [35] shingles (n = 1), [35] carpal tunnel syndrome (n = 1),[35] hospitalisation for colonic decompression (n = 1), [35] more sensitivity to gas-provoking foods (n = 1). [35] None of these conditions were assessed for causality. Worsening pre-existing chronic conditions included IBD (n = 10), [59] and rheumatoid arthritis (n = 1). [59] One retrospective cohort study[63] reviewed the records of 1165 patients who underwent FMT for CDI and 3692 who were given antibiotics for the treatment of CDI. All patients had at least 12 months of follow-up data available with longest follow-up of 2.34 years. The authors reported that there was a slightly higher incidence of myocardial infarction in FMT group compared to non-FMT (aHR 1.68/1000p/year [CI95% 1.01–2.81], *p*-value not reported) and found that the incidence of other conditions including IBD, rheumatoid arthritis, psoriasis, diabetes mellitus, hypertension, stroke or IBS was similar in both

groups. Lastly, at ten-year follow-up, one study[64] reported that there were no new diagnoses of autoimmune diseases, GI disorders or malignancies. After 10 years seven of 34 (20%) patients were still alive and none of the deaths were attributed to FMT.

### *Resolution or improvement of conditions following FMT*

A total of three studies reported resolution or improvement of existing conditions following FMT.[53,59,61] One study[53] reported two patients in whom eradication of multi-drug resistant micro-organisms was observed within six months of FMT and two patients who were cured from hypertension. Another study[61] reported a resolution or improvement of undifferentiated colitis (n = 1), Crohn's disease (n = 2), ulcerative colitis (n = 1), diabetes mellitus (n = 1 – discontinued oral medication) and Parkinson's disease (n = 2 – improved mobility), while the last study[59] reported improvement of IBS (n = 10), IBD (n = 4), and alopecia areata (n = 1, hair started regrowing). As above, none of these studies investigated whether these improvements were directly associated with FMT.

*The Working Party discussed the above evidence and concluded that FMT administered after CDI treatment with appropriate antimicrobials appears to be more effective than placebo, or additional doses of vancomycin or fidaxomicin in prevention of CDI recurrence. However, the sensitivity analyses performed due to high heterogeneity suggest that its effectiveness depends on many factors, including the route of FMT administration, the number of FMTs given, type of the patient and the length of follow-up. It is also important to highlight that the high heterogeneity was also a result of different types of comparisons, which are typically used in clinical practice and constitute standard care, e.g. in some studies, participants were given initial antibiotics to treat CDI and received placebo as a part of standard care while in other studies participants received the initial antibiotics for treatment as well as additional doses of vancomycin or fidaxomicin as a comparison to FMT. In either case, FMT was more effective than any of these standard regimens. The results of one RCT[5] support previous observational reports that retention enema is not an efficient route of administration.*

*Additionally, FMT seems to be beneficial for patients with different types of comorbidity regardless of the severity or phenotype of CDI and the number of CDI episodes preceding FMT. The Working Party acknowledged that some types of comorbidities and multiple comorbidities may make the FMT less effective, and that for these patients, more than one FMT may be required. Clinically, this would be similar for all patients because subsequent FMT, preferably from a different donor, should be offered if the first FMT fails. One dose of FMT may be less effective in patients with pseudomembranous colitis and to achieve a desired effect, these patients could benefit from additional doses. However, clinically, this issue may not be relevant because in practice CDI patients are not routinely assessed for the presence of pseudomembranous colitis. Therefore, the clinical pathway for these patients would remain similar to patients with other CDI types. Nevertheless, FMT in these patients still appears to be better than placebo or antibiotics alone. Thus, FMT should be given for different types of patients, regardless of their comorbidities or the type of CDI. As per the previous iteration of the guidelines, the Working Party discussed that the only absolute contraindication for FMT is the presence of anaphylactic food allergy.*

*In previous guidelines, there was a concern that FMT may cause harm in some types of patients, including those who are immunocompromised or immunosuppressed, those with liver or kidney disease or those with IBD. However, the evidence now suggests that the incidence of adverse events, regardless of their severity, appears to be similar in different types of patients. Thus, the Working Party agreed that FMT should still be considered as a treatment option for patients with comorbidities based*

*on its safety. Moreover, in the general population, the incidence of adverse events in patients who receive FMT does not appear to be different when compared to patients who receive placebo or anti-CDI antibiotics. The Working Party would also like to stress that, due to the similar incidence of occurrence in different treatment groups, GI events such as diarrhoea, nausea or bloating are probably more likely to be associated with CDI itself and possibly some co-interventions (e.g. bowel preparation) rather than with FMT treatment. Based on clinical experience of the Working Party members, adverse events, none of which were captured by the included studies, may occasionally occur but their incidence is very rare. A recent systematic review,[65] which investigated the occurrence of adverse events after FMT, reported that the overall rate of severe adverse events was 0.65% [95% CI 0.45-0.89]. The population in this study included patients with IBD (4.8%) as well as immunosuppressed/immunocompromised patients (8%). For specific adverse events, the incidence was 0.19% [95% CI 0.09-0.31] for sepsis or sepsis-like conditions, 0.27% [95% CI 0.15-0.43] for aspiration pneumonia and 0.20% [95% CI 0.09-0.34] for bowel perforation. Mild adverse events were also relatively rare, with constipation reported in 1.03% [95% CI 0.77-1.33] of the patients, abdominal pain in 1.66% [95% CI 1.33-2.03], nausea in 0.92% [95% CI 0.67-1.20], vomiting in 0.34% [95% CI 0.20-0.52], flatulence in 0.70% [95% CI 0.49-0.94], and febrile episodes in 0.33% [95% CI 0.19-0.50] of patients following FMT. In general, the majority of adverse events seem to occur either due to unsafe FMT products or unsafe practice of administration, both of which are avoidable when careful donor screening is in place and appropriate care is given to FMT recipients. Other events may be unpreventable, e.g. diarrhoea due to glycerol being used as cryoprotectant, but these are relatively minor and self-limiting.*

*The data from the excluded studies point out that the desired effects of FMT are generally long-lasting with many patients experiencing no recurrence of CDI and no evidence of adverse events occurring months to years after FMT. There are some patients who experience recurrence or relapse and the Working Party discussed how these patients should be managed. It was concluded that current evidence[22] and clinical practice support the treatment of these patients with either further FMT or anti-CDI antibiotic therapy.*

*The Working Party discussed whether, due to an apparent benefit, FMT should be offered as a treatment for patients with the first episode of FMT. The effectiveness for patients experiencing the first or second CDI has recently been established in one RCT.[12] However, due to the fact that FMT is more invasive and more expensive, and that a relatively high success rate can be achieved with anti-CDI antibiotics alone, this is not currently recommended. Instead, this issue can be investigated in the future studies.*

**Recommendations**

**1.1:** Avoid FMT as an initial treatment for *C. difficile* infection (i.e. first episode).

**1.2:** Consider FMT for a first recurrence or for patients with refractory *C. difficile* infection.

**1.3:** Offer FMT to all patients with two or more recurrences of *C. difficile* infection.

**1.4:** Ensure that FMT is preceded by the treatment of *C. difficile* infection with appropriate antimicrobials for at least 10 days.

**1.5:** Offer FMT to all types of patients, regardless of their health status, except in those with anaphylactic food allergy.

**1.6:** Offer one or more FMT after initial clinically assessed FMT failure.

**Good practice points**

**GPP 1.1:** Consider early FMT for patients with severe, fulminant or complicated *C. difficile* infection who are not responding to antimicrobial therapy.

**GPP 1.2:** If FMT was given via endoscopy, ensure that immediate management after administration is in line with any local protocols.

**GPP 1.3:** Inform patients about the short-term adverse events, in particular the possibility of self-limiting gastrointestinal symptoms and that serious adverse events are rare.

**GPP 1.4:** Inform Inflammatory Bowel Disease patients with *C. difficile* infection about a small risk of exacerbation of their condition after FMT.

**GPP 1.5:** Follow-up the FMT recipients for at least eight weeks to establish its efficacy and adverse events.

**GPP 1.6:** Do not test for cure by absence of *C. difficile toxin* after FMT, unless the patient has persistent *C. difficile* infection symptoms or is suspected to have relapsed.

**GPP 1.7:** Consider investigation for alternative causes for symptoms in patients who fail to respond to anti- *C. difficile* infection treatment including FMT.

## 4.2 Recipient factors influencing the outcome of FMT for patients with CDI

The evidence above demonstrates that FMT is generally effective in the majority of individuals regardless of their health status. Despite this, there are still patients in whom FMT fails. Risk factors for CDI recurrence after FMT are poorly understood, but certain patient characteristics such as advanced age, female sex and some medications have been proposed as potential predictors for failure.[66] There may also be some additional modifiable factors which could be optimised before FMT is given and these have not yet been explored. Despite some studies reporting some patient characteristics as risk factors, the results have been mostly inconsistent. Additionally, there remain concerns about the safety of FMT for some patients. Underlying vulnerabilities such as older age and the effect of some medications could potentially increase individual's risk of severe adverse events associated with FMT. Previous BSG/HIS guidelines[3] did not identify any risk factors for CDI recurrence other than post-FMT antibiotics. The guidelines also found very little evidence that would demonstrate the safety of FMT in more vulnerable populations. As a result, the guidelines recommended caution when administering FMT to people with certain conditions such as immunosuppression or liver disease and suggested that antibiotic therapy should be avoided or delayed when possible.

## Demographic factors

### *Age*

*Effect on success rates:* There was moderate evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one retrospective cohort study,[67] 12 case control studies[18-22,25,26,36-38,43,68] and two cross-sectional studies.[27,39] From the total of 15 studies, only two[20,37] reported age as a risk factor for failure. One of these studies[20] reported a slightly higher risk of FMT failure when comparing patients of older or younger age (age categories not specified, in multivariate analysis OR = 1.060 [95% CI 1.025–1.097], $p$ = 0.001). Another study[37] reported a lower proportion of patients who were successfully treated with FMT compared to a group of patients in whom FMT failed (47% vs 70%, $p$ = 0.007), however when age was compared in multivariate analysis, it was no longer a risk factor for failure: OR 0.92 [95% CI 0.41-2.1].

*Effect on adverse events:* There was weak evidence which suggested that adverse events are similar across all age groups. Evidence was from one retrospective cohort study,[67] which reported that the proportion of patients who experienced adverse events was similar in the group of those who were very old (7/19, 36.8%) compared to those who were not (16/39, 41%; $p$ = 0.45). Similarly, there was no significant difference in the incidence of severe adverse events (2/19, 10.5% in very old vs 2/39, 5.1% in not very old; $p$ = 0.59). The adverse events included diarrhoea, abdominal pain, vomiting, and constipation, which were considered mild to moderate. The severe events included sepsis and IBD (not related to FMT) in the very old group, as well as sepsis and severe psychiatric collapse in not very old. It was also reported that four deaths occurred in the very old at follow-up and that none of them were due to FMT, although one was due to CDI after FMT failed.

### *Sex*

*Effect on success rates:* There was moderate evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from 10 case control studies[18-20,22,25,26,36-38,43] and two cross-sectional studies,[27,39] none of which reported sex as a risk factor.

*Effect on adverse events:* There were no studies.

### *Body mass index*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from two case control studies.[18,38] One study[18] did not report an effect, although the study might have been underpowered because it only had two patients who failed FMT. Another study[38] reported that odds of successful FMT were slightly reduced for patients with a higher BMI (OR 0.856 [95% CI 0.754–0.970], $p$ = 0.015).

*Effect on adverse events:* There were no studies.

## Factors associated with CDI

### *Number of CDI episodes before FMT*

*Effect on success rates:* There was moderate evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from seven case control[18-20,22,37,43,68] and one cross-sectional study.[27] Seven of these eight studies reported that the number of CDI episodes did not have an effect on the outcome of FMT. The remaining study[37] reported that there was a higher proportion of patients with two or more CDI episodes in whom FMT failed within two months (95%) compared to patients with a successful FMT (79%; $p$ = 0.02). However, when multivariate analysis was performed, the odds for failure were not associated with the number of CDI (OR 3.9 [95% CI 0.89-17.3]). Additionally, one case control study[26] reported that in the group who had a successful FMT the median number of days

from the time CDI was diagnosed until FMT was given was significantly greater than in a group of patients with in whom FMT failed (median 15 days vs 8 days respectively, $p = 0.044$).

*Effect on adverse events:* There were no studies.

### *Hospitalisation due to CDI*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. The evidence was from two case control studies.[18,37] One study[18] reported no significant results ($p = 0.5123$), although it is noteworthy that the sample study was small and that of two patients in whom FMT failed, both were hospitalised (2/2, 100%) while there was a lower proportion of hospitalised patients (16/27, 59%) in the group with a successful FMT. The second study[37] reported a lower proportion of hospitalised patients in a group who had a successful FMT compared to the group of patients who failed (34% vs 54% respectively, $p = 0.02$), although the odds for failure were not significantly different in multivariate analysis (OR 1.6. [95% CI 0.76-3.3]).

*Effect on adverse events:* There were no studies.

### *Antibiotics used for treatment of CDI before FMT*

*Effect on success rates:* There was weak evidence which suggested that these do not influence the effectiveness of FMT. Evidence was from four case control[18,21,38,68] and one cross-sectional study.[39] One of these studies compared the number of antibiotics courses which were given before FMT,[38] three studies assessed vancomycin use,[18,21,68] two studies assessed metronidazole use,[18,21] and two assessed fidaxomicin use.[21,39] One study[38] reported that a higher number of prior antibiotic courses was a risk factor associated with a decreased likelihood of FMT success (OR 0.683 (95% CI 0.476–0.981), $p = 0.039$). Three studies which assessed vancomycin,[18,21,68] metronidazole[18,21] or fidaxomicin[21] use reported no effect of these antibiotics on the success of FMT. However, one study[39] reported that, in univariate analysis, patients who were given fidaxomicin were more likely to require more than one FMT to achieve success (OR 2.33 [95% CI 1.04-5.22], $p = 0.04$; not tested in multivariate analysis).

