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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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(https://his.org.uk/resources-guidelines/faecal-microbiota-transplant/)

"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"*

Keywords: microbiota; faecal microbiota transplantation; Clostridioides difficile; colonic microbiome; enteric bacterial infection; infective colitis; intestinal microbiology

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 *C. difficile* infection
1.1: Offer antibiotics alone in preference to FMT as an initial treatment for *C. difficile* infection (i.e. first episode). **1.2:** Consider FMT for a first recurrence of *C. difficile* infection or as an adjunct to antibiotics in 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 antibiotics for at least 10 days. **1.5:** Offer FMT to all patients, regardless of health status, except those with a known anaphylactic food allergy. **1.6:** Offer one or more FMT after initial clinically assessed FMT failure. *Good practice points* **GPP 1.1:** Consider FMT earlier than after second *C. difficile* infection recurrence for patients with severe, fulminant or complicated *C. difficile* infection who are not responding to antibiotic therapy. **GPP 1.2:** If FMT was given via endoscopy, ensure that immediate post-endoscopic 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* 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.

Recipient factors influencing the outcome of FMT for patients with *C. difficile* infection

2.1: Do not refuse or delay FMT therapy due to any recipient risk factors e.g. age over 75 years old, except for patients with known anaphylactic food allergy.

Donor factors influencing the outcome of FMT for patients with *C. difficile* infection

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 that may adversely influence 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: Discuss and agree on the frequency of rescreening depending on local circumstances, but do not allow the bookend periods to be longer than four months.

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

3.9: 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 *C. difficile* infection

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

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

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

4.4: Add cryoprotectant such as glycerol to frozen FMT products.

4.5: 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: Start processing stools within 150 minutes of defecation.

GPP 4.3: When possible, use at least 50g of stool in each FMT preparation.

GPP 4.5: Use sterile 0.9% saline as a diluent for FMT production.

GPP 4.5: Mix a minimum of 1:5 stool with diluent to make the initial faecal emulsion.

GPP 4.6: Consider homogenisation and filtration of FMT in a closed disposable system.

GPP 4.7: Consider thawing frozen FMT at ambient temperature and using it within six hours of thawing.

GPP 4.8: Avoid thawing FMT in warm water baths, due to the risks of cross contamination with *Pseudomonas species* (and other contaminants) and reduced bacterial viability.

GPP 4.9: 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 *C. difficile* infection

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 *C. difficile* infection

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

6.2: Consult infection specialists, or other appropriate healthcare professional (e.g. gastroenterologists with experience of FMT) 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- *C. difficile* infection 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 only when a patient cannot be entered into a clinical trial and 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.

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 following antibiotic treatment in recurrent *Clostridioides difficile* infection (CDI) in 2013 [2]. The first BSG/HIS-endorsed FMT guidelines were published in 2018 [2], and the 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 (with the focused version presented here, and full version available in Supplementary Materials file A) 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.

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

Box 5: Commonly accepted CDI definitions*

Recurrent CDI: infection symptoms resolved after treatment but recurred within eight weeks. It is currently difficult to establish a difference between a relapse of the disease or the occurrence of a new infection.

Refractory CDI: CDI which is not responding to antibiotic treatment. This type of CDI may or may not be considered fulminant CDI.

Severe CDI: when fever, leucocytosis, and rise in serum creatinine are present, which may also be supported by further diagnostic abnormalities, e.g. distension of the large intestine seen at imaging.

Fulminant CDI: also known as severe-complicated, occurs when one of the following CDI-related factors are present: hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation or a fulminant course of disease.

Please note that clinically, many of these definitions overlap and it is not always possible to clearly group patients into these categories. Additionally, over the disease course this may change, e.g. refractory CDI may become fulminant. *Taken from ESCMID guidelines https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00568-1/fulltext#secsectitle0070

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 effective and safe FMT for recurrent or refractory CDI (defined in Box 5) 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]. Methods were followed in accordance with the NICE manual for conducting evidence syntheses (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 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 checklists (links available in Appendix 3a). The results of quality appraisal are available in Appendix 3b.

Data were extracted by one reviewer and checked by other reviewers. 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).

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.

Consultation process

Feedback on draft guidelines was received from the participating organisations and through consultation with relevant stakeholders. The Working Party reviewed stakeholder comments, and collectively agreed revisions (Supplementary Materials file D).

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, Dr Bin Gao for reviewing the studies related to FMT given to patients with functional constipation, Dr Andrew Flatt for advice on donor screening, Prof Mark Gilchrist for advice on medical product regulation, and Professor Jessica Allegretti, Professor Christian Lodberg Hvas and Dr Simon Baunwall for providing additional data from the included studies. 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.

