Gut

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

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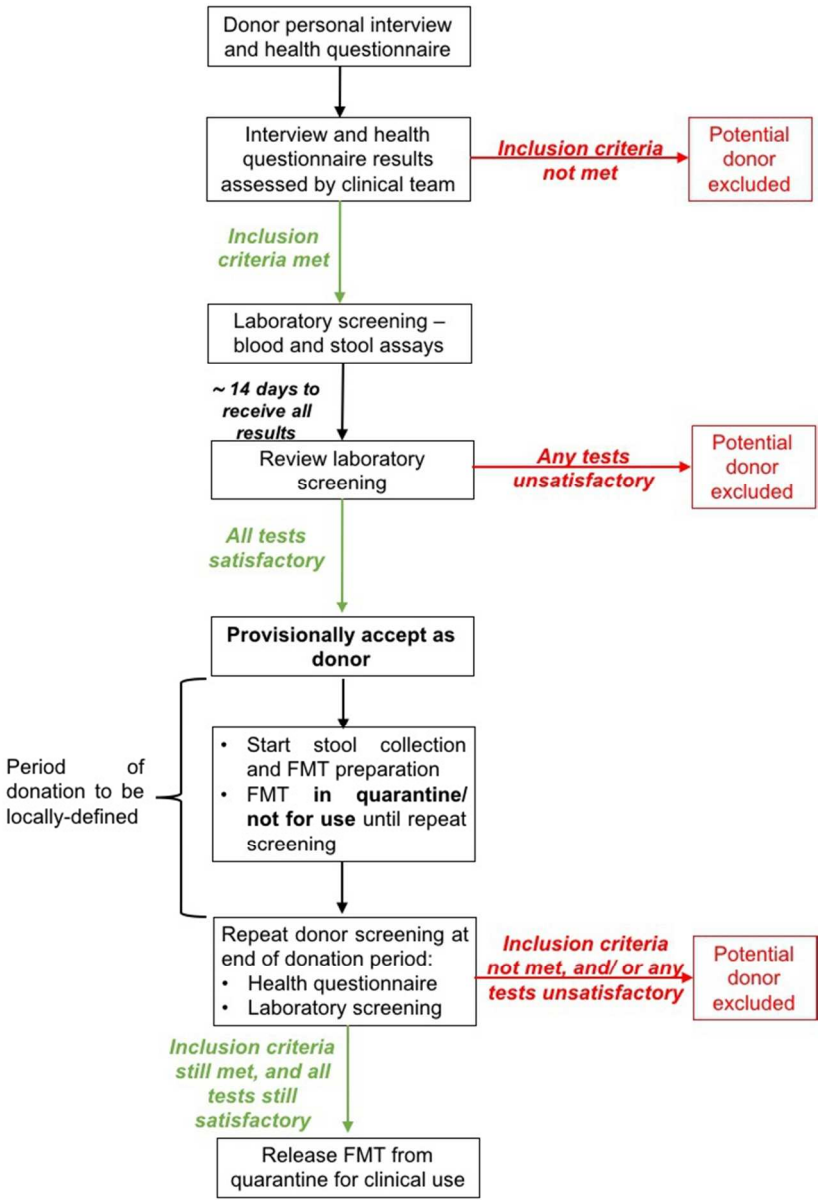

Figure 1: Proposed summary pathway for donor screening for centres preparing frozen FMT from recurring donors.

60x88mm (300 x 300 DPI)

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

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Abbreviations:

FMT	faecal microbiota transplant
CDI	*Clostridium difficile* infection
EBV	Epstein-Barr virus
CMV	cytomegalovirus
BMI	body mass index
GI	gastrointestinal
RCT	randomised controlled trial
NAAT	nucleic acid amplification test
GDH	glutamate dehydrogenase
EIA	enzymes immunoassay
PCR	polymerase chain reaction
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome

HIV	human immunodeficiency virus
AIDS	acquired immune deficiency syndrome
CPE	carbapenemase-producing *Enterobacteriaceae*
ESBL	extended-spectrum beta-lactamase
VRE	vancomycin-resistant *Enterococci*
MRSA	methicillin-resistant *Staphylococcus aureus*
PPI	proton pump inhibitor
UC	ulcerative colitis
HE	hepatic encephalopathy
MELD	Model for End-Stage Liver Disease

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1. Abstract:

Interest in the therapeutic potential of faecal microbiota transplant (FMT) has been increasing globally in recent years, particularly as a result of randomised studies in which it has been used as an intervention. The main focus of these studies has been the treatment of recurrent or refractory *Clostridium difficile* infection (CDI), but there is also an emerging evidence base regarding potential applications in non-CDI settings. The key clinical stakeholders for the provision and governance of FMT services in the United Kingdom (UK) have tended to be in two major specialty areas: gastroenterology and microbiology/infectious diseases. Whilst the National Institute for Health and Care Excellence (NICE) guidance (2014) for use of FMT for recurrent or refractory CDI has become accepted in the UK, clear evidence-based UK guidelines for FMT have been lacking. This resulted in discussions between the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS), and a joint BSG/HIS FMT working group was established. This guideline document is the culmination of that joint dialogue.

2. Executive summary:

2.1. Overview:

The remit of the British Society of Gastroenterology (BSG)/ Healthcare Infection Society (HIS) working group was to provide recommendations as to best practice in the provision of a faecal microbiota transplant (FMT) service. This guideline considers the use of FMT for the treatment of *Clostridium difficile* infection (CDI) – as well as for potential non-CDI indications – in adults. The working group have primarily targeted their report at clinicians involved in the use and provision of FMT services, but have also aimed it to be of interest to patients and their relatives.

2.2. Summary of recommendations:

2.2.1. Which patients with *Clostridium difficile* infection should be considered for faecal microbiota transplant, and how should they be followed up after treatment?

2.2.1.1. Prior to faecal microbiota transplant. Patient selection:

2.2.1.1.1. Recurrent *Clostridium difficile* infection:

We recommend that FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.1.1.2. Refractory *Clostridium difficile* infection:

We recommend that FMT should be considered in cases of refractory CDI *(GRADE of evidence: moderate; strength of recommendation: strong).*

2.2.1.1.3. FMT as initial therapy for *Clostridium difficile* infection:

We recommend that FMT should not be administered as initial treatment for CDI *(GRADE of evidence: low; strength of recommendation: strong)*.

2.2.1.1.4. Antimicrobial/ antitoxin therapy prior to considering FMT for patients with CDI:

i. We recommend that FMT for recurrent CDI should only be considered after recurrence of symptoms following resolution of an episode of CDI that was treated with appropriate antimicrobials for at least 10 days *(GRADE of evidence: low; strength of recommendation: strong).*

ii. We recommend consideration of treatment with extended/ pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI *(GRADE of evidence: low; strength of recommendation: strong).*

iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, we recommend that consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.1.2. Post-FMT follow-up, outcomes and adverse events:

2.2.1.2.1. Management of FMT failure:

We recommend that FMT should be offered after initial FMT failure *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.1.2.2. General approach to follow-up post-FMT:

We recommend that all FMT recipients should routinely receive follow-up. Clinicians should follow-up FMT recipients for long enough to fully establish efficacy/adverse events, and for at least eight weeks in total *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.1.2.3. Management of the FMT recipient:

i. We recommend that immediate management after endoscopic administration of FMT should be as per endoscopy unit protocol *(GRADE of evidence: very low: strength of recommendation: strong).*

ii. We recommend that patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare *(GRADE of evidence: very low; strength of recommendation: strong).*

iii. After enteral tube administration, we recommend that patients may have the tube removed and oral water given from 30 minutes post-administration *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.1.2.4. Definition of cure post-FMT for CDI:

We recommend that a decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.1.2.5. Definition of treatment failure post-FMT for CDI:

We recommend that treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for *C. difficile* toxin after FMT is not recommended, but it is appropriate to consider in the case of persistent CDI symptoms/suspected relapse *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.2. <u>What recipient factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?</u>