*Effect on adverse events:* There were no studies.

### *C. difficile strain*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from two case control studies[20,22] and one cross-sectional study.[40] One study[20] reported that the likelihood of failure at 30 days after FMT was not significantly different in patients with ribotype 027 strain (OR not provided but stated not significant, $p = 0.766$). Another study[22] reported that the number of patients with a hypervirulent clade was similar in the group of patients with successful FMT at two months follow-up (13/65, 20%) when compared to the patients in whom FMT failed (2/8, 25%; $p = 0.66$). However, the last study[40] reported that patients with hypervirulent strain of *C. difficile* were less likely to respond to FMT (OR 13.8 [95% CI 1.2-155] $p = 0.034$).

*Effect on adverse events:* There were no studies.

### *Healthcare-acquired CDI*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one case control study,[19] which reported that, in univariate analysis, there was no difference in outcomes related to success between patients with healthcare-acquired (HCAI) or not HCAI CDI (OR = 1.8 [95% CI 0.3–17.0], $p = 0.795$).

*Effect on adverse events:* There were no studies.

## Other risk factors

### *Use of Proton Pump Inhibitors and other anti-secretory medications*

*Effect on success rates:* There was moderate evidence which suggested that these do not influence the effectiveness of FMT. Evidence was from seven case control[18,19,21,22,25,36,37] and three cross-sectional studies.[27,39,40] Eight of these 10 studies reported that the success rates were similar in patients using PPI,[18,19,21,22,25,36,37,40] $H_2$ blockers[18] and other anti-secretory medications[37] and in those who did not use them. One study[27] reported that at six months follow-up, the proportion of patients in whom FMT failed was higher in the group who used PPI (18/33, 54.5%) than in a group who did not use them (13/50, 26%; $p = 0.01$). The proportion of patients who failed was similar at two months follow-up in these groups (12/46, 26.1% vs 11/72, 15.2% respectively, $p = 0.16$). However, there was also one study[39] which reported that, in the univariate analysis, patients who used PPI were more likely to require more than one FMT before achieving cure (OR 2.13 [95% CI 1.001-4.55], $p < 0.05$); this was not tested in the multivariate analysis.

*Effect on adverse events:* There were no studies.

### *Use of corticosteroids preceding the administration of FMT*

*Effect on success rates:* There was weak evidence which suggested that these do not influence the effectiveness of FMT. Evidence was from one cross-sectional study,[39] which reported that, in the univariate analysis, the odds of requiring more than one FMT were similar for patients who were on steroids and those who were not (OR 1.76 [95% CI 0.73-4.23], $p = 0.21$).

*Effect on adverse events:* There were no studies.

### *Use of lactulose preceding the administration of FMT*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one cross-sectional study,[39] which reported that, in the univariate analysis, the odds of requiring more than one FMT were higher in patients who used lactulose compared to those who did not (OR 5.92 [95% CI 1.26-27.83] $p = 0.02$), however, when controlled for other factors in multivariate analysis, the odds of requiring more FMT were similar in both groups (OR 0.38 [95% CI 0.04-3.61], $p = 0.40$).

*Effect on adverse events:* There were no studies.

### *Probiotic use preceding the administration of FMT*

*Effect on success rates:* There was weak evidence which suggested that these do not influence the effectiveness of FMT. Evidence was from two case control studies,[18,21] which reported that probiotics did not have any positive or negative effect on the success of FMT.

*Effect on adverse events:* There were no studies.

### *Non-CDI antibiotic use preceding the administration of FMT*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from two case control studies[22,25] and one cross-sectional study,[39] none of which reported that non-CDI antibiotics had any positive or negative effect on the success of FMT.

*Effect on adverse events:* There were no studies.

### *Use of narcotics preceding the administration of FMT*

*Effect on success rates:* There was weak evidence which suggested that these do not influence the effectiveness of FMT. Evidence was from one case control study,[38] which reported that the proportion

of patients on narcotics was similar in the group of patients who had a successful FMT vs those who did not (49/168, 29.2% vs 26/67, 38.8%; $p = 0.165$).

*Effect on adverse events:* There were no studies.

### *Hospitalised at or before FMT*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from three case control studies[21,25,38] and one cross-sectional study.[27] Three studies[21,25,38] assessed hospitalisation at the time FMT was given, two of which[21,38] reported no effect on its success, while one study[25] reported that there was a higher proportion of inpatients in the group in whom FMT failed (9/25, 36%) compared to patients who had a successful FMT (19/140, 14%; $p = 0.02$). One study[27] reported no difference in the number of patients in whom FMT failed when comparing groups of patients who were hospitalised 90 days prior to FMT vs those who were not at two months follow-up (12/60, 20% vs 11/58, 19% respectively; $p = 0.89$), or at six-month follow-up (18/37, 49% vs 13/46, 28% respectively; $p = 0.06$). Lastly, one study[25] reported no difference in the proportion of patients who were hospitalised 90 days prior to when they acquired CDI when compared the groups of those who had a successful FMT and those in whom FMT failed (38/140, 27% vs 8/25, 32%; $p = 0.63$).

*Effect on adverse events:* There were no studies.

### *Blood biomarkers*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one retrospective cohort,[50] one case control study,[19] and one cross-sectional study.[27] None of the studies reported any association with blood levels of albumin,[19,27] white blood cells or leukocytes,[19,27] or C-reactive protein.[19] One study[27] reported no difference in mean haemoglobin levels in patients with successful or failed FMT at two months follow-up (10.5g/dL, SD 2.3 g/dL vs 11.6g/dL, SD 1.8 g/dL; $p = 0.10$) but a significant difference was observed at six months (10.8 g/dL, SD 2.1 g/dL vs 12.0 g/dL, SD 1.7 g/dL $p = 0.02$). The last study[50] reported a higher risk of recurrence of CDI in patients with zinc deficiency (HR = 11.3 [95% CI2.2–59.3], $p = 0.004$) as well as a beneficial effect (i.e. lower risk of failure) for deficient patients who were given zinc supplements (HR = 0.12, [95% CI 0.02–0.74], $p = 0.022$). It was reported that patients who received zinc supplementation were typically given 25–50 mg nightly for one or two months.

*Effect on adverse events:* There were no studies.

### *Other risk factors*

*Effect on success rates:* There was weak evidence which suggested that these do not influence the effectiveness of FMT. Evidence was from three case control[26,37,68] and one cross-sectional study.[40] No association with the risk of failure was found for race,[37] high risk population (defined as those working in a healthcare setting or those whose family member had CDI),[40] previous FMT given in the last 12 months,[37] and the number of risk factors.[68] One study[26] reported that there were differences in a microbiome composition between patients who had a successful or failed FMT ($p = 0.001$). Patients whose FMT were successful had higher proportion of Bacillota (Firmicutes) and Bacteroidota (Bacteroidetes; 43% vs 33% in those who failed) and lower proportion of Pseudomonadota (Proteobacteria) and Fusobacteriota (Fusobacteria; 55% vs 66%).

*Effect on adverse events:* There were no studies.

*Upon reviewing the above evidence, the Working Party agreed that there are currently no identified factors which affect the effectiveness of FMT. There may be some characteristics of CDI infection that*

*may result in FMT being less effective; however, as was highlighted in a previous section, FMT is still more effective than standard antibiotics and placebo. Adverse events were assessed only for patients' age and the evidence suggested that age had no effect. The Working Party agreed that the paucity of studies reporting adverse events for patients with different characteristics likely represent the lack of effect of these characteristics on the incidence and severity of adverse events. Based on these conclusions, the Working Party agreed that FMT should not be declined or delayed based on any patient- or CDI-related characteristic.*

*Additionally, the Working Party agreed that further studies investigating the effect of non-modifiable risk factors (e.g. age, sex, etc.) are not necessary because the existing studies suggest that these factors are not likely to influence the effectiveness or adverse events of FMT to the point where antibiotics and/or other therapies should be considered as an alternative. As such, future studies should focus on investigating modifiable risk factors which can be corrected before FMT is given so that its outcomes are optimised. A recent review[69] identified possible recipient factors which facilitated donor microbiota engraftment, including genetics, inflammation status and environmental factors (e.g. diet). Further studies are needed to identify if these factors can influence clinical outcomes of FMT.*

**Recommendations**

**2.1:** Do not refuse or delay FMT therapy due to any recipient risk factors e.g. age over 75 years old.

**Good practice points**

**GPP 2.1:** none

## 4.3 Donor factors influencing the outcome of FMT for patients with CDI

A robust donor screening programme is an essential part of FMT services to ensure safety for FMT recipients. Donor recruitment is challenging; using standard criteria applied in many FMT services to ensure safety and efficacy, one recent study reported that only 1.7% of prospective candidates qualified as suitable donors[70]. Moreover, the study reported that due to a lengthy screening process as many as 39% of the candidates were lost to follow-up even before their suitability was established. The reluctance of the public to donate their stool is also well documented and seems to stem from the social perception of stool, the lack of awareness of the importance of donation, and the logistic difficulties in collection and transport of the stool.[71] Evidently, there is a need for a pragmatic approach for the recruitment and screening of potential donors.

The primary aim of donor screening is mitigating risk of pathogen transmission via FMT. A secondary aim of donor screening is to exclude potential donors who may have an 'aberrant/adverse' gut microbiome. While the complexity and relative novelty of exploration of the gut microbiome means that there is no clear agreed definition of what a 'healthy' or 'unhealthy' gut microbiome is,[72] either compositionally or functionally, there is the theoretical potential for transmission of gut microbiome traits (and therefore potential for transmission of risk for diseases with a link to the gut microbiome) via FMT. There are also some studies that include microbiome sequencing and other approaches to try and find which bacteria transplanted from donor to recipient are associated with success.[73,74] So far, it has been difficult to define a core set of bacteria or functions underlying a good donor or successful FMT. At the moment, there is little evidence which allows FMT services to define a healthy microbiome which is most optimal for donation. Previous BSG/HIS guidelines[3] acknowledged that

research into donor factors is lacking. Therefore, the guidelines recommended a general approach that all healthy adults under 60 years of age with BMI under 30kg/m$^2$ could be potential candidates for donor screening. The recommendations then focused on an initial screening using a health and travel questionnaire, followed up by a battery of laboratory testing of blood and stools to further ensure the safety of FMT material. The guidelines also recommended regular re-assessment of donors to ensure continuing safety. Since the guidelines were published, more evidence has become available, especially around the experience of donor screening and the retention of possible donors. The emergence of the COVID-19 pandemic also raised questions whether prospective donors should be tested for other, non-gastrointestinal pathogens, to ensure the safety of recipients.

### *Related vs not related donor*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from two case control study[21,23] and one cross-sectional study.[51] Two studies[21,51] reported similar success rates for patients who received FMT from a related donor compared to those who received a non-related donor stool. One study[23] reported marginally significant results indicating that FMT from a family donor is a risk factor for failure (multivariate analysis OR 4.13 [95% CI 1.00-17.01], $p = 0.049$).

*Effect on adverse events:* There were no studies.

### *Age of the donor*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from two case control study,[22,26] which reported that there was no significant difference between the age of the donors when comparing groups of patients with a successful and unsuccessful FMT.

*Effect on adverse events:* There were no studies.

### *Sex of the donor*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one case control study,[22] which reported that the proportion of donor females was similar in the group who relapsed within two months of FMT (7/13, 54%) and those who had a successful FMT at two-month follow-up (58/116, 50%; OR 1.2 [95% CI 0.4-3.7], $p = 0.79$). Additionally, the study reported that they assessed the effect of the patient-donor sex mismatch and reported that this had no effect on FMT success (OR 0.7 [95% CI 0.2-2.3], $p = 0.58$).

*Effect on adverse events:* There were no studies.

### *Amount of stool produced*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one case control study,[26] which reported that there was no difference in the number of patients with successful FMT when comparing the group of patients who received the transplant derived from stool which was larger than 100g compared to the stool which was smaller than 100g (10/13, 76.9% vs 5/7, 71.4%; $p = 1.0$).

*Effect on adverse events:* There were no studies.

### *Microbiome composition of the donor*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one case control study,[26] which reported that there were no

differences in stool composition when comparing patients who responded and did not respond to FMT ($p$ = 1.00).

*Effect on adverse events:* There were no studies.

*The Working Party reviewed the above evidence and concluded that it is likely that routinely measured donor factors do not influence the effectiveness of FMT for treatment of CDI. The Working Party agreed that the use of universal donors is the most practical and cost-effective way to obtain donor stools. The previous practice of using related donors, which in early days before stools banks existed were the most reliable source of donor stools, is now outdated and should be avoided. There is no established evidence that stools from a related donor influences the effectiveness of the FMT, but there may be logistical difficulties and potentially additional costs related to donor screening. There is also a concern that stool microbiota may be less diverse in these donors. As a related donor may cohabit with a recipient, the overlap of environmental factors with the patient (e.g. diet) may affect their gut microbiome and the success of FMT.*

*There were no studies which investigated whether the donor factors affected the incidence or severity of adverse events, but the members agreed that, apart from the composition of the microbiota, they are not likely to influence the effectiveness of FMT. As mentioned above, some studies demonstrate that the composition of microbiota of the donor stool may predict the success or failure of FMT,*[73,74] *but none of these studies met the inclusion criteria for these guidelines. The Working Party stressed that wherever donor factors have been investigated, this was done in situations in which all donors were screened for possible transmissible diseases and where safety of FMT material was established. Therefore, they stated that screening of all donors must remain in place to ensure the safety of FMT recipients. All donors should also be re-screened regularly to ensure ongoing safety.*

### Rationale for recommendations on overall approach to donor screening

The Working Party agreed a robust donor screening procedure remains mandatory. As per the original version of these guidelines, the screening should continue to comprise a questionnaire, to identify risk factors for an aberrant microbiome and pathogen carriage, and laboratory-based testing for pathogen detection. This should be an ongoing process that is repeated at appropriate intervals.