Contributions

DJM helped design literature strategy. BHM, BM (Merrick), MNQ and AB screened the literature. AB conducted searches, performed initial data extraction and evidence syntheses, which was checked by BHM, BM (Merrick) and MNQ. All authors except AB also provided advice. BHM, BM (Merrick), MNQ and AB wrote the first draft. BHM, BM (Merrick), MNQ, AB, CAG, DJM, RJP, NTE, JPS, NS, BM (Marsh), GK, SEM, ALH, CS, JJK, PH, THI, SDG and HRTW all attended Working Party meetings and contributed to rating of evidence and recommendations. BHM, BM (Merrick), MNQ, AB, CAG, DJM, RJP, NTE, JPS, NS, BM (Marsh), GK, SEM, ALH, CS, JJK, PH, THI, SDG and HRTW all read, reviewed, contributed to the writing of and approved the final documents.

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). 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 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 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.

Of note, FMT use in the context of CDI is predominantly described as being administered after a course of anti-CDI antibiotics. Depending upon the study reviewed, FMT may be either viewed as a direct part of the treatment of an episode of CDI (i.e. consolidation of therapy after anti-CDI antibiotics), or that the anti-CDI antibiotics are the central therapy and that the role of FMT is primarily prevention of further recurrence. Growing understanding about mechanisms of efficacy of FMT in CDI – including FMT's roles in both direct inhibition of the growth of *C. difficile,* as well as prevention of spore germination [11] mean that both interpretations merit consideration. Reflecting this view, FMT in CDI will interchangeably be referred to as a modality of treatment and intervention to prevention of recurrence within this guideline, with the assumption that FMT has been administered only after a preceding course of anti-CDI antibiotics unless otherwise stated.

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 preventing CDI recurrence in general population [2,12-16].

Adverse events following FMT vs standard care or placebo: There was strong evidence which suggested no negative effect of FMT [2,12-16].

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 [17].

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 [18-24].

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 [25-29].

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 [19,22].

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 [17,18,25].

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

First episode of CDI

Effectiveness of FMT: There was moderate evidence which suggested that FMT is effective in these patients [13,30].

Adverse events: There was moderate evidence which suggested no negative effect [13].

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 [31-35].

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 [18,22,23,25,27,36-41].

Effect on adverse events: There was weak evidence, but it suggested that FMT is safe in patients with IBD treated for CDI [28,31,33,34,36]. However, two studies also highlighted that some IBD patients may experience a flare following FMT [31,36].

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 [42,43].

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 [19,21-23,26,28,37-41,44].

Adverse events: There was weak evidence which suggested that FMT is safe in this patient group [42,43].

Cancer patients with CDI

Effectiveness of FMT: There was weak evidence which suggested that FMT is effective in this patient group [45,46].

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 [19,21,40].

Adverse events: There was weak evidence which suggested that FMT was safe in this patient group [45,46].

Post solid organ-transplant patients with CDI

Effectiveness of FMT: There was weak evidence which suggested that FMT is effective in this patient group [47].

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 [47].

Patients with liver disease and CDI

Effectiveness of FMT: There was weak evidence which suggested FMT is effective in this patient group [48].

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 [38,40,49].

Adverse events: There was weak evidence which suggested that FMT was safe in this patient group [48].

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 [19,23,38,40].

Adverse events: There were no studies.

Patients with diabetes mellitus 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 [19,39,40].

Adverse events: There were no studies.

Patients with cardiovascular disease 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 [39].

Adverse events: There were no studies.

Patients with recurrent urinary tract infections 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 [23].

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 [50].

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 [50].

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 [19,22,38,39].

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 [20,27,37,44,51,52].

Adverse events: There were no studies.

Additional data from excluded studies

Quality of life

One study [53], reported improved quality of life after the patients underwent FMT for CDI.

Mortality

Two studies [54,55] reported no difference in mortality rates, one [56] reported that the incidence of CDI-related mortality decreased when FMT programme was introduced, one [23] reported that early FMT reduced mortality in severe cases and one study [57] reported that patients who received FMT had a 77% decrease in odds for mortality.

Long-term effectiveness

Six studies [23,58-62] which reported that at long-term follow-up (up to one year), FMT was still effective.

Asymptomatic carriage after FMT

One study [63] reported that asymptomatic carriage of *C. difficile* after FMT is rare.