2.2.2.1. General approach to co-morbidities and FMT:

i. We recommend that FMT should be avoided in those with anaphylactic food allergy *(GRADE of evidence: very low; strength of recommendation: strong).*

ii. We suggest that FMT should be offered with caution to patients with CDI and decompensated chronic liver disease *(GRADE of evidence: very low; strength of recommendation: weak).*

2.2.2.2. Immunosuppression and FMT:

i. We recommend that FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects *(GRADE of evidence: moderate; strength of recommendation: strong).*

ii. We recommend that immunosuppressed FMT recipients at risk of severe infection if exposed to EBV or CMV should only receive FMT from donors negative for EBV and CMV *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.2.3. Other comorbidities and FMT:

i. We recommend that FMT should be offered to those with recurrent CDI and inflammatory bowel disease, but patients should be counselled about a small but recognised risk of exacerbation of IBD *(GRADE of evidence: moderate; strength of recommendation: strong).*

ii. We recommend that FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities *(GRADE of evidence: moderate; strength of recommendation: strong).*

2.2.3. What donor factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

2.2.3.1. General approach to donor selection:

We recommend that related or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.3.2. Age and BMI restrictions for potential donors:

We suggest that people should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of ≥18 and ≤30 kg/m^2 *(GRADE of evidence: low; strength of recommendation: weak).*

2.2.3.3. General approach to the donor screening assessment:

It is mandatory to screen potential donors by questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota (**Table 1**) *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.3.4. Laboratory screening of potential donors:

Blood and stool screening of donors is mandatory (**Tables 2 and 3**) *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.3.5. Repeat donor checks, and donation pathway:

i. In centres using frozen FMT, before FMT may be used clinically, we recommend that donors should have successfully completed a donor health questionnaire and laboratory screening assays both before and after the period of stool donation. This is the preferred means of donor screening *(GRADE of evidence: low; strength of recommendation: strong).*

ii. In centres using fresh FMT, we recommend that a repeat health questionnaire should be assessed at the time of each stool donation. To ensure ongoing suitability for inclusion as a donor, the donor health questionnaire and laboratory screening should be repeated regularly *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.4. <u>What factors related to the preparation of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?</u>

2.2.4.1. General principles of FMT preparation:

i. We recommend that stool collection should follow a standard protocol *(GRADE of evidence: low; strength of recommendation: strong).*

ii. We recommend that donor stool should be processed within 6 hours of defaecation *(GRADE of evidence: low; strength of recommendation: strong).*

iii. We recommend that both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI *(GRADE of evidence: moderate; strength of recommendation: strong).*

iv. We recommend that sterile 0.9% saline should be considered as an appropriate diluent for FMT production, and cryoprotectant such as glycerol should be added for frozen FMT *(GRADE of evidence: moderate: strength of recommendation: strong).*

v. We recommend using ≥50g of stool in each FMT preparation *(GRADE of evidence: moderate: strength of recommendation: strong).*

vi. We suggest that stool should be mixed 1:5 with diluent to make the initial faecal emulsion *(GRADE of evidence: low; strength of recommendation: weak).*

vii. We suggest that homogenisation and filtration of FMT should be undertaken in a closed disposable system *(GRADE of evidence: low; strength of recommendation: weak).*

2.2.4.2. Fresh vs frozen FMT:

We recommend that the use of banked frozen FMT material should be considered preferable to fresh preparations for CDI *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.4.3. Use of frozen FMT:

i. We recommend that FMT material stored frozen at -80^{o}C should be regarded as having a maximum shelf life of six months from preparation *(GRADE of evidence: low; strength of recommendation: strong).*

ii. We suggest consideration of thawing frozen FMT at ambient temperature, and using within six hours of thawing *(GRADE of evidence: low; strength of recommendation: weak).*

iii. We suggest not thawing FMT in warm water baths, due to the risks of cross contamination with *Pseudomonas* (and other contaminants) and reduced bacterial viability *(GRADE of evidence: very low; strength of recommendation: weak).*

2.2.5. What factors related to administration of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

2.2.5.1. Use of specific medications in the period around FMT administration:

2.2.5.1.1. General principles of FMT administration:

i. We recommended that bowel lavage should be administered prior to FMT via the lower GI route, and that bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred *(GRADE of evidence: low; strength of recommendation: strong).*

ii. For upper GI FMT administration, we suggest that a proton pump inhibitor should be considered, e.g. the evening before and morning of delivery *(GRADE of evidence: low; strength of recommendation: weak).*

iii. We suggest that a single dose of loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery *(GRADE of evidence: low; strength of recommendation: weak).*

iv. We suggest that prokinetics (such as metoclopramide) should be considered prior to FMT via the upper GI route *(GRADE of evidence: low; strength of recommendation: weak).*

v. We recommend that best practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc) *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.5.1.2. Additional antibiotics pre-FMT:

We recommend the administration of further antimicrobial treatment for CDI for at least 72 hours prior to FMT *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.5.1.3. Washout period between antibiotic use and FMT:

i. To minimise any deleterious effect of antimicrobials on the FMT material, we recommend that there should be a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT *(GRADE of evidence: low; strength of recommendation: strong).*

ii. We suggest considering consultation with infectious disease specialists or medical microbiologists for advice whenever FMT recipients also have an indication for long-term antibiotics, or have an indication for non-CDI antibiotics within eight weeks of FMT *(GRADE of evidence: very low; strength of recommendation: weak).*

2.2.5.2. Route of FMT delivery:

2.2.5.2.1. Upper gastrointestinal tract administration of FMT:

i. We recommend that upper GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate *(GRADE of evidence: high; strength of recommendation: strong).*

ii. Where upper GI administration is considered most appropriate, we recommend that FMT administration should be via nasogastric, nasoduodenal, or nasojejunal tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate *(GRADE of evidence: high; strength of recommendation: strong).*

iii. We recommend that no more than 100ml of FMT is administered to the upper GI tract *(GRADE of evidence: low; strength of recommendation: strong).*

iv. We recommend that upper GI administration of FMT should be used with caution in those at risk of regurgitation and/ or those with swallowing disorders *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.5.2.2. Lower gastrointestinal tract administration of FMT:

i. We recommend that colonoscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate *(GRADE of evidence: high; strength of recommendation: strong).*

ii. Where colonoscopic administration is used, we suggest considering preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate *(GRADE of evidence: low; strength of recommendation: weak).*

iii. We recommend that FMT via enema should be used as a lower GI option when delivery using colonoscopy or flexible sigmoidoscopy is not possible *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.5.2.3. Capsulised FMT:

Capsulised FMT holds promise as a treatment option for recurrent CDI and we recommend that this should be offered to patients as a potential treatment modality where available. Capsule preparations should follow a standard protocol. Further evidence regarding optimal dosing and formulation is required *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.6. What is the clinical effectiveness of FMT in treating conditions other than *Clostridium difficile* infection?