The Working Party discussed the reported FMT complications since the last guidelines which might influence updates in the recommended donor screening protocols. From one perspective, there have been a number of reported cases of infection post-FMT apparently related to pathogen transmission which may have been mitigated by additional donor screening processes, including *C. perfringens*,[75] atypical enteropathogenic *E. coli*,[76] and Shiga toxin-producing *E. coli*.[77] It is also important to highlight the well-publicised case of FMT-related infection transmission in two immunosuppressed patients who developed bloodstream infection after transmission of *E. coli* carrying an extended-spectrum beta-lactamase (ESBL) via FMT, leading to one death.[78,79] There had been considerable concern since the emergence of SARS-CoV-2 regarding its potential for transmission via FMT (particularly related to its potential route of entry via the luminal tract, and well-described GI symptoms related to infection), and rapid consensus updates to donor screening were introduced to mitigate risk.[80] However, despite this theoretical risk, there are no reported cases of FMT-related SARS-CoV-2 transmission described, to the knowledge of the Working Party. Since the last guideline, there has been an increased period of time for reporting of registry data and of prospective case series. Overall, FMT for rCDI appears safe with several years of follow-up post-treatment; there have been very few cases of infection potentially attributable to FMT, and very low rates of new diseases which might feasibly be attributable to FMT. [22,35,53,57-61,63-65] There is a need to strike an appropriate balance between screening practices that are

robust enough to mitigate the potential risks of providing FMT, whilst allowing sufficient pragmatism. Overly stringent screening focused on theoretical risk of every possible pathogen risks making the process impossible to comply with.

Regarding the recommended donor history/questionnaire, the Working Party provided some updates to this compared to the original version of this guideline (Box 1). For instance, the assessment for risk factors for blood-borne viruses has been updated to be consistent with those from UK Blood and Transplant. The Working Party noted that FMT services in certain settings aimed to recruit donors from within blood donation services, given the degree of overlap in assessment between blood and stool donation, although no such approach was currently being undertaken within the UK. Additional assessments have now been recommended, e.g. enquiring about recent cold sores, anal ulcers and/or persistent pruritus ani, to screen for organisms that colonise the oral, rectal or perineal mucosa, including Herpes simplex virus, pinworm and monkeypox (Mpox) virus. Of note, the Working Party discussed that while a health questionnaire assessment is mandatory, it is beyond the scope of the committee to mandate specific content or specific exclusion criteria, and Box 1 represents recommendations based upon suggested best practice rather than compulsory questions. Questionnaire content and clinical interpretation of responses should be discussed and agreed at a local level following a robust risk assessment.

Laboratory-based blood screening of potential donors remains mandatory (Box 2). The Working Party discussed that while a number of the pathogens listed in Box 2 are not recognised to transmit via the faeco-oral route (being predominantly blood-borne pathogens), and the theoretical risk of them being transmitted via FMT being therefore low, there was still justification to screen for them out of a principle of caution. The Working Party again discussed and upheld their recommendation regarding Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) testing being only recommended where there is the potential that the FMT prepared from that donor will be administered to immunosuppressed patients at risk of severe infection. Of interest, recent evidence suggests that only a very small proportion (approximately 1%) of CMV IgG or IgM positive donors have detectable stool CMV DNA on PCR, and no CMV IgM positive donors or those with stool CMV DNA have infectious virus on cell culture.[81] Nevertheless, this recommendation has also been upheld on the principle of an abundance of caution. While the Working Party recommended consideration of a set of general/metabolic blood tests for donors, they did not set specific limits/thresholds for values. The examples were discussed of a donor with, for instance, incidental marked anaemia or raised CRP as being at high risk of having significant undiagnosed disease which may impact the gut microbiome, and therefore being unsuitable for material donation.

The Working Party discussed the need to update stool pathogen screening compared to the last version of the guideline (Box 3). In one respect, they acknowledged the need to recommend additional screening, with faecal SARS-CoV-2 being of relevance given its potential for faecal-oral transmission, as discussed above. The Working Party recognised that a global consensus document designed for European practice developed at the height of the COVID-19 pandemic had recommended SARS-CoV-2 screening of each donated stool sample.[80] The Working Party concluded that while an argument could be made for continuing with this approach based on risk assessment at present, the currently evolving risk landscape related to SARS-CoV-2 (related to a number of factors, including national COVID-19 vaccination roll out) may mean that a modified protocol for SARS-CoV-2 screening may become appropriate over the lifetime of this guideline. Similarly, the Working Party noted a report of

atypical enteropathogenic *E. coli* transmission related to FMT, and as such felt that more considered screening for this in donors was justified.[76] The Working Party also discussed that new evidence had emerged since the last version of the guidelines that suggested against certain GI pathobionts being transmitted via FMT. In particular, a Danish FMT service recently described 13 out of 40 donors as being *H. pylori* stool antigen positive, but that 26 FMTs administered from five positive donors had not resulted in any recipients becoming *H. pylori* stool antigen positive at a median of 59 days.[82] While these data do not support the need for *H. pylori* stool antigen being part of screening, the Working Party also discussed the different risk burden that theoretical *H. pylori* transmission might have in the UK versus in the Far East, given its association with gastric cancer. It was noted that there are recent data demonstrating transmission of *Blastocystis* via FMT, but that this did not influence success of FMT as treatment for rCDI, and it was not associated with any gastrointestinal symptomatology over months of follow-up, suggesting no need to intensify donor screening for this organism.[83]

The Working Party noted recent literature exploring the impact of FMT upon the gut microbiota dynamics of potentially pro-carcinogenic bacteria. This topic first came to light from a study of 11 paediatric rCDI patients (of whom six had underlying IBD), in whom four patients were found to have sustained acquisition of procarcinogenic bacteria post-FMT, after transmission from colonised donors. It was also noted that two patients experienced clearance of such bacteria after FMT from a negative donor.[84] Using full genome sequencing, one of these patients acquiring pro-carcinogenic bacteria was shown to have durable donor-to-recipient transmission of *E. coli* with the colibactin gene (*clbB*), which has been associated with colonic tumours.[85] A further retrospective study[86] analysed stool metagenomes of matched pre- vs post-FMT samples from 49 rCDI patients, together with their matched donors. This showed higher prevalence and abundance of potentially pro-carcinogenic polyketide synthase-positive (pks+) *E. coli* in the gut microbiome of rCDI patients compared to their healthy donors, and that the pks status of the post-FMT gut microbiome related to the pks status of the donor being used (with pks being negative in five out of eight of their donors at all time points sampled and detected in overall low levels otherwise). More specifically, persistence (eight out of nine patients) or clearance (13/18 patients) of pks+ *E. coli* in pks+ patients correlated to pks in the donor ($p$ = 0.004). While these data are of interest, the Working Party concluded that the small number of publications on this topic, unclear understanding of the true potential causative procarcinogenic nature of the bacteria being studied, and overall reassuring safety profile of FMT meant that there was no current clinical indication for routine metagenome screening for such bacteria or their genes as part of donor screening. Further studies within this field should be undertaken and results monitored. The Working Party noted that FMT for rCDI is often being used in an older and frail population for whom the risk-to-benefit ratio of FMT is being considered over a fairly short period, i.e. patients with limited alternate therapeutic options, with the aim of minimising further hospital admissions. This ratio would be different in the context of younger patients, where FMT was used on a more exploratory basis, and this may influence the importance of considering the potential future role for screening for such bacteria.

The Working Party also noted that a number of studies had proposed using stool metagenomics as a tool to assess stool donors, and proposed a variety of ecological or taxonomy-based metrics to select out and stratify potentially 'ideal' donors.[87] Discussions within the Working Party concluded that while this was of research interest, there was no justification for use of any assessment of this nature as part of the donor screening/selection process at present. It was also observed that a small number of studies had suggested a potential role for additional modalities of laboratory assessment as part of

donor screening; for instance, one study observed a trend towards increased gastrointestinal symptoms post-FMT for rCDI after receipt of FMT from a donor with positive small intestinal bacterial overgrowth, as assessed by positive lactulose breath test.[88] Again, the Working Party felt that while this was of interest and supported future research, there was no current justification for this to be incorporated into the donor screening process.

As per their discussions regarding the health questionnaire, the Working Party felt that it was beyond the scope to mandate or exclude specific laboratory tests. Thus, the lists given in Boxes 2 and 3 reflect suggested best practice but not compulsory testing. Laboratory-based testing and clinical interpretation of results should be performed and agreed at a local level following a robust risk assessment. Consistent with this, the Working Party noted the differences in laboratory donor screening approaches that are reported in different regions globally. These are consistent with the different prevalence and risk profile of different pathogens within each region.[89] As highlighted by the case of COVID-19, the list of pathogens for which testing is undertaken needs to be constantly reviewed, revised, and updated, based on local epidemiology and the latest evidence base. One area that may require particular focus in this regard is the potential for emergence of new viral pathogens, or rise in population prevalence of known viral pathogens with established faecal-oral transmission e.g. poliovirus; the pertinence of this is highlighted by its detection within sewage water in London in 2022.[90,91]

The Working Party no longer supports the use of fresh FMT, because this approach does not allow for direct testing of the donor stool used to manufacture FMT prior to administration and does not allow for a period of quarantine in the case where additional donor testing may be required. Stool may be processed into FMT immediately from donors who have passed baseline screening, but the Working Party agreed that it should initially be quarantined. The Working Party also agreed that post-baseline screening is required prior to release of FMT from quarantine to further mitigate the risk of pathogen transmission. This post-baseline donor screening needs to take a safe but pragmatic approach, and should cover two aspects:

- Bookend testing on donated stool to pick up acquisition of asymptomatic, transmissible enteric pathogens during the donation period. Again, exact framework should be defined by local policies and donation schedules, ideally following a robust risk assessment. It could include testing of pooled aliquots of donor stool used for manufacturing FMT. FMT could only be considered for release from quarantine once results have been demonstrated to be clear.
- Bookend assessment and/or testing of donor to identify risk factors for pathogen acquisition since baseline screening. The exact framework should be defined by local policies and donation schedules, ideally following a robust risk assessment. It could involve a donor questionnaire at each donation. FMT could only be considered for release from quarantine if no specific risks were identified. FMT manufactured from donors identified as having acquired risk factors during the donation period (such as unprotected sex with a new partner) would need to undergo continued quarantine, and only be considered from release once the appropriate repeat blood testing had been performed, and results were demonstrated to be clear, ensuring that there had been a sufficient time period to allow for seroconversion.

**Recommendations**

**3.1:** Use FMT from universal donors in preference to related donors.

**3.2:** All potential donors must be screened by questionnaire or personal interview to establish risk factors for transmissible diseases and for factors influencing the gut microbiota (Box 1).

**3.3:** Blood and stool of all donors must be tested for transmissible diseases to ensure FMT safety (Box 2 and 3).

**3.4:** Discuss and agree the content of donor health questionnaire and laboratory testing at a local level, following a robust risk assessment.

**3.5:** Undertake ongoing review, revision and updating of the list of pathogens for screening/testing based on local epidemiology and the latest evidence.

**3.6:** Blood and stool of all donors must be re-screened periodically to ensure FMT safety.

**3.7:** Health assessment which captures the donor's ongoing suitability must be completed at each stool donation.

**3.8:** Ensure that FMT manufactured from donors is quarantined pending post-baseline screening and test results.

**Good practice points**

**GPP 3.1:** Follow suggested recommendations in Boxes 1-4 for conditions to be included in screening and health questionnaire.

## Box 1: Recommended donor history questionnaire

Positive response to any of these questions may exclude further consideration regarding donation at that time, it may be appropriate to rescreen and consider for donation at a later time point based upon the particular scenario.

- Receipt of antimicrobials and/or other medications potentially associated with gut microbiome perturbation, to include (but not limited to) proton pump inhibitor, statin, immunosuppression, chemotherapy, within the past three months.
- Known prior exposure to HIV and/or viral hepatitis.
- Known previous or latent tuberculosis.
- Use of illicit drugs, any tattoo, body piercing, needlestick injury, blood transfusion, acupuncture (outside of licensed or approved UK facilities), all within the previous four months.
- New or multiple (more than one) sexual partners within the past three months.
- Sex with somebody diagnosed with HTLV-1 and -2*.
- Previously living in areas with high prevalence of HTLV-1 and -2*.
- Receipt of a live attenuated vaccine within the past six months.
- Cold sores, anal ulcers, anal sores, pruritus ani within the past three months.
- Underlying gastrointestinal conditions/symptoms (e.g. history of IBD, IBS, chronic diarrhoea, chronic constipation, coeliac disease, bowel resection or bariatric surgery).
- Acute diarrhoea/gastrointestinal symptoms within the past two weeks.
- Family history of any significant gastrointestinal conditions (e.g. family history of IBD, or colorectal cancer).
- History of atopy (e.g. asthma, eosinophilic disorders).
- Any systemic autoimmune conditions.
- Any metabolic conditions, including diabetes and obesity.
- Any neurological or psychiatric conditions.
- History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia.
- History of any malignancy.
- History of receiving growth hormone, insulin from cows, or clotting factor concentrates, or known risk of prion disease.
- History of receiving an experimental medicine (including vaccines) within the past six months.
- History of travel to tropical countries within the past six months.

*This question to be asked in centres where laboratory screening for HTLV-1 and -2 may be difficult; areas to focus on, but not limited to: Japan, the Caribbean, and South America.

## Box 2: Recommended blood screening

**Pathogen Screening:**

- Hepatitis A IgM
- Hepatitis B (HBsAg And HBcAb)
- Hepatitis C antibody
- Hepatitis E IgM
- HIV -1 and -2 antibodies
- HTLV-1 and -2 antibodies
- *Treponema pallidum* antibodies (TPHA, VDRL)
- Epstein-Barr virus IgM and IgG*
- Cytomegalovirus IgM and IgG*
- Strongyloides stercoralis IgG
- *Entamoeba histolytica* serology
- Cysticercal serology.