New or worsening symptoms following FMT

One study [23] reported that one year after follow-up nausea was present in 18% of the patients, abdominal pain in 21% and diarrhoea in 33%, but that no serious events related to FMT occurred. One study [59] reported that within a year after FMT, the prevalence of constipation increased, but that most of the cases did not need treatment. Other symptoms included urgency, cramping and an increased incidence of IBS. Two years after FMT, new conditions included weight gain, diabetes mellitus, dyslipidaemia, thyroid problems, GI problems, and serious infections. These conditions were not considered directly linked to FMT. Other studies reported the onset of the following new issues [36,54,60,62], but none of these conditions were assessed for causality. One study reported worsening pre-existing chronic IBD and rheumatoid arthritis [60]. One study [64] that there was a slightly higher incidence of myocardial infarction in FMT group compared to non-FMT at one year follow-up, but that the incidence of other conditions was similar. At ten-year follow-up, one study [65] reported that there were no new diagnoses of autoimmune diseases, GI disorders or malignancies and that there were no deaths which were attributed to FMT.

Resolution or improvement of conditions following FMT

Three studies reported resolution or improvement of existing conditions following FMT [54,60,62], including eradication of multi-drug resistant micro-organisms [54], improvement of undifferentiated colitis, Crohn's disease, ulcerative colitis, diabetes mellitus and Parkinson's disease [62] and improvement of IBS, IBD, and alopecia areata [60]. 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 antibiotics 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 severe or 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 [66], 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 [23] 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 CDI. The effectiveness for patients experiencing the first or second CDI has recently been established in one RCT [13]. However, due to the fact that FMT is more invasive, appears to be more expensive, grapples with challenges in donor recruitment, 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: Offer antibiotics alone in preference to FMT as an initial treatment for *C. difficile* infection (i.e. first episode). **1.2:** Consider FMT for a first recurrence of *C. difficile* infection or as an adjunct to antibiotics in 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 antibiotics for at least 10 days. **1.5:** Offer FMT to all patients, regardless of health status, except those with a known anaphylactic food allergy.

1.6: Offer one or more FMT after initial clinically assessed FMT failure.
Good practice points
GPP 1.1: Consider FMT earlier than after second *C. difficile* infection recurrence for patients with severe, fulminant or complicated *C. difficile* infection who are not responding to antibiotic therapy. **GPP 1.2:** If FMT was given via endoscopy, ensure that immediate post-endoscopic 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* 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 [67]. 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 [19-23,26-28,37-40,44,68,69].

Effect on adverse events: There was weak evidence which suggested that adverse events are similar across all age groups [68].

Sex

Effect on success rates: There was moderate evidence which suggested that this does not influence the effectiveness of FMT [19-21,23,26-28,37-40,44].

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 [19,39].

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 [19-21,23,28,38,44,69].

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 [19,38].

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 [19,22,39,40,69].

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 [21,23,41].

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 [20].

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 [19,20,22,23,26,28,37,38,40,41].

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 [40].

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 [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 [19,22].

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 [23,26,40].

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 [39].

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 [22,26,28,39].

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 [20,28,51]. However, one study [51] reported a higher risk of recurrence of CDI in patients with zinc deficiency as well as a beneficial effect for zinc-deficient patients who were given zinc supplements.

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 [27,38,41,69].

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 [70] 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, except for patients with known anaphylactic food allergy.
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 [71]. 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 [72]. 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 [73], 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 [74,75]. 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 [22,24,52].

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 [23,27].

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 [23].

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 [27].

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 [27].

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 [74,75], 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 [76]*, atypical enteropathogenic *E. coli [77]*, and Shiga toxin-producing *E. coli [78]*. 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 [79,80]. 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 [81]. 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 [23,36,54,58-62,64-66]. 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 Mpox (previously monkeypox) 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 [82]. 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 [81]. 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 [77]. 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 [83]. 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 [84].

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 [85]. 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 [86]. A further retrospective study [87] 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. Additionally, since the durability of engraftment of donor strains after a single FMT is variable but may be only several months in the case of a reasonable proportion of taxa [88], the real procarcinogenic risk could be even lower than previously suggested, should bacteria with these gene cassettes be those with limited colonisation duration. 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 [89]. 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 [90]. 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 [91]. 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 [92,93].

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 (Box 4) 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. However, the Working Party recognised that there is a need to define the longest period the donor can donate without testing to ensure that safety of the recipient is not compromised. The Working Party agreed that this period should be no longer than four months. Bookend testing 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 that may adversely influence 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: Discuss and agree on the frequency of rescreening depending on local circumstances, but do not allow the bookend periods to be longer than four months.

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

3.9: 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.

787

788

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 antibiotics 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, within the past three months.
- 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 for donors

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.

790

Box 3: Recommended stool screening for donors

- *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*****

* Glutamate Dehydrogenase (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.