We do not currently recommended FMT as treatment for inflammatory bowel disease. Apart from CDI, there is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease *(GRADE of evidence: moderate; strength of recommendation: strong).*

2.2.7. Basic requirements for implementing a FMT service:

2.2.7.1. General considerations:

i. The development of FMT centres should be encouraged *(GRADE of evidence: very low; strength of recommendation: strong).*

ii. We suggest that FMT centres should work to raise awareness about FMT as a treatment option amongst clinicians caring for patients with CDI, and provide training to relevant healthcare professionals on the practicalities of delivering an FMT service *(GRADE of evidence: very low; strength of recommendation: weak).*

2.2.7.2. Legal aspects and clinical governance:

In the UK, FMT must be manufactured in accordance with MHRA guidance for human medicines regulation. When FMT is supplied on a named patient basis, within a single organisation, a pharmacy exemption may be used, subject to ensuring proper governance and traceability. All centres that are processing and distributing FMT should seek guidance from the MHRA and where necessary obtain appropriate licenses prior to establishing an FMT service. This is a legal requirement. In countries other than the UK, FMT should only be manufactured following appropriate approval from the national authority of that country *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.3. Multidisciplinary teams:

We recommend that a multidisciplinary team should be formed to deliver FMT services *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.4. Infrastructure:

We recommend utilisation of suitable laboratory facilities and infrastructure for FMT production *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.5. FMT manufacturing:

We recommend ensuring the traceability of supply *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.6. FMT production quality control:

We recommend monitoring, notification and investigation of all adverse events and reactions related to FMT *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.7. Donor screening governance:

We recommend ensuring the clinical governance of donor screening *(GRADE of evidence: very low; strength of recommendation: strong).*

3. Introduction:

The aim of the BSG/ HIS FMT working group was to establish a guideline that defined best practice in all aspects of a FMT service, by providing evidence-based recommendations wherever possible, and consensus multi-disciplinary expert opinion where specific published evidence is currently lacking. This included the evaluation of the use of FMT in the treatment of *Clostridium difficile* infection (CDI; also referred to as *Clostridioides difficile*[1]), and also in potential non-CDI indications. Relevant guidance published to date includes the interventional procedure guidance from the National Institute for Health and Care Excellence (NICE)[2], UK, European and US microbiological guidelines on the treatment of *Clostridium difficile* infection (CDI)[3–5], and recent expert consensus documents on FMT in clinical practice[6,7]. Furthermore, there have also been national recommendations regarding FMT produced by working groups in several different countries[8–10]. Principally as a result of randomised studies that have been published in recent years[11–18], FMT has become an accepted treatment for recurrent/refractory CDI.

The unique remit and objectives of this guideline when commissioned by the BSG and HIS was:

i. To review the rapidly-growing body of randomised trial evidence for the efficacy of FMT in the treatment of adults (≥18 years), both in CDI and in other clinical conditions, much of which has been published after the publication of current CDI treatment algorithms[3,4].

ii. To provide specific guidance about best practice for an FMT service within the context of the regulatory framework for the intervention as it currently exists in the UK[19,20].

The elucidation of the mechanisms underlying the efficacy of FMT in treating CDI remains an active area of global research, with the aim of rationalising FMT from its current crude form to a more targeted, refined therapeutic modality[21]. Previous research has demonstrated that commensal bacteria cultured from the stool of healthy donors[22], sterile faecal filtrate[23], and/ or spores of *Firmicutes* derived from ethanol-treated stool from healthy donors[24], may have similar efficacy to conventional FMT in treating CDI, although results of the latter approach produced disappointing outcome data when extended to a Phase II clinical trial[25]. For the purposes of this guideline, the BSG/HIS working group considered only studies that used the administration of manipulated whole stool (including encapsulated faeces). They deemed studies using cultured microorganisms (or their

proteins, metabolites or other components), or microbiota suspensions, to be in the pre-clinical research stage, without firm evidence.

FMT has been shown to be very acceptable to patients, both in the setting of CDI[11,26] and in non-CDI settings, e.g. ulcerative colitis[27]. However, the absence of appropriate protocols[28–31] specifically taking into account UK clinical practice and regulation of FMT has been perceived as a barrier to the use of FMT in the UK and Ireland; these guidelines seek to rectify this problem.

4. Guideline development:

4.1. Guideline development team

BSG and HIS commissioned the authors to undertake the Working Party Report. The authors represent the membership of both societies. The working group included gastroenterologists, infectious diseases/microbiology clinicians, a clinical scientist, a systematic reviewer, and patient representatives. The views expressed in this publication are those of the authors, and have been endorsed by BSG and HIS following consultation.

4.2. Scope of the guidelines

The main scope of the guidelines is to provide guidance for the optimal provision of an effective and safe FMT service, principally for recurrent or refractory CDI, but non-CDI indications are also considered. These guidelines only apply to adult patients (≥18 years); the working party did not consider the role of FMT in the treatment of either CDI or non-CDI indications in children or young people. The guidelines were written with a focus upon UK practice, but also with consideration of more global practice as it applied. The diagnosis and management of *Clostridium difficile* infection in general are outside the remit of these guidelines.

4.3. Evidence appraisal

Questions for review were derived from the Working Party Group, which included patient representatives in accordance with the PICO process[32]. To prepare these recommendations, the working group collectively reviewed relevant peer-reviewed research.

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4.4. Data sources and search strategy

A systematic literature search was undertaken using MEDLINE, EMBASE databases and Cochrane Library for relevant articles published from 1st January 1980 to 1st January 2018. The MEDLINE and EMBASE strategy are shown in **Supplementary Material 1, Appendix 2ii**. Free text and MESH/ index terms for faecal microbial transplant and *Clostridium difficile* or other diseases of interest were combined. In addition, conference proceedings from microbiology, infectious disease, and gastroenterology conferences were also searched to identify additional studies.

4.5. Study eligibility and selection criteria

The members of the guideline group determined criteria for study inclusion. Two reviewers (BHM, MNQ) screened the titles and abstracts of each article for relevance independently; any disagreements were resolved by discussion with a third reviewer (JPS). Copies of relevant articles were obtained and assessed for inclusion as evidence in the guideline by all three reviewers. The reason for not selecting studies was recorded. Only articles published in English and human clinical studies were included. For evidence on FMT for CDI, both randomised studies (including randomised controlled trials (RCTs)) and case series with at least 10 patients were selected. Only randomised trials were included as evidence for FMT for non-CDI indications. Conference abstracts were only included for CDI and non-CDI indications if they reported a randomised trial; where abstracts were available reporting data from a randomised trial that was subsequently published, only the published paper was reviewed.

4.6. Data extraction and quality assessment

The initial search identified 2658 publications, and of these, 802 duplicates were excluded. 1856 studies were subsequently screened, from which 78 studies were assessed by reviewing the full text for eligibility (see **Supplementary Material 1, Appendix 2iii** and **Supplementary Material 2, Additional Appendix D**). Of these 78 studies, 58 studies were included as the basis of evidence for writing this guideline. In total, 39 were case studies in CDI including at least 10 patients (see **Supplementary Material 2, Additional Appendix C.1)**, and ten were randomised studies in CDI (see **Supplementary Material 2, Additional Appendix C.2**). Nine were randomised trials for non-CDI indications (see **Supplementary Material 2, Additional Appendix C.3**). Data were extracted for patient demographics, disease characteristics, donor screening characteristics, stool preparation and administration, clinical outcomes and adverse events. The quality of randomised studies was

assessed with the Cochrane Collaboration's risk of bias tool. Case series were assessed using the Centre for Reviews and Dissemination guidance.

4.7. Rating of evidence and recommendations

The BSG version of these guidelines was prepared in keeping with the BSG Clinical Services & Standards Committee (CSSC) advice document on the writing of clinical guidelines[33]. Evidence tables were presented and discussed by the working group, and guidelines were prepared according to the nature and applicability of the evidence regarding efficacy and patient preference and acceptability. For the BSG version of this guideline, the GRADE system (Grades of Recommendation Assessment, Development and Evaluation)[34] was used to assess the strength of evidence (high/ moderate/ low/ very low) and strength of recommendation (strong/ weak) (**Table 4**). The section entitled 'Basic requirements for implementing an FMT service' (**Supplementary Material 3**) was based on expert opinion, since this was a key area of the working party's remit but not one amenable to evaluation by the PICO process. Face-to-face meetings and group teleconferences were held to agree on recommendations. Any disagreements on recommendations or the strength of recommendation were resolved by discussion and, where necessary, voting by the members of the working group, with consensus achieved when >80% were in agreement.

4.8. Consultation process

Feedback on draft guidelines was received from the Scientific Development Committee (SDC) of HIS, and changes made. These guidelines were then opened to consultation with relevant stakeholders (see **Supplementary Material 1, Appendix 3** of this document). The draft report was available on the HIS website for one month. Views were invited on format, content, local applicability, patient acceptability, and recommendations. The working group reviewed stakeholder comments, and collectively agreed revisions. Final changes were made after repeat reviews from HIS (Chair of the SDC and HIS Council) and BSG (BSG CSSC and BSG Council), and after further external peer review.