**General/Metabolic Screening:**

- Full blood count with differential
- Creatinine and electrolytes
- Liver enzymes and liver function tests.
- C-reactive protein

*EBV and CMV testing is recommended where there is the potential that the FMT prepared from that donor will be administered to immunosuppressed patients at risk of severe infection if exposed to CMV and EBV.

1413

## Box 3: Recommended stool screening

- *Clostridioides difficile tcdB (toxin B) by PCR**
- *Campylobacter, Salmonella and Shigella, preferably by PCR*
- *Shiga toxin-producing Escherichia coli by PCR*
- *Other enteropathogenic E. coli, including, but not limited to Enteropathogenic E. coli (EPEC), by PCR*
- *Multi-drug resistant bacteria, including but not limited to, carbapenemase-producing Enterobacterales (CPE), extended-spectrum beta-lactamases (ESBL), and vancomycin resistant Enterococci (VRE) ***.*
- *Stool ova, cysts and parasite analysis, including:*
- *Cryptosporidium and Giardia antigen or PCR*
- *Acid fast staining for Cyclospora, Isospora and Microsporidia.*
- *Norovirus and rotavirus PCR.*
- *SARS-CoV-2****
- *H. pylori stool antigen*****

*GDH screening for possible *C. difficile* is not required or recommended; where performed, a positive GDH would not be sufficient to exclude a donor on the grounds of "positive *C. difficile* status".
**Methicillin-resistant *Staphylococcus aureus* (MRSA) is primarily recognised as a skin rather than a gastrointestinal organism; therefore screening is not universally recommended.
***Based upon current prevalence and laboratory expertise, a broader viral screen may be appropriate, ideally via multiplex panel, which may include e.g. sapovirus and poliovirus.
****Consider testing but not necessarily to exclude as a donor; may potentially wish to consider informing any recipients of *H. pylori* stool antigen-positive material, especially if recipients do not have a background of/are not currently *H. pylori* stool antigen positive.

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Box 4: Post-baseline bookend screening stool

- *Clostridioides difficile tcdB (toxin B)*
- *Campylobacter, Salmonella and Shigella*
- *Shiga toxin-producing Escherichia coli*
- *Other enteropathogenic E. coli, including, but not limited to Enteropathogenic E. coli (EPEC)*
- *Microsporidia*
- *Norovirus and rotavirus PCR*
- *Cryptosporidium*
- *SARS-CoV-2*
- *Cyclospora*

## 4.4 Preparation-related factors influencing the outcome of FMT for patients with CDI

The effectiveness of FMT is presumed to depend upon transferred commensal microbiota being able to engraft and proliferate in the recipient's colon. Thus, preservation of viability of relevant bacteria during processing and storage is considered an important factor for FMT effectiveness. At the moment, there is no standard approach to how donated stools are processed and stored, although it has been suggested that variations in processing seem to have little influence on FMT effectiveness for rCDI.[92] Due to the difficulties with donor recruitment, as well as an additional benefit of quarantine of the donor stools, the desire is to keep FMT product for as long as possible. Longer storage is also helpful if an interruption of donor supply or manufacturing process occurs, an example of which was observed during the recent pandemic. There is a need for studies to determine the time thresholds and optimal conditions in which FMT products need to be processed and used. The determination of appropriate storage temperatures is also important for cost-effectiveness and environmental considerations. Previous BSG/HIS guidelines[3] found mostly low-quality evidence in relation to stool processing and storage. Based on standard practice, they recommended that stools should be processed within six hours of defecation, stored at -80°C and used within six months of processing.

### *Fresh vs frozen stool*

*Effect on success rates:* There was moderate evidence which suggested that fresh and frozen stools are equally effective. Evidence was from four case control[18,20,26,28] and two cross-sectional studies,[27,68] none of which reported an effect on the success of FMT.

*Effect on adverse events:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one case control study[28] which reported that there were no cases of bacteraemia in a group of patients who received FMT from a frozen stool (0/87, 0%) while there were two cases (2/31, 6%, *p*-value not reported) in a group who received the FMT obtained from a fresh stool. The authors reported that it was not possible to determine whether these two cases were due to FMT because these two patients were also reported to have the same pathogens in their urine.

### *Stool frozen at -20°C vs -80°C*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one retrospective cohort study,[93] which reported that there was no difference in symptom resolution at three month-follow-up in the group of patients who

received FMT prepared from the stool stored at -80°C (44/45, 98%) when compared to the group of patients who received FMT from the stool stored at -20°C (56/59, 95%; p > 0.05). There was also no difference in the number of patients who remained symptom free at one-year follow-up (38/42, 90% vs 50/57, 88% respectively; p > 0.05).

*Effect on adverse events:* There were no studies.

### *Lyophilised stool*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from three case series,[94-96] which assessed the effectiveness of lyophilised stool for administration of FMT. In one study,[94] patients chose a route of administration themselves and that the capsule was broken, and the contents were dissolved in normal saline for those who had it delivered via colonoscopy. The study reported that 85% (23/27) patients had symptom resolution and no CDI recurrence at follow (duration not reported) after receiving one dose of FMT and that the remaining four patients achieved cure after the second or a third dose of FMT, (thus, reporting overall success of 100%). Another study[95] reported that at six weeks follow-up, 78% (15/19) of patients achieved a sustained cure after one FMT and 89% (17/19) achieved with one or two doses. It was reported that of the remaining two patients one died within six weeks of follow-up and another patient was successfully treated with CDI antibiotics after the first FMT. The last study[96] reported similar rates of success at two-month follow-up with 81% (26/32) experiencing no recurrence after one FMT and 88% (28/32) after being given more than one dose.

*Effect on adverse events:* There was weak evidence which suggested FMT from lyophilised stools is safe. Evidence was from one case series,[95] which reported that there were no self-reported adverse events in patients who received lyophilised stools.

### *Type of capsule*

*Effect on success rates:* There was weak evidence which suggested that this does not influence the effectiveness of FMT. Evidence was from one RCT,[97] which reported that there was no significant difference in the number of patients who responded to FMT after receiving one or more doses (15/16, 94% for supernatant capsule vs 8/12, 67% for sediment capsule; $p$ = 0.133), although there is a possibility that this study was underpowered, and it was not possible to determine the follow-up period for these patients.

*Effect on adverse events:* There were no studies.

### *Processing time*

*Effect on success rates:* There was weak evidence which suggested that processing time for 150 minutes or longer does not influence the effectiveness of FMT. Evidence was from one prospective cohort[98] and one case control study.[22] One of these studies[98] compared different 30-minute time intervals varying from under 30 minutes to over 150 minutes of processing time (from defecation to freezing) and reported that the cure rates (response and no recurrence within two- month follow-up) varied from a minimum of 80% for the processing time of 61-90 minutes to a maximum 88% for the processing time over 150 minutes ($p$ = 0.48). Another study[22] reported that when comparing the groups who relapsed and those who were cured within two months of FMT, there were no significant differences in the mean length of time that it took for the stools to be processed from defecation to freezing (163min vs 168min; $p$ = 0.73).

*Effect on adverse events:* There were no studies.

*Storage time*

*Effect on success rates:* There was weak evidence which suggested that storing frozen products for more than a year may not influence the effectiveness of FMT. Evidence was from one prospective cohort,[98] one retrospective cohort,[93] and one case control study.[22] Neither study reported an effect. One of these studies[98] compared different time intervals varying from under 30 days to over 700 days of storage time for frozen products and reported that the cure rates (response and no recurrence within two months of follow-up) varied from a minimum of 80% for the storage time of 61-90 days to a maximum 85% for the storing time of 91-180 days. Even at storage time of 360 to 720 days, the cure rates remained high and were not significantly different than those compared to other times ($p$ = 0.34). In another study,[93] the cure rates at one year of the follow-up were the highest for the products stored at -20°C for less than two months (94%) and lowest for those stored for more than six months (83%), but these differences were not considered significant ($p$-value not reported). The last study[22] reported that when comparing the groups who relapsed and those who were cured within two months of FMT, there were no significant differences in the mean number of days that the stool samples were frozen at -80°C (214 days vs 275 days respectively; $p$ = 0.27).

*Effect on adverse events:* There were no studies.

**Additional data from excluded studies:**

*Anaerobic vs aerobic processing*

Two studies[92,99] which examined the effect of aerobic and anaerobic conditions reported that processing the stool samples under anaerobic conditions helps to preserve microbial diversity[92] and viability.[99] The studies also reported that anaerobic bacteria are particularly affected if samples are processed under aerobic conditions. On the other hand, one study[100] reported that oxygen-free atmosphere was not necessary as long as the air above collected samples was removed (this was achieved by using a self-collection device which was equipped with a port that allowed the air to be expelled and which resulted in a very low partial pressure of oxygen in the inoculum).

*Effect of freezing*

Two studies[92,101] reported that freezing resulted in the loss of microbial diversity of the processed stool samples. One of these studies[101] also reported that the changes occurred progressively throughout the year during which the samples were tested with the abundance of Bacteroidetes decreasing while the Bacillota remained stable over time. Another study[101] reported that if stool samples were to be frozen and stored for up to three months, preparation in maltodextrin-trehalose solutions, storage at -80°C standard freezer and rapid thawing at 37°C, provided the best results for the samples to retain their revivification potential. The same solution was also reported to be effective in preserving lyophilized samples.[100]

*Emulsion process*

One study[102] described using two different protocols for processing stool samples. The results showed that magnet plate emulsion (MPE) and Seward Stomacher Emulsion (SSE) were similar in terms of maintaining microbial load, with SSE being marginally better preserving anaerobic bacteria.

*The Working Party concluded that there is currently no evidence to suggest that any preparation factors in particular have an effect on the effectiveness or the incidence and severity of adverse events of FMT for CDI. The literature from the excluded studies suggests that anaerobic process and freezing the products has an effect on the viability of the microbiota, but there still seems to be an adequate clinical effect regardless of these findings. In terms of efficacy, it is currently not known how long fresh*

*stools can be kept before they are processed and how long the FMT products can stored frozen. However, the literature suggests that up to 180 minutes before processing starts and up to 12 months of storage time is acceptable. Due to a relatively low impact on effectiveness, the Working Party suggested that other factors such as overall safety, cost-effectiveness, convenience and environmental concerns should be considered when preparing and storing FMT products. It is preferred that the products are stored frozen because this provides convenience and additional safety as the delay in administration allows more time to withdraw faeces if a donor becomes ill or tests positive for a transmissible pathogen. Current practice in the UK is to start the processing of the stools as soon as possible and no longer than within 150 minutes from the time of defecation to freezing. The Working Party stated that there is no reason to challenge this practice. Either aerobic or anaerobic process is acceptable, and in line with standard practice, cryoprotectant needs to be added. Additionally, the Working Party reported that many centres in the UK and in mainland Europe have successfully used older products and they concluded that the storage time of the frozen FMT products can be extended from six to 12 months and that the temperature of the freezer can be reduced to -70°C to minimise the environmental impact. It is currently not known whether the products could be stored at -20°C for up to 12 months. The Working Party expressed concerns that storage at this temperature could result in the loss of bacterial count and therefore recommended that this practice should be avoided until there is more evidence to support it. The decision whether and how stools should be encapsulated or lyophilised can be left to individual laboratories and will depend on the availability of the equipment.*

*The Working Party agreed to provide the advice in line of the recommendations from the previous edition of the guidelines,[3] which suggested, based on data from two systematic reviews, that 50g of stool should be used for FMT. Previous edition of the guidelines also recommended that stools should be mixed with 1:5 proportion to a dilutant. However, the Working Party also agreed that these should be considered as arbitrary figures, not currently supported by the evidence. Thus, FMT processing facilities may choose to adjust this volume and proportion depending on a clinical need and the availability of the donor stools. While the bottom limit for the volume of the stool to be used has not yet been established, it has been acknowledged that some FMT centres use 30g of stools diluted to 1:6 ratio and this is still clinically effective.*

**Recommendations**

**4.1:** Frozen FMT must be offered in preference to freshly processed products.

**4.2:** Start processing stools within 150 minutes of defecation.

**4.3:** Process stools aerobically or anaerobically – both methods are acceptable.

**4.4:** Store prepared FMT products frozen at -70°C for up to 12 months.

**4.5:** Add cryoprotectant such as glycerol for frozen FMT products.

**4.6:** If capsules are used, these can be obtained from frozen or lyophilised faecal slurry.

**Good practice points**

**GPP 4.1:** Follow a standard protocol for stool collection.

**GPP 4.2:** When possible, use at least 50g of stool in each FMT preparation.

**GPP 4.3:** Use sterile 0.9% saline as a diluent for FMT production.

**GPP 4.4:** Mix a minimum of 1:5 stool with diluent to make the initial faecal emulsion.

**GPP 4.5:** Consider homogenisation and filtration of FMT in a closed disposable system.

**GPP 4.6:** Consider thawing frozen FMT at ambient temperature and using it within six hours of thawing.

**GPP 4.7:** Avoid thawing FMT in warm water baths, due to the risks of cross contamination with *Pseudomonas* (and other contaminants) and reduced bacterial viability.

**GPP 4.8:** Where glycerol is used as a cryopreservative, ensure it is at 10-15% final concentration of the prepared faecal material/slurry, with vortexing or other methods used to fully mix the cryopreservative into the material.

## 4.5 Route of delivery and other administration factors influencing the outcome of FMT for patients with CDI

FMT can be delivered via upper and lower GI tract allowing it to reach different parts of the digestive tract. Different delivery routes may have different rates of success but are also associated with different risk and adverse events and may therefore not be suitable for all patients. There are also other factors to consider during FMT administration. It is still not clear whether taking certain medications or undergoing bowel preparation shortly before FMT could influence its outcome. Previous BSG/HIS guidelines[3] acknowledged that lower and upper GI administration have similar success rates and adverse events and that both could be used if clinically appropriate. However, due to the evidence suggesting lower efficacy associated with enema administration, this route of delivery was only recommended when neither upper GI endoscopy, nor colonoscopy, would be considered appropriate. Additionally, at the time of publication, there was a paucity of evidence regarding encapsulated FMT, thus no recommendations were made regarding its use. Regarding other factors, the evidence was low, but the guidelines suggested the use of bowel lavage and a single dose of antimotility agent if FMT was to be delivered via lower GI route and the use of PPI and prokinetics when FMT was via upper GI tract.