791

Box 4: Post-baseline bookend screening stool microbiology

- *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 [94]. 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 [19,21,27,28,69].

Effect on adverse events: There was weak evidence which suggested that this does not influence the effectiveness of FMT [29].

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 [95].

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 [96-98].

Effect on adverse events: There was weak evidence which suggested FMT from lyophilised stools is safe [97].

Type of capsule

Effect on success rates: There was weak evidence which suggested that this does not influence the effectiveness of FMT [99].

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 [23,100].

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 [23,95,100].

Effect on adverse events: There were no studies.

Additional data from excluded studies

Anaerobic vs aerobic processing

Two studies [94,101] reported that processing the stool samples under anaerobic conditions helps to preserve microbial diversity [94] and viability [101]. On the other hand, one study [102] reported that oxygen-free atmosphere was not necessary as long as the air above collected samples was removed.

Effect of freezing

Two studies [94,103] reported that freezing resulted in the loss of microbial diversity of the processed stool samples. One study [103] reported that 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 [102].

Emulsion process

One study [104] showed that magnet plate emulsion (MPE) and Seward Stomacher Emulsion (SSE) were similar in terms of maintaining microbial load.

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. A threshold of 150 minutes is used with in a number of studies, reflecting a balance between enough time to pragmatically transfer stool from production by donor to an FMT laboratory, and yet a short enough time to mitigate alterations to microbiome composition and functionality [105]. 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 increased 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. Since the FMT needs time to be thawed, and there is a concern that the microbial cultures will start to deteriorate, the Working Party recommended that this is done in an ambient temperature and used within six hours of thawing. The Working Party also agreed that thawing in water baths should be avoided because this may lead to contamination of FMT with waterborne pathogens. 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 dilutent. 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:** Process stools aerobically or anaerobically – both methods are acceptable. **4.3:** Store prepared FMT products frozen at -70°C for up to 12 months. **4.4:** Add cryoprotectant such as glycerol to frozen FMT products. **4.5:** 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:** Start processing stools within 150 minutes of defecation.

GPP 4.3: When possible, use at least 50g of stool in each FMT preparation.

GPP 4.5: Use sterile 0.9% saline as a diluent for FMT production.

GPP 4.5: Mix a minimum of 1:5 stool with diluent to make the initial faecal emulsion.

GPP 4.6: Consider homogenisation and filtration of FMT in a closed disposable system.

GPP 4.7: Consider thawing frozen FMT at ambient temperature and using it within six hours of thawing.

GPP 4.8: Avoid thawing FMT in warm water baths, due to the risks of cross contamination with *Pseudomonas species* (and other contaminants) and reduced bacterial viability.

GPP 4.9: 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 that a colonoscopic route may be slightly more effective when compared to other administration routes combined [19,21,25,26,38,39,96,106,107].

Effect on adverse events: There was weak evidence which suggested colonoscopic delivery has no effect on adverse events [25,38,107].

Enema vs other methods

Effect on success rates: There was inconsistent evidence but it suggested that enema may be less effective than other methods [26,108,109].

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,[42,109].

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 when combined [23,27,110].

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 [110].

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 when combined [19,21,23,25-27,106,107,110].

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 [25,106,107,110].

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 when combined [21,26,38,96,106-110].

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 [38,43,44,106,107,110].

Bidirectional (upper and lower GI simultaneously) 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 when combined [106].

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 [106].

Other factors

Location of delivery

Effect on success rates: There was very weak evidence which suggested this did not influence the effectiveness of FMT [39].

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 [26,39].

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 [21].

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 [21,39].

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 [21,22,39].

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 considered 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 [112]. 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.

The Working Party also discussed the effect of anti-CDI antibiotics administered before FMT. Overall, the Working Party noted that this was not supported by evidence, but, intuitively, recognised that there is a need for a balance between sufficient anti-CDI antibiotics to minimise the burden of C. difficile *prior to administration of FMT and enough of a gap from the time antibiotics were given so that the risk of damaging the new microbiome is minimised. The opinion of the Working Party was that 24 hours met an appropriate balance.*

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 antibiotic 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 antibiotic 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 [19,22,23].

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 [15,22,23].

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 infection specialists or other appropriate specialist healthcare professionals. 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 antibiotics for at least eight weeks after FMT.

6.2: Consult infection specialists, or other appropriate healthcare professional (e.g. gastroenterologists with experience of FMT) 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 [113]. Although no studies were identified, the recognition has grown that CDI pathogenesis relates to gut microbiome disruption [114], 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 [115].

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 [116-126].

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 [116-118].

Additional data from excluded studies: One study [127] reported that patients who received FMT and also followed an anti-inflammatory diet were more likely to achieve remission at eight weeks when compared to patients who received standard care.