4.9. Guideline accreditation and scheduled review

The guidelines will be reviewed at least every four years and updated if change(s) in the evidence are sufficient to require a change in practice.

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4.0. Additional information:

Additional information related to this guideline (including a lay summary, background on the working party report, and information on the implementation of these guidelines) is contained within **Supplementary Material 1, Section 1**.

5. Rationale for recommendations:

5.1. Which patients with *Clostridium difficile* infection should be considered for faecal microbiota transplant, and how should they be followed up after treatment?

5.1.1. Prior to faecal microbiota transplant. Patient selection:

5.1.1.1. Recurrent *Clostridium difficile* infection:

As already described, there is widespread consensus that FMT is an efficacious treatment for recurrent CDI. In defining recurrent CDI, some studies have relied on a minimum threshold of return of clinical symptoms (e.g. at least three unformed bowel movements within 24 hours, for at least two consecutive days)[12,18] following previous successful CDI treatment; most studies have also included a requirement for a positive microbiological test[12,14,18,35–45]. Other studies explicitly state that a positive test was not required[46]. Recommendations for CDI testing are beyond the scope of this guideline, and there are already well-established evidence-based guidelines[47]. These recommend testing with either a nucleic acid amplification test (NAAT) or GDH assay, followed by detection of free toxin (either by toxin A/B enzyme immunoassay (EIA) or cytotoxin neutralisation assay), which allows differentiation of patients with active disease as well as those who are likely colonised[47]. However, the working group discussed the importance of the accurate diagnosis of true recurrent CDI prior to consideration of FMT; in particular, they noted a study which observed that of 117 patients with presumed recurrent CDI referred for work-up for FMT, 25% (*n*=29/117) were determined to have a non-CDI diagnosis, with irritable bowel syndrome (*n*=18) and inflammatory bowel disease (*n*=3) being the most common alternative diagnoses, and younger patients more likely to be misdiagnosed[48].

All of the reviewed studies have included patients with recurrent CDI, however some studies offered FMT to patients at the first recurrence (second episode)[12,15,16,18,35,37,42,43,46,49], whereas others offered FMT after the second recurrence (third episode)[13,14,39,41,44,45,50,51]. Some protocols offered FMT after three or more recurrences[52], whilst others did not define the point at which it was adminstered[40,53].

The severity of infection has been used as a parameter to decide at which stage FMT is offered. Youngster *et al.* offered FMT to patients with at least three episodes of mild to moderate CDI, or at least two episodes of severe CDI resulting in hospitalisation and associated with significant morbidity[17]. Another study selected patients for FMT using four categories of severity, which also accounted for prior anti-CDI therapy and requirement for hospitalisation[54].

None of the studies directly compared the efficacy of FMT according to the stage at which it was offered (i.e. first recurrence vs. ≥ two recurrences). A small number of studies[55–57] included patients with severe CDI (defined as hypoalbuminaemia with increased peripheral white cell count and/or abdominal tenderness) or complicated CDI (defined as admission to Intensive Care, altered mental status, hypotension, fever, ileus, white blood cell count > 30 x 10^9/l, lactate > 2.2mmol/l, or evidence of end organ damage). A single study described an apparent lower rate of treatment success when FMT was used to treat patients with recurrent CDI with disease caused by ribotype 027[43], but this is the case for all anti-CDI treatment modalities for this ribotype in comparison to others. The working group agreed that there was insufficient evidence to suggest that *C. difficile* ribotype should influence whether or not FMT is offered.

A lower primary cure rate was reported for complicated CDI (66%) compared with recurrent CDI (82%) and severe CDI (91%) in one study[55]; in a case series of 17 patients who all had severe and/or complicated CDI, a primary cure rate of 88% was described[57]. A cohort of 328 patients was analysed to determine which factors were associated with failure of FMT[58]. Higher early (one month) failure rates were found in patients with severe (72%, *n*=19/25) or severe-complicated (52.9%, *n*=9/17) CDI than for recurrent CDI (11.9%, *n*=34/286). This study also identified that patients who were treated with FMT as an inpatient were nearly four times more likely to fail as those who had FMT as an outpatient; however, the working group noted that the authors of this study themselves identified that inpatient status is likely a proxy of severity of CDI and/or co-morbidities. A further similar study, including 64 patients treated with FMT as treatment for recurrent CDI, also identified severe CDI as the strongest independent risk factor for FMT failure on multivariate analysis[59].

The working group discussed their experience of treating patients with CDI whose disease fitted an intermediate pattern to the typical descriptions given of recurrent or refractory CDI, e.g. patients with CDI who have some (but incomplete) symptomatic improvement with anti-CDI antibiotics and worsening of disease when these are stopped. The experience of the working group was that such

patients experienced excellent responses to FMT, and that these patients should be considered for FMT.

As FMT is currently an unlicensed medicine with poorly-studied long term sequelae, the working group considered that it should generally be reserved for patients who have had three or more episodes of infection. There are no studies directly comparing its effectiveness with some of the newer agents such as fidaxomicin or bezlotoxumab, hence this recommendation is made on the basis of safety. However, the working group agreed that it may be reasonable in certain patient groups with ongoing risk factors for further recurrence to offer FMT after the second episode.

Recommendation:

We recommend that FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI (GRADE of evidence: high; strength of recommendation: strong).

5.1.1.2. Refractory *Clostridium difficile* infection:

Two randomised trials allowed the recruitment of patients with refractory CDI. The first defined this as at least three weeks of ongoing severe symptoms despite standard antimicrobial therapy for CDI[17]. The second required persistent or worsening diarrhoea and one of the following: ongoing abdominal pain, fever > 38^{o}C, or white blood cell count > 15x 10^{9}/l despite oral vancomycin at a dose of 500mg four times daily for at least five days[16]. Both studies included only small numbers of patients with refractory CDI (*n*=4/20 (20%) and *n*=15/219 (6.8%), respectively). There did not appear to be any significant difference in primary outcome measure (clinical cure) in patients with recurrent or refractory CDI, although neither study was designed to assess this difference. There are also a number of case series in which FMT was given to patients with refractory CDI; however, outcome measures were not reported for these groups individually in these studies[37,38,54,60].

Overall, the working group concluded that there is little consensus on the definition of refractory CDI, with some studies using the terms 'refractory' and 'recurrent' interchangeably (as well as other terms, e.g. 'salvage therapy'). Consequently, the quality of evidence for the utility of FMT in

refractory cases of CDI is lower than for recurrent CDI. The standardisation of definitions will allow more robust comparison between patient cohorts.

Recommendation:

We recommend that FMT should be considered in cases of refractory CDI (GRADE of evidence: moderate; strength of recommendation: strong).

5.1.1.3. FMT as initial therapy for *Clostridium difficile* infection:

Experience of the use of FMT as initial therapy for CDI is very limited. In a case series of patients with CDI with ribotype 027, use of anti-CDI antibiotics together with nasogastric FMT within a week of diagnosis during an initial episode of CDI was associated with reduced mortality when compared to using FMT only after the failure of three courses of antibiotics (mortality of 18.75% (*n*=3/16 patients) vs 64.4% (*n*=29/45 patients))[61]. However, 37.5% (*n*=6/16) of the patients treated with FMT within a week of CDI diagnosis required further antibiotics and a second FMT within one month of the first FMT because of relapse[61]. In a small pilot randomised trial, patients were randomised to either vancomycin or multi-donor FMT (administered either via upper or lower GI routes) as initial therapy for CDI; CDI resolution occurred in 88.9% (*n*=8/9) patients with vancomycin, compared to 57.1% of patients (n=4/7) patients with one FMT, and 71.4% of patients (n=5/7) after two FMTs[62]. Given the small size of these studies and equivocal results, the working group concluded that the reviewed studies did not support FMT as initial therapy for CDI.

Recommendation:

We recommend that FMT should not be administered as initial treatment for CDI (GRADE of evidence: low; strength of recommendation: strong).