### Route of delivery

#### *Colonoscopy vs other methods*

*Effect on success rates:* There was moderate evidence which suggested a benefit of colonoscopic route compared to other administration routes. Evidence was from four retrospective cohort,[24,37,103,104] four case control,[18,20,25,38] and one cross-sectional study.[94] The studies assessed the effectiveness of colonoscopy compared to other FMT delivery methods including delivery via upper GI,[18,20,24,103,104] oral capsules,[20,37,94,103,104] bidirectional delivery (i.e. simultaneously via upper GI and colonoscopy)[103] and unspecified delivery methods different than colonoscopy.[20,25] When comparing to upper GI delivery, four studies[18,20,24,103] reported no difference in the number of patients who were successfully treated. One study[104] reported that colonoscopy appeared to be better than the delivery via nasojejunal (NJ) tube (100% vs 80%), both, when comparing patients who underwent one and when comparing more

than one FMT. The significance was not tested because it only included two patients who underwent colonoscopy and five patients who had FMT delivered via NJ. When compared to oral capsules, four studies[37,20,94,103] reported no difference in the number of patients who were successfully treated. One study[104] reported that colonoscopy appeared to be better than oral capsules (100% vs 80%) when comparing patients who underwent one FMT, but all patients in both groups were cured when more than one FMT was given. As above, the significance was not tested because it only included two patients who underwent colonoscopy and five patients who were given capsules. There was no difference when colonoscopy was compared to bidirectional delivery.[103] Lastly, two studies reported that when comparing the groups who achieved a cure with one or more FMT compared to those in whom FMT failed, there was a higher proportion of patients who received their FMT via colonoscopy (122/140, 87% vs 17/25, 68%; $p = 0.003$[25] and 161/168, 96% vs 59/67, 88%; $p = 0.033$[38]).

*Effect on adverse events:* There was weak evidence which suggested colonoscopic delivery has no effect on adverse events. Evidence was from three retrospective cohort studies.[24,37,104] One study reported no adverse events in colonoscopy patients,[24] one reported that one patient had *E. coli* bacteraemia,[104] and one reported that one patient was admitted to ICU with chest pain (but no organic pathology was identified), while one patient had aspiration pneumonia.[37]

### *Enema vs other methods*

*Effect on success rates:* There was inconsistent evidence but it suggested that enema may be less effective than other methods. Evidence was from one RCT,[105] one retrospective cohort[106] and one case control study.[25] One study[105] reported no difference in the effectiveness of FMT between enema and capsules (30/34, 88% vs 26/31, 84%; $p = 0.76$). Another study[25] reported that a proportion of patients who received enema was similar in the groups which had a successful FMT vs those in whom FMT failed (1/140, 1% vs 0/25, 0%; $p = 1.00$). The last study[106] reported that patients who received one dose of FMT via oral capsules had a significantly higher likelihood of achieving symptom resolution and no recurrence within eight weeks comparing to patients who received one FMT via enema (aOR: 3.79 [95% CI 1.82 - 8.26] for capsule success). The capsules remained significantly more effective when comparing the number of patients who had no recurrence at 12-month follow-up (75% vs 41%, $p < 0.0001$).

*Effect on adverse events:* There was very weak evidence which suggested that delivery via enema had no effect on adverse events when compared to other administration routes. Evidence was from one retrospective cohort study[106] and one case series,[41] which reported adverse events following FMT via enema. One study[106] reported that there was no significant difference in the incidence of different adverse events immediately after or three months after FMT when comparing enema to oral capsules. Adverse events which occurred in both groups included diarrhoea, nausea, vomiting, abdominal cramps or pain, flatulence, faecal urgency, constipation and other (not specified) events. There was also no difference in the number of patients who experienced serious adverse events. In the oral capsule group, these included hospitalisation due to severe CDI (two days after FMT), hospitalisation for pneumonia (14 days after FMT), death due to cerebral vascular accident (14 days after FMT) and death due to COPD and cardiac failure (five months after FMT); in control group, adverse events included hospitalisation for IBD flare-up (seven days after FMT), two hospitalisations for CDI recurrence (seven and 14 days after FMT), hospitalisation for diverticulitis (five months after FMT), death due to head trauma after a fall (three months after FMT). The study reported that none of these severe events were related to FMT. Additionally, a case series[41] reported that of a total of 47 given

enema, one immunocompetent patient developed VRE-BSI within 60 days post-FMT, although it wasn't established that this was specifically due to the route of administration.

### *Lower GI (unspecified) vs other methods*

*Effect on success rates:* There was very weak evidence which suggested no difference in effect when comparing lower GI administration to other methods. Evidence was from one prospective cohort[107] and two case control studies.[22,26] Two studies[22,26] reported no difference in outcomes for Lower GI and other delivery methods. One study[107] reported that lower GI delivery method (which include colonoscopy, sigmoidoscopy or enema) was more effective in achieving cure at eight weeks than the upper GI delivery (OR for upper GI success 0.57 [0.48-0.68], $p < 0.01$) and oral capsules (OR for capsules success 0.59 [0.43-0.81], $p < 0.01$).

*Effect on adverse events:* There was very weak evidence which suggested that delivery via lower GI route had no effect on adverse events when compared to other administration routes. Evidence was from one prospective cohort study,[107] which reported no adverse events in either group of patients who had FMT delivered via lower GI, upper GI or via oral capsules.

### *Upper GI vs other methods*

*Effect on success rates:* There was weak evidence which suggested no difference in effect when comparing upper GI administration to other methods. Evidence was from one prospective cohort,[107] three retrospective cohort[24,103,104] and five case control studies.[18,20,22,25,26] Five of these studies[20,22,24-26] reported no difference in outcomes for upper GI and other delivery methods. Of the remaining four, one study[107] reported that upper GI delivery method was less effective in achieving cure at eight weeks than lower GI delivery method (which include colonoscopy, sigmoidoscopy or enema, OR 0.57 [0.48-0.68], $p < 0.01$). Another study[103] showed that upper GI success was similar when compared to oral capsules and lower GI delivery but significantly lower when bidirectional delivery was used (59/78, 76% vs 47/56, 84% respectively; $p = 0.0489$ for follow-up at 30 days and 57/78, 73% vs 47/56, 84% respectively; $p = 0.0413$ for follow-up at 90 days). Another study[104] reported that the success rate appeared to be lower in upper GI group (80%) than in colonoscopy group (100%) but this was only based on five and two patients in each group respectively. Lastly, one study[18] reported that there was a higher proportion of patients who underwent upper GI delivery (6/25, 24%) in the group who failed FMT compared to the group in whom FMT was successful (4/140, 2.9%; $p < 0.001$). There was also one UBA study[108] which described switching FMT delivery in their centre from nasogastric (NG) to nasoduodenal (ND). The study reported that there was no significant difference between the groups ($p = 0.313$), although they also reported that ND delivery resulted in all 16 patients responding to therapy after just one FMT.

*Effect on adverse events:* There was weak evidence which suggested that upper GI had no effect on adverse events when compared to other administration routes. Evidence was from one prospective cohort study[107] and three retrospective cohort studies.[24,103,104] Two studies[24,107] reported that no adverse events occurred following upper GI delivery as well as after lower GI delivery. One study[103] reported a slightly higher incidence of adverse events in upper GI group (4/32, 13%) compared to colonoscopy (0/32, 0%), oral capsules (2/32, 6%) or bidirectional delivery (1/32, 3%). Adverse events in all groups included constipation and diarrhoea. There were also two patients who experienced severe adverse events which included aspiration and bleeding from small intestine, and it was reported that both patients were given FMT via upper GI. The last study[104] reported that none of the

patients experienced any adverse events in upper GI delivery group but that one patient who received FMT via colonoscopy developed *E. coli* bacteraemia.

### *Oral capsules vs other methods*

*Effect on success rates:* There was weak evidence which suggested no difference in effect when comparing oral capsules to other delivery methods. Evidence was from one RCT,[105] one prospective cohort,[107] four retrospective cohort,[37,103,104,106] two case control,[20,25] and one cross-sectional study.[94] Five of these studies reported no difference in outcomes for capsules and other delivery methods which included retention enema,[105] colonoscopy,[37,94] and a combination of other methods.[20,25] One study[106] reported that patients who received oral capsules were more likely to achieve cure and no relapse at eight week follow-up when compared to retention enema (OR: 3.79 [95% CI 1.82 - 8.26]) and that this difference still remained at 12-month follow-up ($p < 0.0001$). The remaining three studies showed that oral capsules were less successful than other delivery methods. One study[107] reported lower likelihood of success for patients who received oral capsules when compared to patients who received FMT via lower GI (OR 0.59 [95% CI 0.43-0.81], $p < 0.01$). Another study[103] reported no difference between oral capsules and upper GI and colonoscopy delivery but bidirectional delivery was more successful 90 days after FMT (32/32, 100% for bidirectional vs 26/37, 70% for oral capsules; $p = 0.0356$ – there was no effect at 30-day follow-up). The last study[104] reported that FMT appeared to be less successful (80%) than colonoscopy (100%) when only one dose of FMT was given but when comparing multiple deliveries, patients in both groups achieved 100% cure. However, the study only used five patients in oral capsule and two patients in colonoscopy groups.

*Effect on adverse events:* There was weak evidence which suggested that oral capsules had no effect on adverse events when compared to other administration routes. Evidence was from one prospective cohort,[107] one retrospective cohort study,[37,103,104] and two case series.[42,53] Two studies[104,107] reported no adverse events in the group receiving oral capsules. One study[37] reported no severe adverse events in the capsule group, while two patients in the colonoscopy cohort experienced severe events which included hospitalisation due to a chest pain and aspiration pneumonia. The authors also reported that there were some minor events including diarrhoea, constipation, bloating, flatus and fever which were reported to occur at the same frequency in both groups. One study[103] reported that diarrhoea or constipation occurred in two patients (6%) in their oral capsule group while none of these occurred in the colonoscopy group, four occurred in an upper GI group (13%) and one occurred in the group which received bidirectional endoscopic FMT (3%). The authors reported that no severe events occurred in the group which was given oral capsules. One case series[53] reported that seven out 18 (39%) patient receiving FMT experienced severe adverse events within eight weeks following FMT. Six of these events were unrelated to FMT but one included a worsening of ulcerative colitis which was determined to be possible due to FMT. The study also reported two deaths which occurred within six months but neither was related to FMT. Another case series[42] reported only one adverse event in one immunocompetent patient (1/15, 6.7%) who had fever of 38°C and fatigue for 48 hours after FMT, both of which resolved without treatment.

### *Bidirectional vs other methods*

*Effect on success rates:* There was very weak evidence which suggested a potential benefit when comparing bidirectional method of FMT administration to other routes. Evidence was from one retrospective cohort study.[103] which reported that, when combining all other delivery methods together, bidirectional delivery was more effective in preventing recurrence 30 days after FMT (RR for

recurrence 0.784 [95% CI 0.724–0.848], $p$ = 0.004), as well as 90 days after FMT (RR for recurrence 0.760 [95% CI 0.699–0.827], $p$ = 0.002).

*Effect on adverse events:* There was very weak evidence which suggested that bi-directional method had no effect on adverse events when compared to other administration routes. Evidence was from one retrospective cohort study,[103] which reported that there was only one patient (3%) who experienced diarrhoea or constipation in bidirectional group while no patients in colonoscopy, two patients in oral capsule (6%) and four patients (13%) in upper GI delivery groups experienced these adverse events. It was also reported that no patients in bidirectional FMT delivery group experienced severe adverse events.

## Other factors

### *Location of delivery*

*Effect on success rates:* There was very weak evidence which suggested this did not influence the effectiveness of FMT. Evidence was from a case control study,[38] which reported that there was no significant difference when comparing different types of most distal sites where FMT was delivered, which included upper GI, terminal ileum, right colon, transverse colon and left colon ($p$ = 0.524). However the authors reported that when comparing the group who had a successful FMT to the group in whom FMT failed, there was a higher proportion of patients who had their FMT delivered to ileum in the successful FMT group (42.3% vs 37.3; OR for ileum success 4.830 (1.359–17.167), $p$ = 0.015).

*Effect on adverse events:* There were no studies.

### *Volume of FMT infused*

*Effect on success rates:* There was very weak evidence which suggested this did not influence the effectiveness of FMT. Evidence was from two case control studies.[25,38] One study[25] reported that the mean volume infused was 337.1ml (SD  137.1ml in the group of patients who had a successful FMT compared to 313.5ml (SD  139.8ml) in the group in which FMT failed ($p$ = 0.12). Another study[38] reported a median of 250ml (IQR 250–300ml) in successful FMT group and a median of 250ml (IQR 250–450) in failed FMT group ($p$ = 0.254).

*Effect on adverse events:* There were no studies.

### *PPI use*

*Effect on success rates:* There was very weak evidence which suggested this did not influence the effectiveness of FMT. Evidence was from one case control study,[20] which reported that that the proportion of patients who were given PPI before FMT was not significantly different when comparing groups who had successful and failed FMT (OR not reported but insignificant, $p$ = 0.114).

*Effect on adverse events:* There were no studies.

### *Antimotility agents used*

*Effect on success rates:* There was very weak evidence which suggested this did not influence the effectiveness of FMT. Evidence was from two case control studies.[20,38] One study[20] reported that that the proportion of patients who were given antimotility agents before FMT was not significantly different when comparing groups who had successful and failed FMT (OR not reported but insignificant, $p$ = 0.925). Another study[38] reported that there was no difference in the proportion of patients who were given loperamide when comparing groups with successful and failed FMT

(126/168, 75% vs 47/67, 70% respectively; multivariate OR for success with loperamide: 1.263 (0.217–7.367), $p$ = 0.795).