Crohn's Disease

Effect on success rates: There was weak evidence which suggested FMT is effective in maintaining remission in patients with CD [129].

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 [130-131].

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 [130,131].

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 [121,126,132-144].

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 [132-134].

Effect on quality of life: There was moderate evidence which suggested that IBS may improve quality of life for patients with IBS [132-134].

Additional data from excluded studies: One review [140] 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.

Constipation

Effect on success rates: There was weak evidence which suggested FMT is effective in improving symptoms in patients with functional constipation [145].

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[145].

Preventing hepatic encephalopathy in patients with decompensated cirrhosis

Effect on success rates: There was weak evidence which suggested FMT is effective in preventing hepatic encephalopathy [146,147].

Effect on adverse events: There was weak evidence which suggested a possible negative effect of FMT on adverse events in this patient group [146].

Metabolic syndrome

Effect on success rates: There was weak evidence which suggested that FMT had no effect on improving biomarkers of metabolic syndrome [148,149].

Effect on adverse events: There were no studies.

Additional data from excluded studies: Four RCTs [150-153] reported no improvements in most of the markers associated with metabolic syndrome.

Obesity

Effect on success rates: There was moderate evidence which suggested no effect on reducing BMI in obese patients [154].

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 [155], one study which reported an increase in gut motility and some self-reported improvement in symptoms of Parkinson's disease [156], one study which reported no effect on controlling peripheral psoriatic arthritis [157], and one study which reported a reduced intestinal inflammation and an improvement in symptoms of progressive supranuclear palsy-Richardson's syndrome [158].

Data from excluded studies

Infection/colonisation of gastrointestinal tract with multidrug resistant organisms

One RCT [159] reported no difference in decolonisation success when comparing patients who received FMT with antibiotics compared to patients who did not receive any treatment. A follow-up to this RCT [160] reported that the treatment with oral antibiotics temporary decreased the richness and diversity of gut microbiota but that after the administration of FMT, the proportion of *Enterobacteriaceae* decreased. One review [161] reported that decolonisation rates after FMT ranged from 20% to 90% for different types of microorganisms, but it reported that the spontaneous clearance was not considered in the studies.

Alcoholic hepatitis

One RCT [162] reported that, at 28 days and 90 days follow-up, patients who received FMT and antibiotics had higher rates of survival and that hepatic encephalopathy and ascites resolved in more patients in this group. Another RCT [163] 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%, $p = 0.044$).

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 [117,124,164-166]. The Working Party agrees with the recent consensus [167] 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

While clinical trials are a preferred option for accessing unlicenced medicinal products, this is not always possible. This may be because a patient may be too ill to enter a clinical trial, fails to meet some aspects of inclusion criteria, or that no trial is ongoing at the time the treatment is needed. For this reason, compassionate use programmes (also known as early access, or special access) were developed to provide access to unlicenced treatments [168]. These treatments may include products which are still in clinical development, or those that are already licenced in other countries. Example of compassionate use programmes include Expanded Access Program in the USA, Compassionate Use Program (for a group of patients with a specified condition) and Named Patient Program (NPP, for named patients) in the European Union (EU) and Early Access to Medicines (EAMS) in the UK [169]. The EAMS scheme is available for manufacturers to apply for the early access to their products, however, another scheme The Supply of Unlicenced Medicinal Products ("specials") allows the clinicians to request the unlicenced products in a manner similar to the EU's NNP [170]. This scheme allows a supply of the medicinal products to the individual patients with "*special needs which a licenced product cannot meet*" [170] and also includes the off-label use of these products. In the section below, the term Compassionate Use Program was used to refer to the "specials" scheme as well as other similar programmes in other countries.

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 [171]. 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 [172,173], and also shows promise as an approach to potentially mitigate ICI-induced colitis in patients refractory to conventional immunomodulatory therapy [174].

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, it must be determined that a patient cannot be entered into ongoing relevant clinical trials, and potentially receive FMT instead via this pathway. Secondly, 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. Thirdly, 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. Lastly, there should be comprehensive documentation/reporting 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 only when a patient cannot be entered into a clinical trial and 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 [175]. 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 [176].

The Working Party recognised some of the challenges related to this, which have already been discussed elsewhere [177]. 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) [178]. 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 [179] ("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") [170]. 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) [180]. 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.

Research recommendations

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 needed/justified.

RR17: Studies which investigate whether FMT has a role in reducing antibiotic use and thus reducing the development of resistance to existing antibiotics.

RR18: 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 [8]), and SER-109/Vowst (Seres/Nestle; a purified spore-based product [9]); 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 medicinal product. 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