5.1.1.4. Antimicrobial/ antitoxin therapy prior to considering FMT for patients with CDI:

There are now at least two licensed agents (fidaxomicin and bezlotoxumab) which have been shown to significantly reduce the risk of recurrence compared with vancomycin[63,64]. There is also some evidence that pulsed/tapered dosing of vancomycin and fidaxomicin (including pulsed fidaxomicin[65]) results in fewer recurrences than with standard dosing of these agents[66,67] (although this finding has

not been replicated in all studies[68]). Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, *n*=12/92) than when treated with vancomycin (26.6%, *n*=29/209)[63]; this finding was replicated in another randomised controlled trial, with 8.3% (*n*=4/48) and 32.6% (*n*=14/43) experiencing a recurrence respectively[69]. In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared to standard of care antibiotics alone (10.9% (*n*=6/55) vs 20% (*n*=13/65) respectively)[64].

As discussed above, the working group noted that there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT[12]. The working group agreed that in the absence of this evidence, on the balance of safety and potential risks, consideration should be given to using antimicrobial/antitoxin therapy associated with reduced CDI recurrence prior to considering the use of FMT.

Several studies specify that patients should be treated with anti-*C. difficile* antibiotics for a minimum period of 10 days before diagnosing recurrent CDI and offering FMT[12,15,16,18].

Recommendations:

i. We recommend that FMT for recurrent CDI should only be considered after recurrence of symptoms following resolution of an episode of CDI that was treated with appropriate antimicrobials for at least 10 days (GRADE of evidence: low; strength of recommendation: strong).

ii. We recommend consideration of treatment with extended/ pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI (GRADE of evidence: low; strength of recommendation: strong).

iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, we recommend that consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT (GRADE of evidence: low; strength of recommendation: strong).

5.1.2. Post-FMT follow-up, outcomes and adverse events:

5.1.2.1. Management of FMT failure:

Where patients were deemed not to have responded to an initial FMT, many studies have offered repeat FMT and success rates have been excellent even in patients with modest response to a first FMT[14,15,17,18,35,43,46,51,54,70,71]. The success of a second FMT appears to be high whether treatment failure represents non-response to the first FMT, or a late failure (i.e. further relapse of CDI after an initial response); however, these terms have been defined variably between different studies (also see **Section 5.1.2.5**). Second FMTs have been offered as soon as 24-72 hours after an initial FMT for presumed non-response[37,72,73]. For FMT failure in patients with pseudomembranous colitis, repeat FMT every three days until resolution of pseudomembranes has been a successful approach[18]. Good outcomes in pseudomembranous disease have also been achieved through a protocol that routinely restarted five days of vancomycin if FMT failed, before offering another FMT[73]. Other studies have demonstrated potential success in treating initial FMT failure with further antibiotics, including repeat FMT with vancomycin between procedures[42], or anti-CDI antibiotics alone[35,42,43,45,51,70,71]. Patients unresponsive to two FMTs have been offered further FMT or antibiotic therapy[16], or even the administration of intravenous immunoglobulin[35]. Whilst the working group collectively agreed that there was strong evidence to recommend repeat FMT after initial FMT failure, they were not able to recommend a specific protocol for administering repeat FMT and/ or maximum number of FMTs, given the wide heterogeneity of approach described within the reviewed literature.

Recommendation:

We recommend that FMT should be offered after initial FMT failure (GRADE of evidence: high; strength of recommendation: strong).

5.1.2.2. General approach to follow-up post-FMT:

Follow-up post-FMT (in terms of duration, modality and regimen for follow-up) varies considerably between studies, and is largely dependent upon study design. Follow-up regimens vary not only between studies but within them too, reflecting the retrospective nature of many early FMT studies in CDI, where follow-up mostly reflected pragmatic routine clinical care.

Modalities of follow-up have included outpatient review[14,43,58,71,74–76], telephone interview[17,39,43,46,58,71,74] and case note/ database review[35,39,70,71,74,40,42,43,45,46,49,51,54]. Follow-up duration has varied from 60 days[45] to 8 years[36], with very different durations used in each study. Once again, however, this variability in follow-up largely reflects the retrospective analysis of case

series rather than being justified by any specific methodology. The working group decided by consensus that at least eight weeks of follow-up was appropriate post-FMT to fully assess efficacy and potential adverse events; this figure was also influenced by discussions regarding the timepoint after FMT at which a decision could be made regarding cure/ remission of CDI (see **Section 5.1.2.4**).

Recommendation:

We recommend that all FMT recipients should routinely receive follow-up. Clinicians should follow-up FMT recipients for long enough to fully establish efficacy/adverse events, and for at least eight weeks in total (GRADE of evidence: low; strength of recommendation: strong).

5.1.2.3. Management of the FMT recipient:

Procedural adverse events during administration of FMT have predominantly occurred with colonoscopic administration of FMT. These have included mild nausea and vomiting attributed to sedation for the colonoscopy, minor mucosal tears during colonoscopy[49,60], and microperforation following biopsy of an area of presumed ischaemic small bowel injury in a patient with chronically dilated small bowel (which resolved with conservative management[46]). One death occurred due to witnessed aspiration at the time of colonoscopy[60]. Faecal regurgitation and vomiting with temporal association to upper GI FMT administration has also been described (discussed further in **Section 5.5.2.2**)[77].

The predominant short term adverse events post-FMT for CDI are mild: self-limiting GI symptoms have been the most frequently reported adverse events. These may be related to the route of administration and include belching[15], nausea[15,16,49,60], abdominal cramps/ discomfort/ bloating/ pain[15,18,49,60,72], and diarrhoea[15,16,18,60]. One patient with a history of autonomic dysfunction experienced dizziness with diarrhoea after FMT[15]. These symptoms are typically short-lived, resolving in hours to days[15,16,18,49,72]. Minor subsequent adverse events have included a range of GI side effects including self-limiting abdominal discomfort[14,17,57,76], nausea[14,49,70], flatulence[14,16,17,41,42,49,57], self-limiting irregular bowel movements[41], *C. difficile*-toxin negative diarrhoea[52,55], constipation[14,15,42,55,70] and constitutional symptoms/ temperature disturbance[14,17].

As such, immediately post-endoscopic administration of FMT, most FMT centres typically manage patients using standard protocols for an endoscopic procedure[41,49], without any specific adaptations (apart from to reiterate advice about the possibility of self-limiting GI side effects, and the use of departmental infection control protocols). There is often a relatively short period of post-procedural observation[15,18]. Most studies allow patients to leave the administration site after the period of observation, although overnight observation was the protocol used for a cohort of very elderly patients with multiple comorbidities[51]. Where enteral tube administration is used, post-procedure management has ranged between removal of the tube after 30 minutes (following nasoenteral administration of 500ml of FMT[15]) to prompt post-procedure removal and oral water administration (after nasogastric administration of 90ml of FMT[72]), with no direct adverse outcomes in either case. The working group felt that removal of the tube at 30 minutes, with administration of water at this point, was a pragmatic approach.

The definition of post-FMT serious adverse events has varied between studies, but has included significant morbidity necessitating hospital admission and death in the follow up period. Many of these events are described as not directly caused by the FMT, including the scenario of post-FMT severe CDI recurrences[72] and probable or certain CDI-related deaths[16,60,70] occurring in the context of FMT failure, or deaths related to patient comorbidities[17,55]. One patient was admitted to hospital with self-limiting abdominal pain post-FMT[60], and four patients with flares of inflammatory bowel disease[60]. Three patients underwent colectomy during the post-FMT follow-up period, with all related to ulcerative colitis and not believed to be due to CDI[60]. Other reported serious adverse events include recurrent urinary tract infection[15], fever during haemodialysis[15] and upper gastrointestinal haemorrhage after nasogastric FMT (in a patient taking NSAIDs[51]), none of which were thought to be strongly linked to FMT. There have also been a number of new onset autoimmune, inflammatory and metabolic conditions described post-FMT, although these have been described from single centres only, with these findings not replicated elsewhere. Such conditions include microscopic colitis, Sjögren's syndrome, follicular lymphoma, peripheral neuropathy, immune thrombocytopenia and rheumatoid arthritis[53,55].