*Effect on adverse events:* There were no studies.

*Bowel lavage/prep used*

*Effect on success rates:* There was very weak evidence which suggested that this increases the effectiveness of FMT. Evidence was from three case control studies.[20,21,38] One study[20] reported no effect when bowel lavage was given, although this also included patients who received FMT via routes other than lower GI. Two studies[21,38] reported a positive outcome for patients who were given bowel lavage or preparation and in whom, the quality if this preparation was considered good. One of these studies[38] reported that the quality of patients' quality of bowel preparation was stratified into poor, adequate, fair and good and reported that when they stratified these patients into successful and failed FMT, the successful group had a higher proportion of patients with good bowel preparation (66% vs 42%) and lower proportion of patients who had poor (4% vs 6%) and fair (6% vs 16%). In multivariate analysis, poor or adequate bowel prep was associated with a decreased likelihood of success when compared to fair and good bowel prep (OR for success when poor or inadequate: 0.409 [95% CI 0.208–0.803], $p$ = 0.009). Another study[21] reported that patients who were given bowel prep which was not rated as poor were significantly more likely to achieve a cure (multivariate analysis OR 3.84 [95% CI 1.59-9.28], $p$-value not reported).

*Effect on adverse events:* There were no studies.

*The Working Party discussed the above evidence and concluded that most routes of administration are effective and where differences in effectiveness exist, they are subtle and not significant clinically. Thus, any of these methods can be considered for FMT delivery. Based on the current evidence presented here and in section 4.1, there is some concern that enema may be the least effective route and, as such, it is preferred that whenever possible this should be avoided. Enema could still be considered as a method of delivery when other options are not feasible. The Working Party observed that there was no additional review regarding flexible sigmoidoscopy specifically; it was felt that given the nature of this procedure, the efficacy of FMT via this route (and therefore recommendations pertaining to it) would broadly be similar to colonoscopy, whilst recognising that colonoscopy allows more proximal access to the colon and therefore a higher chance of material retention (and therefore potentially success). For all routes of delivery, FMT appears to be equally safe, although there may be some general risks associated with some delivery methods (e.g. endoscopy). Therefore, the Working Party recommends that other factors, such as cost, patient preference, patient safety and environmental concerns should be taken into account when choosing the route of FMT delivery. As an example, when available, oral capsules could be offered to avoid unnecessary endoscopy to reduce potential unnecessary harm, cost, and environmental impact.[109] However, the Working Party also noted that the methods of encapsulation and the administration of encapsulated FMT to patients differ considerably between the centres and more research is currently needed to determine the most optimal regimen for this route of FMT delivery.*

*There is currently very little evidence that the site of delivery (within the GI tract) is important for FMT effectiveness, and the Working Party agreed that the only important factor to consider is that FMT must be delivered to a part of the colon where it can be retained. The members agreed that bowel lavage/preparation, which is currently recommended for lower and upper GI delivery, should continue*

*in the light of the evidence suggesting a potential benefit. While the quality of the evidence is low, the Working Party concluded that there is no benefit associated with the administration of PPI or other anti-secretory medications nor antimotility medication. Therefore PPI and other anti-secretary medications are not necessary, and the Working Party advises against the use of antimotility agents in line with general consensus that these may promote* C. difficile *toxin retention. Additionally, there seems to be no effect associated with the volume of FMT used, although the Working Party acknowledged that it is not the volume of the infusion but the amount and concentration of the stool microbiota which is a determining factor and that the volume of faeces that needs to be infused will also depend on other factors such as water and undigested food content, and the overall mass of the stool. Future studies need to address the issue of a minimum effective dose that needs to be administered for a successful FMT.*

**Recommendations**

**5.1:** Choose any route of FMT delivery but, if possible, avoid enema.

**5.2:** When choosing the route of delivery, consider patient preference and acceptability, cost, and the impact on environment.

**5.3:** Consider enema for patients in whom other FMT delivery methods are not feasible.

**5.4:** There is no need to administer proton pump inhibitors or other antisecretory agents as a preparation for FMT.

**5.5:** Do not use antimotility agents as a preparation for FMT.

**5.6:** Use bowel preparation/lavage as a preparation for FMT.

**5.7:** After upper gastrointestinal tract administration is used, remove the tube following the flushing with water.

**5.8:** For patients at risk of regurgitation or those with swallowing disorders, avoid administration via upper gastrointestinal tract and deliver FMT via lower gastrointestinal tract instead.

**5.9:** If colonoscopic administration is used, ensure that the FMT is delivered to a site that will permit its retention.

**Good practice points**

**GPP 5.1:** Use polyethylene glycol preparation as a preferred solution for bowel lavage.

**GPP 5.2:** Consider using prokinetics (such as metoclopramide) prior to FMT via the upper gastrointestinal tract route

**GPP 5.3:** Follow best practice for prevention of further transmission of *C. difficile* when administering FMT to patients.

**GPP 5.4:** Consider a washout period of at least 24 hours between the last dose of antibiotic and treatment with FMT.

**GPP 5.5:** If upper gastrointestinal tract administration is used, nasogastric, nasoduodenal or nasojejunal tube, upper GI endoscopy or a permanent feeding tube may be used for delivery.

**GPP 5.6:** If upper gastrointestinal tract administration is used, administer no more than 100 mL of FMT to the gastrointestinal tract.

## 4.6 Post-FMT factors influencing the outcome of FMT for patients with CDI

The risk factors for failure after administration of FMT, especially associated with the use of antimicrobial therapy, started to emerge at the time the first BSG/HIS guidelines[3] were about to be published. The guidelines identified two studies which mentioned a potential link between the administration of non-CDI antibiotics in a short time after the FMT was given, and subsequently suggested that antimicrobial therapy should ideally not be administered within the first eight weeks, and that an infectious disease specialist or a medical microbiologist should be consulted before the therapy is given. Other potential factors (e.g. diet or the use of probiotics) have also been discussed but their influence on FMT outcome remains unclear.

### *Use of non-CDI antibiotics*

*Effect on success rates:* There was weak evidence which suggested a potential negative effect on the effectiveness of FMT. Evidence was from three case control studies.[18,21,22] One study[18] reported no difference in the number of patients who received non-CDI antibiotics when comparing patients who had a successful FMT vs those in whom FMT failed within 12 weeks. Two studies reported that non-CDI antibiotics were a risk factor for FMT failure. One of these studies[21] reported that, in multivariate analysis, non-CDI increased the likelihood of failure within five years of FMT (OR for failure: 7.39 [95% CI 3.02-18.07]; p < 0.001), while another study[22] mentioned that the use of non-CDI antibiotics increased the likelihood of failure within the first two months (OR for failure 3.6 [95% CI 1.0-12.6], *p* = 0.03).

*Effect on adverse events:* There were no studies.

### *Other post-FMT factors*

*Effect on success rates:* There was very weak evidence which suggested these do not influence the effectiveness of FMT. Evidence was from three case control studies.[14,21,22] The studies assessed the effect of post-FMT infections,[22] use of anti-secretory therapy (unspecified),[21] hospitalisation[22] and the length of time from FMT to first defecation.[14] None of these factors were reported to affect the outcome of FMT. No other factors have been explored.

*Effect on adverse events:* There were no studies.

*The Working Party agreed that there is a concern, although evidence is weak, that post-FMT, non-CDI antibiotics are a potential risk factor for FMT failure. As such, the Working Party recommended that for patients who require antibiotics, either long-term or within eight weeks of FMT, decision needs a formal assessment and a discussion with infectious disease specialists or microbiologists. Currently, there is no reason to suspect that factors other than post-FMT antibiotics are risk factors for FMT failure.*

**Recommendations**

**6.1:** Wherever possible, avoid using non- *C. difficile* infection antimicrobials for at least eight weeks after FMT.

**6.2:** Consult infectious disease specialists or medical microbiologists for advice whenever FMT recipients have an indication for long term antibiotics or have an indication for non- *C. difficile* infection antibiotics within eight weeks of FMT.

## 4.7 Prophylactic FMT treatment to prevent *C. difficile* infection

Prophylaxis has become one area of interest in CDI more broadly and FMT is proposed as a potential therapy among other more traditional agents such as vancomycin, probiotics and bezlotoxumab.[110] Although no studies were identified, the recognition has grown that CDI pathogenesis relates to gut microbiome disruption,[111] therefore, there is a biological rationale that restoration of gut microbiome in vulnerable patients (e.g. patients with extensive exposure to antibiotics) via FMT could be a reasonable strategy to prevent CDI. Current debate also focuses on the definition of prophylaxis, specifically whether it should describe the prevention of recurrence or the prevention of new CDI in patients at risk. Previous BSG/HIS guidelines did not address this topic and thus, no recommendations were made.

No studies were found in the existing literature which assessed the effect of prophylactic treatment on any of the included outcomes.

### Additional data from excluded studies:

The working party are aware of one ongoing trial which aims to evaluate the effectiveness of FMT (oral capsules) for the prevention of CDI in patients with history of CDI currently taking antibiotics.[112]

*Due to the lack of existing evidence the Working Party agreed that no recommendation can be made in favour or against prophylactic FMT. Instead, the Working party suggests that studies addressing this issue should be undertaken in the future to establish its feasibility and cost effectiveness.*

**Recommendations**

**7.1:** No recommendation

**Good practice points**

**GPP 7.1:** none

## 4.8 FMT for non-CDI indications

In current clinical practice, FMT is only recommended for the treatment of recurrent CDI. Due to its success with CDI, FMT has been investigated for other diseases in which the gut microbiota has been implicated as a pathogenic agent. Previous BSG/HIS guidelines[3] reported that the majority of the studies investigating the effectiveness of FMT for non-CDI indications were of poor design and quality, and that only a small number of RCTs existed. The conditions which were reported in the previous guidelines included ulcerative colitis, irritable bowel syndrome, hepatic encephalopathy and metabolic syndrome, all of which showed a potential benefit. However the lack of evidence regarding the choice of suitable patients and the most appropriate methods for FMT preparation and administration, led the Working Party to a decision not to recommend FMT in the context other than

research. At the time the guidelines were published, it was also noted that there were ongoing trials for other conditions. Since then more diseases have now been linked with gut microbiome and a large number of systematic reviews and meta-analyses investigating the effectiveness of FMT for these conditions have become available.

## Ulcerative colitis

*Effect on inducing remission:* There was moderate evidence which suggested FMT is effective in inducing remission in patients with UC. Evidence was from one systematic review[113] and two RCTs[114,115] (same studies were also covered in eight duplicate reviews[116-123]). The meta-analysis, which included six RCTs[113] showed the overall likelihood of sustained remission of ulcerative colitis was significantly higher in patients who received FMT when compared to those who received placebo (OR = 4.11 [95% CI 2.19-7.72]). The non-inferiority RCT of FMT for the management of left-sided ulcerative colitis,[114] reported that the proportion of patients with sustained remission (clinical and endoscopic) after FMT was not significantly different when compared to those who were given a standard treatment of topical mesalamine (12/21 (57%) vs 8/22 (36%); *p*-value not reported). The last study[115] reported that there was no significant difference in the number of patients with ulcerative colitis who achieved remission after being treated with FMT in combination with mesalamine (22/26, 85%) when compared to those who received mesalamine only (19/27, 70%; p=0.215) at eight-week follow up. However, they reported that the Mayo score for ulcerative colitis activity was significantly lower in the group which received FMT when compared to a group who received mesalamine only (mean 1.34 (SD = 1.44) vs 2.14 (SD = 1.4); p=0.045).

*Effect on adverse events:* There was strong evidence which suggested that FMT does not have an effect on the adverse events in this group of patients. Evidence was from one systematic review[113] and two RCTs.[114,115] The meta-analysis of six RCTs[113] reported that the incidence of any adverse events within one week after an intervention was similar in FMT and placebo group (OR = 1.38 [95% CI 0.58-3.30], *p* = 0.46). No differences in the incidence were also reported for worsening colitis (OR = 0.89 [95% CI 0.26-3.05]), colectomy (OR = 1.39 [95% CI 0.22-8.99]), and CDI (OR = 4.27 [95% CI 0.45-40.64]). One RCT,[114] also reported a similar incidence in groups of patients who received FMT and those who received topical mesalamine (12/21 (57%) vs 13/22 (59%), *p*-value not reported). This study reported that more patients in the FMT group experienced severe adverse events (4/21 (19%) vs 1/22 (5%) – all were worsening colitis), although this was still insignificant (*p*-value not reported). Another RCT[115] reported a similar incidence of adverse events in a group who received FMT in combination with mesalamine (6/26, 23%) and the group of patients who received mesalamine alone (2/27, 7%); p=0.113). The study reported that in FMT group, adverse events included abdominal pain or bloating, diarrhoea, or constipation, while in the mesalamine group, the events included constipation and headaches; no serious events were reported in either group.

*Additional data from excluded studies:* One study, which was excluded because the intervention comprised of FMT in combination with anti-inflammatory diet,[124] reported that patients who received FMT and followed the diet were more likely to achieve remission at eight weeks when compared to patients who received standard care (OR = 6.0 [95% CI 1.2-30.2]; *p* = 0.003). Another study,[125] which assessed the effectiveness of FMT as a maintenance therapy for patients with ulcerative colitis in remission, reported that 12 months after the intervention, the incidence of remission was similar in a group of patients who received FMT from a healthy donor and those who received autologous FMT (13/24, 54% vs 10/24, 41%; *p* = 0.660).

## Crohn's Disease

*Effect on success rates:* There was weak evidence which suggested FMT is effective in inducing remission in patients with CD. Evidence was from one RCT,[126] which reported that seven (7/8, 88%) patients with Crohn's disease in FMT group and four (4/9, 44%) patients in sham FMT were flare-free at 10-weeks follow-up. The study reported that this was insignificant ($p$ = 0.13), although this could have been because the study was underpowered. Similar results were obtained at 20-week follow-up with higher proportion of FMT patients experiencing no flare (5/8 (63%) vs 3/9 (33%) respectively, $p$-value not reported).