Significant adverse events are therefore rare but well-described. Furthermore, the procedure is relatively novel, and longer-term follow-up data regarding safety are required. Therefore, the working group opined that formal follow-up post-FMT to assess outcome and possible adverse events is essential.

The use of questionnaires to compare symptoms pre- and post-FMT is common. Specifically, data collected have included clinical response to symptom severity[55], stool frequency[15,17,46,55,57,72], stool consistency[14,15,72], abdominal pain or tenderness[55,57], rating of gastrointestinal symptoms[72], general well-being[55,72], days to improvement post-FMT[57], weight change[72], functional status[55], and changes in medication/use of antibiotics[57,72]. Additionally, certain patients have been given specific advice post-FMT to contact their clinical team if there is recurrence of diarrhoea or symptoms[14,35,41,43]. Where patients underwent outpatient clinical evaluation, this was generally undertaken relatively early post-FMT[39,52,76]. In one study, patients were additionally given instructions for cleaning and disinfection at home, with the aim of reducing the possibility of *C. difficile* reinfection[43], and counselling on the risk of recurrent CDI with future antibiotic courses[76].

Recommendations:

i. We recommend that immediate management after endoscopic administration of FMT should be as per endoscopy unit protocol (GRADE of evidence: very low: strength of recommendation: strong).

ii. We recommend that patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare (GRADE of evidence: very low; strength of recommendation: strong).

iii. ***After enteral tube administration, we recommend that patients may have the tube removed and oral water given from 30 minutes post-administration (GRADE of evidence: very low; strength of recommendation: strong).***

5.1.2.4. Definition of cure post-FMT for CDI:

It is recognised that symptoms of CDI resolve relatively promptly post-successful FMT, although this has been variably described (within hours in some studies[52], at an average of 4-5 days in others[57,71]). Treatment success post-FMT for CDI has no uniformly-agreed definition, with the time point at which cure/ remission is defined on clinical grounds varying between 3-5 days[36] up to six months[42]. A consensus document from the USA recommends 'resolution of symptoms as a primary end point; absence within eight weeks of FMT as a secondary end point'[78]. The working group recommended that this definition should be made on a case-by-case basis; however, they agreed that an

assessment for cure/ remission of CDI within eight weeks post-FMT was reasonable in most cases, and therefore that this was also a reasonable minimum length of time to undertake follow-up post-FMT (see **Section 5.1.2.2**).

Recommendation:

We recommend that a decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis (GRADE of evidence: very low; strength of recommendation: strong).

5.1.2.5. Definition of treatment failure post-FMT for CDI:

There is no uniformly-agreed definition of treatment failure/recurrence post-FMT for CDI, with varied definitions used in studies. The use of *C. difficile* toxin as a marker of treatment success or failure is variable, with some studies opting not to test for CDT unless symptoms consistent with CDI recurred[49,52–54,60,72,74]. Some studies have routinely performed CDT testing without specifying any action taken after a positive result[14,15,18,36,39,41], whilst others have tested for *C. difficile* PCR but relied on clinical criteria (even if PCR was positive) post-FMT for evaluating FMT efficacy[14]. A recent prospective study from the USA identified that only 3% (3/129) of patients who were asymptomatic at four weeks post-FMT for recurrent CDI had positive *C. difficile* PCR, again emphasising that symptoms rather than laboratory assays are more useful contributors to establishing FMT success[79].

Recommendation:

We recommend that treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for C. difficile toxin after FMT is not recommended, but it is appropriate to consider in the case of persistent CDI symptoms/suspected relapse (GRADE of evidence: low; strength of recommendation: strong).

5.2. What recipient factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

5.2.1. General approach to co-morbidities and FMT:

Most published studies had a core set of general recipient exclusions which included: significant/ anaphylactic food allergy[14,17], pregnancy[12–15,17,18], breastfeeding[14], admission to Intensive Care or the

requirement for vasopressors[12,15,18], chronic diarrhoea or other infectious cause of diarrhoea[12,14,18,50], inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS)[14,36], immunodeficiency due to recent chemotherapy and/ or neutropenia[12,14–18,50], HIV/AIDS[14,17,18], prolonged use of corticosteroids[15,17,18], graft versus host disease[12], and decompensated cirrhosis[14,15,17,18].

The working group discussed the reported practice of several centres of treating patients with recurrent CDI and food allergies through the use of FMT prepared from a patient-directed donor instructed to avoid trigger foods before stool donation. They agreed that this seemed reasonable for patients with true adverse immunological reactions to defined food groups (e.g. gluten-free diet donor for a recipient with coeliac disease). However, the working group noted that food allergies are often poorly-defined clinically, and also expressed concerns that there was no means to verify how closely a donor had followed an exclusion diet; as such, they felt unable to make any specific recommendation about FMT in patients with food allergies in general. In contrast, whilst the working group were unaware of any reports in the literature of anaphylaxis attributable to FMT, they felt that the theoretical risk of a serious adverse outcome in patients with anaphylactic food allergy merited a specific recommendation that such individuals should not be offered FMT. Similarly, the working group expressed concern about the theoretical risk of adverse outcomes when administering FMT to patients with advanced decompensated chronic liver disease (including translocation of microbial material from the intestinal tract into the portal and systemic circulations, and theoretical risk of sepsis), and felt that FMT should be used with caution in this patient group.

Recommendations:

i. ***We recommend that FMT should be avoided in those with anaphylactic food allergy (GRADE of evidence: very low; strength of recommendation: strong).***

ii. ***We suggest that FMT should be offered with caution to patients with CDI and decompensated chronic liver disease (GRADE of evidence: very low; strength of recommendation: weak).***

5.2.2. Immunosuppression and FMT:

One randomised study[16] included patients with immunodeficiency (treatment with immunosuppressive therapy (azathioprine, ciclosporin, infliximab, methotrexate alone, or in combination with corticosteroids) (*n*=18), renal transplant (*n*=5), chronic haemodialysis (*n*=5), solid organ tumours (*n*=3) and haematological malignancy (*n*=4)) at the time of FMT. Clinical resolution

rates after up to two FMTs were high: 27/29 (93%) for immunocompromised individuals, 5/6 (83%) for patients with IBD.

There are also limited data from case series and single case reports describing the use of FMT in patients with immunocompromise. Agrawal and colleagues[55] included 46/146 (32%) patients with a history of cancer, and an additional 15/146 (10%) patients with non-cancer-related immunologic dysfunction, although primary outcome measures were not specifically reported for these groups. Overall cure at 12 weeks in a case series of 80 patients with immunocompromise was reported in 71 (89%) of patients[60]. Adverse events occurred in 12 (15%) immunocompromised patients; this included two deaths (one due to respiratory failure and another due to pneumonia resulting from aspiration at the time of FMT administration)[60]; however, such adverse events have also been reported in non-immunocompromised patient populations[80]. Hefazi and coauthors described high efficacy rates in a case series of FMT for recurrent CDI and a range of haematological or solid organ malignancies (remission after one FMT in 11/12 with haematological patients, and 8/10 in solid organ malignancy patients). No significant FMT-related complications were reported[81]. A further case series[45] reported FMT treatment for 75 patients with recurrent CDI and found no significant difference in primary cure rates for patients with diabetes mellitus, malignancy, or steroid use in the preceding three months.

The working group discussed the potential impact of donor EBV and CMV status for the immunocompromised FMT recipient at risk of severe infection if exposed to these viruses. Their opinion was that such recipients should only receive FMT from donors with negative EBV and CMV status.

Recommendations:

i. ***We recommend that FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (GRADE of evidence: moderate; strength of recommendation: strong).***

ii. We recommend that immunocompromised FMT recipients at risk of severe infection if exposed to EBV or CMV should only receive FMT from donors negative for EBV and CMV (GRADE of evidence: very low; strength of recommendation: strong).

5.2.3. Other comorbidities and FMT:

Only a limited number of cited studies included specific detail about the presence of comorbidities in patients receiving FMT. However, several studies reported median Charlson comorbidity scores[12,14,15,18,50]. One randomised study reported the presence of IBD in 10/17 (59%) FMT recipients[16], and there did not appear to be any significant difference in primary outcome measures in this group. Another randomised trial included 14/72 (33%) patients with IBD and reported clinical cure of CDI in 12/14 (86%) of these patients[13]. This study also included 64/72 (89%) patients with cardiac, respiratory, renal, central nervous system or multi-organ system comorbidities[13]; however outcomes were not stratified according to co-morbidity. Kelly and coauthors[60] reported an overall cure rate of 94% in a subset of CDI patients with IBD. A meta-analysis of studies in which patients with IBD received FMT (either primarily as treatment for concurrent recurrent CDI, or with the aim of treating IBD) noted a small risk of exacerbation of IBD in association with the use of FMT[82]. The working group noted the complexity of the relationship between IBD and CDI, given that IBD is itself a risk factor for CDI.

Other exclusions have been more directly related to the mode of administration. For upper gastrointestinal delivery, exclusion criteria have included delayed gastric emptying, chronic aspiration, 'swallow dysfunction', and dysphagia[17,50]. Exclusions for lower GI administration have included colostomy/ileostomy[16,50], significant bleeding disorders[12], untreated colorectal cancer[14,36,54], and ileus/small bowel obstruction[50].

In summary, the working group noted that co-morbidities amongst patients with recurrent CDI are common. Most studies did not analyse primary outcome measures according to co-morbidity; however, a small number of studies have analysed primary outcome measures (clinical cure) for patients with IBD receiving FMT for recurrent CDI and have found no significant difference compared to those without IBD, along with no overall significant worsening of IBD activity.

Recommendations:

i. We recommend that FMT should be offered to those with recurrent CDI and inflammatory bowel disease, but patients should be counselled about a small but recognised risk of exacerbation of IBD (GRADE of evidence: moderate; strength of recommendation: strong).

ii. We recommend that FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities (GRADE of evidence: moderate; strength of recommendation: strong).

5.3. What donor factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

5.3.1. General approach to donor selection:

Excellent efficacy has been shown in treating recurrent CDI using FMT derived from both related[14,36,54,57,59,61,83,38,40,41,43,45,46,49,53] and unrelated[14,15,57,59,61,72,74,83–87,16,17,35,37,38,41,43,53] donors. To date, there have been no randomised studies comparing differences in efficacy. Case series have tended to rely more on donation of stool from healthy family members. In randomised studies using FMT, all donors were healthy unrelated individuals[12–18,88]. Three case series used donor stool from healthcare professionals[39,61,85]; no randomised studies have used stool from this cohort. However, the working group noted that there were clear advantages to using FMT from a screened anonymous donor, in particular with regards to monitoring and traceability, as discussed further later.

Recommendation:

We recommend that related or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor (GRADE of evidence: low; strength of recommendation: strong).

5.3.2. Age and BMI restrictions for potential donors:

There are no well-defined age restrictions on donors. Randomised studies have used donors of ≥18[12,72] and ≤60 years old[15,17,18] with satisfactory outcomes. Two of the case series defined age limitations for donors as ≥18 and ≤ 50 years[72,89]. A recent study demonstrated that *Bacteroides: Firmicutes* ratio and microbial diversity was similar for donors above and below 60 years, and their stool donations had similar clinical efficacy as FMT; however, there were loss of the phylum *Actinobacteria* and family *Bifidobactericeae* from donors older than 60 years[90]. On balance, the working group agreed that an age range of 18 – 60 years was appropriate for donors.

A widely-reported case study noted apparent weight gain in a recipient of FMT for treatment of CDI when an overweight donor was used[91], but any association between a donor with a raised BMI and weight gain post-FMT has not been replicated elsewhere in the literature[92]. Whereas most randomised studies did not report donor-specific BMIs, some have excluded those without a 'normal' BMI[13,17]. The working group considered an acceptable BMI for donors as between ≥18 to ≤30 kg/m^2.

Recommendation:

We suggest that people should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of ≥18 and ≤30 kg/m^2 (GRADE of evidence: low; strength of recommendation: weak).

5.3.3. General approach to the donor screening assessment:

There is a clear theoretical risk of the transmission of infection by FMT; furthermore, given the large number of conditions in which perturbation of the gut microbiota has been described[93], there is a concern regarding a risk of transmission of microbiota associated with vulnerability to disease. Whilst FMT is efficacious for recurrent CDI, adverse events may be associated with its use (discussed further later), and long-term safety follow-up is lacking. The aim of a donor screening questionnaire and interview is to minimise post-FMT adverse events by excluding potential donors from whom FMT may be associated with risk to recipients. Randomised studies performed to date used various pre-screening questionnaires, including self-screening questionnaires which focused on high risk behaviours for blood-borne infections[12–16], questionnaires that focused on previous potential transferable medical conditions[18], and adaptations from the American Association of Blood Banks Donor Questionnaire[14,17]. One randomised study used the OpenBiome questionnaire as a screening questionnaire[94]. Some studies have suggested excluding potential donors who have recently travelled to defined regions (typically tropical areas), varying between 3-6 months prior to donation[38,39,49,52,55,59,74,87]; this is also the protocol employed in randomised studies[14,16,18]. Another important point for assessment is recent use of medications by potential donors. In particular, given the profound effects of antimicrobials on the gut microbiota[95–98] (along with the theoretical concern that recent antimicrobials might precipitate gut colonisation with antimicrobial-resistant bacteria that could be transferred during FMT), studies advocate either a three month[14,46,53–55,57,61,74] or six month[16–18,35,38,39,43,49,85,99,100] period without antimicrobial use prior to FMT donation.

The working group agreed that, given the growing evidence for the contribution of the gut microbiota to the aetiopathogenesis of colorectal carcinoma, patients with a significant personal or family history of (or risk factors for) this condition should be excluded as donors (**Table 1**). However, the working group noted an added complexity, in that their recommendation was that potential donors may be up to 60 years of age, but bowel scope screening for colorectal carcinoma currently begins within the UK at 55 years of age, and formal NHS bowel cancer screening starts at the age of 60 years[101]. The working group agreed that potential donors living in countries with bowel cancer screening programmes that start before the age of 60 years should have therefore completed appropriate screening with negative/ normal tests before they are considered further as donors.

The working group was of the opinion that a screening process is mandatory; any positive responses should usually result in exclusion from donation, although this will depend upon the particular circumstances/ answers given. A donor screening questionnaire should be performed both prior to considering a person as a donor, and also at a further point in time (discussed further in **Section 5.3.5**).

Recommendation:

It is mandatory to screen potential donors by questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota (Table 1) (GRADE of evidence: low; strength of recommendation: strong).

5.3.4. Laboratory screening of potential donors:

Currently, there are no known confirmed cases of blood-borne pathogens being transmitted by FMT, but strict preventative measures are important, as the potential risk of transmission is unknown. Many of the suggestions are extended from established blood screening guidelines[102]. Case series almost universally screen for HIV, hepatitis B and hepatitis C as a minimum[35,36,52–55,59,61,72,74,84,86,37,87,103,39–43,46,49]; other studies (including the randomised trials) have a more thorough blood screening process[14–18]. Many studies have also included a 'metabolic/general blood screen', to select out donors with hitherto undiagnosed chronic illness. **Table 2** shows the suggested blood screening protocol of the BSG/HIS working group.

The working group specifically discussed the role of screening donors for their EBV and CMV status; the importance of the rationale for this is discussed in **Section 5.2.2.** They agreed that EBV and CMV testing was only required where there is the potential that the FMT prepared from that donor would be administered to immunosuppressed patients at risk of severe infection if exposed to CMV and EBV.