*Effect on adverse events:* There were no studies.

**Pouchitis**

*Effect on success rates:* There was weak evidence which suggested that FMT has no effect on treatment of pouchitis. Evidence was from two RCTs.[127,128] One study[127] reported no remission cases in either FMT (n = 4) or placebo (n = 2) group in patients with antibiotic dependent pouchitis. Another study[128] reported no significant difference in the group which received FMT (4/13, 31%) compared to the group which received autologous FMT (5/13, 38%, $p$ = 0.183) in patients with chronic pouchitis.

*Effect on adverse events:* There was weak evidence which suggested that FMT does not have an effect on the adverse events in this group of patients. Evidence was from two RCTs,[127,128] One study,[127] which was conducted in patients with antibiotic dependent pouchitis, reported no adverse events in either group (n = 4 for FMT and n = 2 for placebo). Another study[128] of patients with chronic pouchitis, reported mild adverse events in three patients receiving FMT (fever, abdominal pain, faecal urgency and/or nausea) and one patient with mild adverse event (fever) in a group which received autologous FMT); there were no severe adverse events in either group.

**Irritable Bowel Syndrome**

*Effect on success rates:* There was inconsistent evidence, and it was not possible to determine the effectiveness of FMT on achieving IBS remission. Evidence was from one systematic review[129] and two RCTs[130,131] (same studies were also covered in 12 duplicate reviews[118,123,132-141]). A meta-analysis from seven RCTs[129] showed that the risk of not achieving cure (defined as symptom remission within 12 weeks) was similar in patients who received FMT and those who received placebo (RR = 0.75 [95% CI 0.43–1.31]) and that the incidence of sustained cure remission at one-year follow-up was also similar in both groups (RR = 0.90 [95% CI 0.72-1.12]). The meta-analysis showed high heterogeneity ($I^2$ = 87%) suggesting that the results varied between different studies. Sensitivity analyses showed that FMT delivered via oral capsules was significantly less effective when compared to other methods (RR for not achieving cure 1.88 [95% CI 1.06–3.35]), while positive effect was seen for FMT delivered via colonoscopy (RR for not achieving cure 0.70 [95% CI 0.51–0.96]), upper GI (RR = 0.37 [95% CI 0.14–0.99]) and when the fresh stool was given (RR = 0.59 [95% CI 0.41–0.85]). One RCT,[130] which compared FMT alone, FMT with pre-treatment with rifaximin, FMT with pre-treatment with ciprofloxacin and metronidazole to placebo reported that the mean change in the severity score system (IBS-SSS) at ten-week follow-up was not significant between any of these groups (−32.3 (±124.8), −85.3 (±94.6), −114 (±149.3), −93.4 (97.1) respectively, $p$ = 0.55), and that, if anything, FMT group alone achieved the lowest reduction of IBS-SSS. There was also no difference when comparing the number of patients with adequate relief ($p$ = 0.66) and the number of patients achieving overall improvement ($p$ = 0.95). Another RCT,[131] which compared the IBS-SSS scores for patients with post-infectious IBS who received FMT and patients who received standard care (consisting of prescription of Otilonium Bromide and probiotic and recommending low FODMAP diet) reported no significant difference at 12 weeks of follow-up (mean 179.80 (SD = 26.1) vs 189.17 (SD = 25.80); $p$ = 0.705).

*Effect on adverse events:* There was strong evidence which suggested that FMT does not have an effect on the adverse events in this group of patients. Evidence was from one systematic review[129] and two RCTs.[130,131] A meta-analysis from seven RCTs[129] showed that FMT was not associated with a higher incidence of adverse events when compared to placebo (RR = 1.20, [95% CI 0.59–2.47]) with adverse events including included transient and self-resolved abdominal pain, bloating, nausea, and diarrhoea. One RCT[130] reported a slightly higher incidence of adverse events in the FMT group (19/21, 90%) when compared to placebo (13/17, 76%), although this difference was not significant ($p$ = 0.27). There were also four severe events in FMT group and two in placebo group (not specified). Another RCT[131] reported that the incidence of adverse events in FMT was 27% (8/30) and the events included abdominal pain or bloating, diarrhoea, constipation and nausea; the study did not report whether or not any events occurred in the group receiving standard care.

*Effect on quality of life:* There was moderate evidence which suggested that IBS may improve quality of life for patients with IBS. Evidence was from one systematic review[129] and two RCTs.[130,131] A meta-analysis from seven RCTs[129] showed mean IBS-QoL score increased in FMT group (mean difference 9.39 [95% CI 3.86-14.91] when compared to the group which received placebo. One RCT[130] did not show a significant change in the groups receiving FMT alone, FMT with pre-treatment with rifaximin, FMT with pre-treatment with ciprofloxacin and metronidazole to placebo (mean change 15.4 (±20.8), 19.3 (±25.2), −1.2 (±7.6), 9.4 (±18.4) respectively, $p$ = 0.61). Another RCT[131] reported no significant difference in IBS-QoL scores in the group which received FMT when compared to a group which received standard care consisting of Otilonium Bromide, probiotic and the recommendation of low FODMAP diet (mean 128.79 (SD = 18.63) vs 129.46 (SD = 17.88), p=0.948).

*Additional data from excluded studies:* One duplicate systematic review,[137] suggested that while FMT may not show an overall advantage, the delivery via upper GI (via duodenoscopy or nasojejunal tube) may be more effective than the delivery via other methods and suggested further studies to explore this possible effect.

### Constipation

*Effect on success rates:* There was weak evidence which suggested a benefit. Evidence was from one systematic review.[142] A meta-analysis which included two RCTs demonstrated that patients who received FMT in combination with oral laxatives were more likely to achieve an improvement in symptoms (reported as defecation at least three times per week, improvement in stool characteristics and improvement in defecation difficulty) when compared to patients who used laxatives alone (RR = 1.35 [95% CI 1.14-1.6]). A meta-analysis which included three RCT which assessed the Bristol Stool Form Scale (BSFS) reported significant difference in scores for patients who received FMT with laxatives to laxatives alone (mean difference 1.04 [95% CI 0.57-1.51]), while the Wexner score (based on two RCTs) and the Knowles-Eccersley-Scott Symptom (KESS) scores (based on two RCTs) significantly decreased (mean difference -3.25 [95% CI -5.58 to -0.92] and -5.65 [95% CI -7.2 to -3.69] respectively).

*Effect on adverse events:* There were no studies.

*Effect on quality of life:* There was weak evidence which suggested FMT may improve the quality of life in patients with constipation. Evidence was from one systematic review.[142] A meta-analysis, which included three RCTs, demonstrated that the impact of constipation on patients' quality of life (PAC-QoL) score significantly decreased in patients who received FMT with oral laxatives (mean difference -18.56 [95% CI -26.43 to -10.68]) when compared to patients who received laxatives alone.

### Preventing hepatic encephalopathy in patients with decompensated cirrhosis

*Effect on success rates:* There was weak evidence which suggested a benefit. Evidence was from one systematic review[143] (same studies also covered in a duplicate review[144]). The review comprised of a narrative analysis of two RCTs which reported inconclusive results. One RCT reported that the number of patients with recurred HE was significantly lower in the group which received FMT (0%, number of patients not reported) when compared to those who received standard care (50%, $p = 0.03$). In this study, the mean change in Psychometric Hepatic Encephalopathy Score (PHES) was significantly reduced in FMT group ($p = 0.03$) while the Model for End-Stage Liver Disease (MELD) change was the same ($p = 0.78$). Another RCT also reported lower incidence in FMT group (1/10, 10% vs 3/10, 30% in standard care), although this difference was insignificant (*p*-value not reported). They also reported that Encephal App performance score improved significantly in FMT group only ($p = 0.02$ for mean change between groups).

*Effect on adverse events:* There was weak evidence which suggested a possible negative effect of FMT on adverse events in this patient group. Evidence was from one systematic review.[143] The review reported that there was one death (in case series), which was not associated with FMT and one serious adverse event (spontaneous bacterial peritonitis in case series). There were a range of other, not severe, adverse events reported by two RCTs and one case series, but it is not possible to establish whether these were associated with FMT administration.

## Metabolic syndrome

*Effect on success rates:* There was weak evidence which suggested that FMT had no effect on improving biomarkers of metabolic syndrome. Evidence was from two RCTs.[145,146] One RCT[145] reported a significant difference in HOMA2-IR and HOMA2-IS scores when comparing the group of patients who received FMT in combination with low-soluble fibre when compared to patients who received low-soluble fibre alone (mean difference (−24.0% (±12.0%), $p = 0.02$ and 27.6% (± 12.3%) $p = 0.02$ respectively). However, they reported no difference when comparing this group to the groups which received FMT and high-soluble fibre or high-soluble fibre alone (*p*-values not provided). Another RCT[146] reported no significant difference in mean Hb1Ac ($p = 0.48$), glucose ($p = 0.62$), insulin ($p = 0.78$), total cholesterol ($p = 0.94$), LDL cholesterol ($p = 0.85$) and HDL cholesterol ($p = 0.47$) levels when comparing patients who received FMT to those who received autologous FMT at two weeks follow-up. There were also no significant differences when before-after scores were compared for these groups.

*Effect on adverse events:* There were no studies.

*Additional data from excluded studies:* There were further four RCTs[147-150] which were excluded because they reported before-after data,[147,148] included patients with insulin resistance,[149] and because both groups had FMT (from obese donors after bariatric surgery or obese donors with metabolic syndrome).[150] These studies reported no improvements in most of the markers associated with metabolic syndrome. In one study,[147] there were significant improvements reported (all groups) for weight, cholesterol (total, LDL and HDL) and HbA1c, however these already started to improve at the time FMT was given as a result of patients following a Mediterranean-style diet for two weeks before FMT. The improvements continued for the next six weeks, but the patients also continued, and adhered to, the diet during this time. Another study[148] reported a significant decrease of HbA1c levels in patients with insulin resistance given FMT when compared to those who received placebo, but the difference observed (0.1%) would not have been important clinically.

## Obesity

*Effect on success rates:* There was moderate evidence which suggested no effect on reducing BMI in obese patients. Evidence was from one RCT,[151] which compared the change in BMI from baseline to a

period of 12 weeks follow-up in subjects with BMI 35kg/$m^2$ or higher. The data showed that the mean change in BMI in a group which received FMT capsules was 0.2 (SD = 1.2) while in the group who received placebo capsules, the mean change was 0.7 (SD = 1.3, *p* =0.51). Thus, both groups experienced an increase in BMI.

*Effect on adverse events:* There were no studies.

## Other conditions

Literature searches were conducted for other conditions for which it was known that FMT was investigated as a potential treatment options. No studies which fit the inclusion criteria were identified for the following conditions: autism spectrum disorder, multidrug resistance, immune checkpoint inhibitor colitis and graft vs host disease.

The searches identified other conditions which were not searched for systematically but for which RCTs now exist. These included one study which reported that FMT may halt a progression of new-onset type 1 diabetes mellitus,[152] one study which reported an increase in gut motility and some self-reported improvement in symptoms of Parkinson's disease,[153] one study which reported no effect on controlling peripheral psoriatic arthritis,[154] and one study which reported a reduced intestinal inflammation and an improvement in symptoms of progressive supranuclear palsy-Richardson's syndrome.[155]

## Data from excluded studies

### *Infection/colonisation of gastrointestinal tract with multidrug resistant organisms*

There was one RCT[156] which investigated the effect of FMT which was preceded by five days of oral colistin and neomycin. The study was excluded because patients in control group did not receive the antibiotics. The likelihood of decolonisation success was insignificant between the groups (OR 1.7 [95% CI 0.4 - 6.4]). A follow-up to this RCT[157] reported that the treatment with oral antibiotics (colistin and neomycin sulphate), patients who were carriers of extended-spectrum beta-lactamase or carbapenemase-producing *Enterobacteriaceae* experienced a temporary decreased the richness and diversity of gut microbiota but that after the administration of FMT, the proportion of *Enterobacteriaceae* decreased but was not statistically different than the proportion observed at baseline. During this period, no changes were observed in a group which received no treatment (i.e., no antibiotics and no FMT). A recent systematic review[158] of seven cohort studies and five case reports showed decolonisation rates ranged from 20% to 90% for different types of microorganisms, but the review reported that the spontaneous clearance was not considered in these studies.

### *Alcoholic hepatitis*

There was one RCT,[159] which was excluded because it included an administration of pre-treatment antibiotics (metronidazole, ciprofloxacin and amoxycillin) in a group which received FMT but not in a control group. Participants were patients with the diagnosis of severe alcoholic hepatitis presenting with acute-on-chronic liver failure. The study reported that, at 28 days and 90 days follow-up, patients in FMT group had higher rates of survival and that hepatic encephalopathy and ascites resolved in more patients in FMT group. The study also reported that there were no significant differences in the incidence of adverse events between the groups. Another RCT,[160] which included subjects with severe alcoholic hepatitis, reported that there was a lower rate of 90-day survival in patients who received prednisolone (34/60, 57%) when compared to those who received FMT (45/60, 75%; HR = 0.528 [95% CI 0.279-0.998], *p*=0.044). The study reported that FMT was safe for this group of patients and that the severity scores remained similar over time in both groups.

*The Working Party reviewed the above evidence and concluded that FMT cannot currently be recommended as a treatment of conditions other than CDI. The evidence indicates that patients with ulcerative colitis may benefit from FMT, however, at the moment, there is little information about the most effective protocols for the use of FMT in this condition and how its effectiveness and cost compare to other well-established treatment options. Most of the studies focused on the induction of remission in these patients but there is also a need for future studies to determine the role of FMT in maintaining remission. Some studies already identified that further FMT may be needed for achieving long-lasting effect.[114,121,161-163] The Working Party is in agreement with the recent consensus[164] of the experts who concluded that, at the moment, the studies are too small and methodologically heterogenous to determine the effectiveness of FMT for IBD, including ulcerative colitis, and that the risk of serious side effects, including exacerbation of IBD, cannot be ignored. As such, the Working Party agreed that FMT may be offered to patients with ulcerative colitis who are not suitable for the licenced treatment options or in whom these options have failed. There is also weak evidence which suggests that patients with other conditions, namely Crohn's disease, IBS and constipation may benefit from FMT, but more research is required before any clinical decisions are made. For other conditions, including metabolic syndrome, autism spectrum, pouchitis, preventing hepatic encephalopathy, obesity and the treatment of multi-drug resistant microorganisms, further research is required to establish whether or not FMT is safe and effective. In the meantime, the Working Party agreed that FMT may be considered when the conventional treatment fails, and when the patients meet the eligibility criteria for compassionate use of FMT (described in the next section).*

**Recommendations**

**8.1:** Do not offer FMT routinely to patients with indications other than *C. difficile* infection.

**8.2:** Consider FMT on case by case basis for patients with ulcerative colitis in whom licenced treatment options have failed or for those who are not suitable for currently available treatments.

**Good practice points**

**GPP 8.1:** none

## 4.9 Compassionate use of FMT

Since publication of the last iteration of the guidelines, the range of medical conditions with a potential pathogenic link to a perturbed gut microbiome has continued to expand. Many of these conditions have no or limited treatment options. In many cases, the Working Party recognised that these remained associations, often without clear supporting mechanistic links that might deconvolute whether gut microbiome perturbation was a cause of the condition, consequence, or an epiphenomenon. A body of research has also explored whether FMT, alongside a conventional drug treatment, might augment the efficacy of that therapy, help to recover efficacy where this has been lost, or mitigate side effects of that medication. One prominent example of this scenario is cancer immunotherapy with immune checkpoint inhibitors (ICI), where early phase trial evidence suggests healthy donor FMT prior to anti-PD1 treatment for melanoma may boost efficacy in a subset of patients.[165] Further clinical trials demonstrated that FMT derived from anti-PD1 responders may be

used to regain treatment response in certain melanoma patients who had become refractory to treatment.[166,167]

The Working Party discussed their clinical experience of considering potential suitability of FMT for patients with non-CDI medical conditions associated with perturbation of the gut microbiome. They felt that if all below three criteria were fulfilled, there were potential grounds for consideration of administration of FMT on a compassionate use basis.

- There was a reasonable case from published literature to support a contribution of the gut microbiome to pathogenesis of the condition, and at least some published data relating to safety and efficacy of FMT in either a pre-clinical or clinical setting for this condition.
- The patient had been unresponsive to/was not suitable for a range of conventional treatment options for their condition and had very limited treatment alternatives, which had already been utilised. The scenario in which this is envisaged is one in which the limited ability to provide further effective treatment of the condition may cause significant ongoing symptoms, significantly impair the patient's quality of life, and/or may risk progressive morbidity or even mortality for the patient.
- The patient understood the treatment options that were available, including the potential risks and benefits of FMT (especially the potential for no benefit and/or complications related to the FMT), but was still willing to provide informed consent for FMT.

However, the Working Party emphasised that a few additional criteria merited consideration. Firstly, such cases should be considered in a multidisciplinary team (MDT) setting (including senior clinical representation from the specialist team referring the patient, and clinicians with experience in FMT, likely with a background in gastroenterology or microbiology/infectious diseases). The role of this MDT is to better clarify any prior experience of FMT within this setting, and/or the balance of risks and benefits from FMT versus alternative treatment options. Secondly, there should be agreement as to what should be defined as success or failure of FMT in this particular scenario. There must also be a plan prior to treatment initiation, for a strategy regarding potential further FMT based upon the response to the initial therapy. Thirdly, there should be comprehensive documentation of clinical data (and/or potentially stool and other biofluids collected from the patient for research, where such a resource exists) related to the outcome of this patient from FMT, to build knowledge and experience of the potential role for FMT within novel settings.

**Recommendations**

**9.1:** Consider offering compassionate use of FMT in non- *C. difficile* infection settings after discussion and approval in a multidisciplinary team setting.

**9.2:** When offering compassionate use of FMT, the following conditions must be met:

- There is a biological rationale to justify consideration.
- Patient is at risk of significant clinical compromise due to a limited alternative range of therapeutic options.
- Patient understands the risks and benefits of FMT compared to other treatment options.

**9.3:** Prior to treatment, define what will be considered as a success or failure of FMT.

**9.4:** Prior to treatment, agree potential strategy for further FMTs based upon initial clinical success.

**Good practice points**

**GPP 9.1:** none

## 4.10 Self-banking of stool for potential future autologous FMT

The Working Party members reported that, in the past, they have been contacted by other clinicians and by patients enquiring about banking their own stool with a view to potential future autologous FMT. One such scenario might be a patient who has been informed about the imminent need for medical treatment which might be expected to significantly disrupt their gut microbiome, i.e., a prolonged course of antibiotics that might risk CDI, or a patient due to undergo intestinal surgery, immunosuppression, etc.). The Working Party discussed the published literature regarding this approach, including clinical evidence that stool collected from patients prior to their haematopoietic cell transplantation (HCT) could safely be given as FMT to them post-HCT, with associated restoration of pre-morbid microbiome diversity and composition.[168] A further enquiry that the Working Party had received related to whether a person in entirely good health could be considered for stool banking in case the scenario arose whereby autologous FMT might become an appropriate treatment option at some point in the future based upon changes of their health status. This conceptually might be considered to have a degree of comparability to cord blood banking, for which there is an HTA-regulated structure in the UK.[169]

The Working Party recognised some of the challenges related to this, which have already been discussed elsewhere.[170] Firstly, there are uncertainties related to how much stool might optimally be stored (with associated resource issues, such as freezer capacity), and for how long (raising concerns about the long-term stability of a gut microbiome community when potentially frozen for a prolonged period). Given that many conventional potential healthy stool donors fail screening due to the stringency of the process, there is a reasonable likelihood that a significant proportion of those considering self-stool banking would also fail conventional screening. While the fact that the patients would be receiving autologous FMT may reduce health risks compared to unrelated donor stool, there are clear issues related to laboratory processing and storage of material, particularly from a regulatory perspective, if this does not reach the same status on pathogen screening as healthy donor faecal material conventionally prepared into FMT. Other outstanding issues related to the regulatory framework which might govern this process, and/or potential funding arrangements and cost effectiveness of such an approach. As such, the Working Party concluded that while self-stool banking was of potential interest, it could not be currently advocated. However, this can be considered as a concept for further studies.

**Recommendations**

**10.1:** Do not routinely self-bank stool from faecal material donated by patients or healthy people for potential future autologous FMT.

**Good practice points**

**GPP 10.1:** none

## 4.11 Regulation and oversight of FMT

There is no agreed definition as to what constitutes FMT, nor its active pharmaceutical ingredient(s), not its mechanism of action. This leads to variability in how and what is classified as FMT, and how it should be regulated. Briefly, FMT is either a biological product (e.g. USA), human tissue product (e.g. Italy), medicinal product (e.g. UK), or medical procedure (e.g. Denmark).[171] In the UK, FMT is considered an unlicensed medicinal product that may be prepared, prescribed, and administered to patients on a named basis under section 10 of the Medicines Act, 1968[172] ("pharmacy exemption"), provided that defined conditions are met. These include that the medicinal product is prepared or dispensed in a hospital or health centre by, or under the supervision of, a pharmacist, and in accordance with a doctor's prescription. This process is overseen by regional Specialist Pharmacy Services (SPS) Quality Assurance (QA). If FMT is prepared as an unlicensed medicinal product and is to be shipped to another hospital or health centre for administration, this requires a license to supply unlicensed medicinal products ("specials").[173] Licensed facilities are regulated and audited by the Medicines and Healthcare Products Regulatory Agency (MHRA). If FMT is used as part of a clinical trial, it is considered an Investigational Medicinal Product (IMP) and must be manufactured in a Manufacturer's/ Importation Authorisation - MIA (IMP) - licensed facility adhering to Good Manufacturing Practice (GMP).[174] Each batch should be released by a qualified person (QP) against an approved, trial specific, Investigational Medicinal Product Dossier (IMPD) prior to participant administration. Licensed facilities are regulated and audited by the MHRA, and all trials must have received Clinical Trials Authorisation (CTA), amongst other approvals, prior to participant recruitment.

**Recommendations**

**11.1:** Centres that manufacture and dispense FMT must adhere to any regulations applicable to the area in which they are located.

**Good practice points**

**GPP 11.1:** none

# 5. Further research

As highlighted above, there are gaps in the evidence for almost every topic presented in these guidelines. While the list is not exhaustive, the Working Party made some recommendations for research which they thought represented current research priorities.

**RR 1:** Studies which investigate the effectiveness and cost effectiveness of FMT for a first episode of *C. difficile* infection.

**RR 2:** Studies which investigate potentially modifiable patient risk factors which, if corrected, can optimise the outcome of FMT, e.g. genetics, gut microbiota composition or functionality (e.g. via metabolomics), immunological status.

**RR 3:** Studies which investigate donor characteristics that determine the success or failure of FMT.

**RR 4:** Studies which investigate preparation and storage times beyond those currently recommended.

**RR 5:** Studies which investigate the highest temperature at which FMT preparations can be stored and for how long.

**RR 6:** Studies which investigate the optimal methods for capsule preparation.

**RR 7:** Studies which investigate the best regimen for administration of oral capsules (i.e. how many, over how many days etc.).

**RR 8:** Studies which investigate the clinical utility, feasibility and cost effectiveness of prophylactic FMT.

**RR 9:** RCTs which establish the effectiveness and cost-effectiveness of FMT for induction of remission as well as the maintenance of remission of ulcerative colitis compared to licenced treatment options.

**RR 10:** Studies which compare different types of FMT protocols for the management of ulcerative colitis.

**RR 11:** RCTs which investigate the effectiveness and cost-effectiveness of FMT for treatment of constipation using well-established, objective outcome measures.

**RR 12:** Larger RCTs which establish the effectiveness and cost-effectiveness of FMT for the management of patients with Crohn's disease.

**RR 13:** Studies which establish which subgroups of irritable bowel syndrome patients may benefit from FMT.

**RR 14:** RCTs which establish the effectiveness and cost-effectiveness of FMT for treatment, management or prevention of other conditions, including metabolic syndrome, autism spectrum, pouchitis, hepatic encephalopathy and colonisation with multi-drug resistant microorganisms.

**RR 15:** Studies which evaluate the effectiveness, feasibility and cost-effectiveness of utilising self-bank stools for potential future autologous FMT.

**RR 16:** Studies which investigate whether microbiological screening of donors for pathogens with low prevalence in healthy individuals is indeed/justified.

**RR17:** Avoid producing duplicate reviews, i.e. where the evidence has recently been reviewed in a peer-reviewed journal and there is no new evidence to change the conclusions.

# 6. Further considerations: next-generation FMT and novel microbiome therapeutics

The Working Party discussed several microbiome therapeutics, which have evolved from FMT, and are at various stages of development and clinical trials. There are several different approaches being used, including full spectrum microbiome products (which have the most direct comparability with conventional FMT), as well as products involving particular microbiome components (e.g., spore-

based therapies, or defined microbial consortia). At the time of writing, two microbiome therapeutics have been approved by the US FDA for prevention of CDI relapses, namely RBX2660/Rebyota (Ferring; a rectally-administered FMT-type product), and SER-109/Vowst (Seres/Nestle; a purified spore-based product); no such products have been licensed for the use in any non-CDI indication.

The Working Party discussed their expectation that several early and late phase clinical trials involving such products were ongoing globally, and there was a reasonable expectation of applications for licensing for use within the UK within the lifespan of this guideline. If such licensing was granted, there would be clear implications for use of 'conventional' FMT within the UK. For instance, licensing of a microbiome therapeutic for use in recurrent CDI would potentially negate the ability to supply FMT under a UK specials license, given that FMT is an unlicensed medicine. This may potentially also impact upon the ability to use FMT within a UK research setting, where there is currently highly-active clinical and translational research activity.

The Working Party concluded that there was a clear need for ongoing dialogue between entities developing novel microbiome therapeutics, academic and hospital centres providing FMT, and regulators to ensure no interruption at any point in provision of therapy to eligible CDI patients, and that clinical and translational FMT/microbiome therapeutics research in this field in the UK remains globally competitive.

The Working Party concluded that the following topics are now resolved and should not be included for an update in the future editions of the guidelines:

1. *Effectiveness of FMT for recurrent CDI vs anti-CDI antibiotics/placebo in general population*. This topic can be revisited if new therapies, more effective than current antibiotic treatment, become available. Topics in relation to patients with different conditions and factors related to CDI infections (e.g. severity, first occurrence) should still be investigated.
2. *Non-modifiable recipient factors e.g. age*. Current evidence suggests that these factors do not reduce the effectiveness of FMT to the point where recommendations would change. Future studies need to focus on identifying modifiable recipient and donor factors, optimising FMT administration and preventing CDI recurrence after FMT.

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## List of abbreviations

BSG – British Society of Gastroenterology

CBA – controlled before/after

CDI - *Clostridioides difficile* (*C. diff*) infection

CI – confidence interval

CMV - cytomegalovirus

CPD – continuing professional development

CVD – cardiovascular disease

FMT – faecal microbiota transplant(ation)

GRADE – Grading of Recommendations Assessment, Development and Evaluation

HIS – Healthcare Infection Society

HR – hazard ratio

ITS – interrupted time series

NICE – National Institute for Health and Care Excellence

nRCT – non-randomised controlled trial

OR – odds ratio

PCR – polymerase chain reaction

PICO – Population-Intervention-Comparison-Outcome

PFO – Population-Predictive Factor-Outcome

RCT – randomised controlled trial

RR – risk ratio

SSI – surgical site infection

UBA – uncontrolled before/after

UK – United Kingdom