The primary aim of stool screening of potential donors is to minimise the risk of transmission of pathogens; again, the relative novelty of FMT for CDI means that these risks are not currently well-defined. Stool screening protocols are universal amongst published studies, though widely-variable protocols have been used. **Table 3** displays the suggested stool screening protocol of the working group. The working group discussed stool screening for multi-drug resistant bacteria carriage, and agreed that carbapenemase-producing *Enterobacteriaceae* (CPE) should be screened for. Although these bacteria are carried only by a minority of the UK population, transfer into debilitated patients with CDI is clearly undesirable given that CPE are potentially so difficult to treat. They also agreed that extended-spectrum beta-lactamase (ESBL)-producing organisms could also potentially cause severe disease (with limited antimicrobial options) if transplanted into patients with CDI, and so should also be screened for. Whilst vancomycin-resistant *Enterococci* (VRE) carriage is relatively common in the community (probably related to food consumption)[104], community strains of VRE are genetically distinct from (and generally of much lower pathogenicity than) those found nosocomially[105]; as such, the working group thought that routine screening was not justified. The working group also noted that methicillin-resistant *Staphylococcus aureus* (MRSA) carriage is very rare in healthy adults in non-healthcare settings (with significant intestinal carriage even rarer), so did not justify routine screening. However, the working group acknowledged that the potential infection risk from VRE and MRSA would vary regionally dependent upon local prevalence and pathogenicity, and as such recommended that a risk assessment is performed to assess whether screening for these organisms should be considered.

A donor laboratory screening should be performed both prior to considering a person as a donor, and also at a further point in time (discussed further in **Section 5.3.5**).

Recommendation:

Blood and stool screening of donors is mandatory (Tables 2 and 3) (GRADE of evidence: low; strength of recommendation: strong).

5.3.5. Repeat donor checks, and donation pathway:

Almost all reviewed studies have repeated at least some elements of the initial donor screening process either at the time of donation of each stool sample used to prepare FMT, or at the end of a period of donation to assess ongoing suitability for inclusion. However, protocols have differed widely between studies.

The opinion of the working group was that when a donor had met criteria for donation (both with an acceptable health questionnaire and satisfactory laboratory tests), they were suitable to begin donation of stool that may be prepared into FMT. Repeat donor screening was also deemed necessary. In centres where frozen FMT is being prepared, stool may be collected and processed immediately after the first donor screen is successfully completed, but should be stored in 'quarantine' pending further donor screening, rather than used immediately for clinical use. At the end of the locally-defined period of donation, potential donors should undergo repeat testing, with a further health questionnaire and laboratory screening. If the donor's health questionnaire remains acceptable and repeat laboratory screening is negative at this point, then the frozen FMT may be released from 'quarantine', and used. The working group thought that donor screening both before and after donation was the safest route possible, and that this represented the preferred scenario. A proposed summary pathway for donor screening in this scenario is provided in **Figure 1.**

In centres using fresh FMT, the working group agreed that a repeat health questionnaire should be completed at the time of donation of each stool sample used to prepare FMT. Formal repetition of both the personal interview/ health questionnaire and laboratory screening tests should occur at regular intervals to ensure ongoing suitability for inclusion as a donor. The working group's opinion was that this repetition of the screening process should occur at least once every four months.

Recommendations:

i. In centres using frozen FMT, before FMT may be used clinically, we recommend that donors should have successfully completed a donor health questionnaire and

laboratory screening assays both before and after the period of stool donation. This is the preferred means of donor screening (GRADE of evidence: low; strength of recommendation: strong).

ii. ***In centres using fresh FMT, we recommend that a repeat health questionnaire should be assessed at the time of each stool donation. To ensure ongoing suitability for inclusion as a donor, the donor health questionnaire and laboratory screening should be repeated regularly (GRADE of evidence: low; strength of recommendation: strong).***

5.4. What factors related to the preparation of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

5.4.1. General principles of FMT preparation:

There is very little evidence or guidance on the collection of donor stool. Critical steps during this process centre on the reduction of environmental cross-contamination risk, so the use of clean collection devices and clean collection procedures is advocated. To promote standardised practice and a safe and effective product, clear instructions should be provided to the donor for stool collection (**Table 5)**.

Regardless of the methods used to prepare FMT, stool donations should be processed within six hours of defaecation. The period of six hours has been generally applied across many successful studies of FMT treatment in CDI[14,18,35,39,43,52], although no formal comparative study has been undertaken. This strategy aims to minimise sample degradation and alteration over time, which may occur due to the complex metabolic and environmental requirements of the faecal microbiota.

There are no comparative trials of anaerobically versus aerobically prepared FMT in the treatment of recurrent CDI. With the exception of small observational studies[41,74], the vast majority of FMT preparation has been undertaken aerobically for the treatment of CDI and has proved highly efficacious. There appears to be no clear need to process anaerobically, a method which introduces complexity and cost for the treatment of CDI.

The reviewed randomised studies reported variable amounts of stool used in the preparation of each FMT aliquot, and the lack of comparative data means that it is not possible to link stool mass to outcome from these studies. However, a previous systematic review of case series using FMT as treatment for recurrent CDI reported similar rates of treatment efficacy, but an approximate fourfold increase in recurrence rates, if <50g of stool was used compared to ≥50g[106]. Similarly, the initial volume of diluent used to create the faecal emulsion is variable between studies, although the most common practice appears to be creation of a stool: diluent ratio of approximately 1:5. The overwhelming majority of the reviewed studies used stool from only a single donor per FMT (rather than stool pooled from a mixture of donors), and there are no comparative studies of outcomes of CDI from single donor vs pooled donor FMT; as such, the working group found no justification to recommend donor stool pooling for FMT for CDI.

The majority of studies have used preservative-free sterile 0.9% saline as the diluent for FMT production, although there have been a handful of reports of other diluents including potable water[16,35,43]. There have been no comparative studies of FMT diluent. In cases where frozen FMT is prepared, an appropriate cryoprotective substance should be added prior to freezing. Most studies use glycerol at a final concentration of ~10%[16,41]. It has been demonstrated that storing stool at -80°C for up to six months in saline without glycerol decreases viable aerobic and anaerobic bacterial counts; the reduction was statistically significant in all bacterial groups with the exception of *E. coli* and total anaerobes. When stored with glycerol, no significant reduction in viable counts was observed[74].

A variety of homogenisation and open filtration systems have been used, with no apparent major variation in efficacy. Open filtration systems such as gauze[16,37,40,55], filter paper[39] and strainers/ sieves[17,41] are unpleasant to use and pose a risk of external contamination. In order to best comply with GMP standards, a sterile, single-use closed homogenisation and filtration system is recommended. An example of such a system includes the use of sterile filter bags inside a laboratory paddle homogeniser.

Recommendations:

i. We recommend that donor stool collection should follow a standard protocol (GRADE of evidence: low; strength of recommendation: strong).

ii. We recommend that donor stool should be processed within 6 hours of defaecation (GRADE of evidence: low; strength of recommendation: strong).

iii. We recommend that both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI (GRADE of evidence: moderate; strength of recommendation: strong).

iv. We recommend that sterile 0.9% saline should be considered as an appropriate diluent for FMT production, and cryoprotectant such as glycerol should be added for frozen FMT (GRADE of evidence: moderate: strength of recommendation: strong).

v. We recommend using ≥50g of stool in each FMT preparation (GRADE of evidence: moderate: strength of recommendation: strong).

vi. We suggest that stool should be mixed 1:5 with diluent to make the initial faecal emulsion (GRADE of evidence: low; strength of recommendation: weak).

vii. We suggest that homogenisation and filtration of FMT should be undertaken in a closed disposable system (GRADE of evidence: low; strength of recommendation: weak).

5.4.2. Fresh vs frozen FMT:

Two randomised studies have examined this area. One double-blind randomised study concluded that enema frozen FMT (*n*=91) was non-inferior for clinical resolution of diarrhoea to fresh FMT (*n*=87) for the treatment of recurrent or refractory CDI[16] (with frozen FMT in this study stored at -20^{o}C for up to 30 days). A further randomised study demonstrated statistically comparable remission rates for recurrent CDI with fresh or frozen FMT delivered colonoscopically (*n*=25/25 vs 20/24 respectively, *p*=0.233) (using frozen FMT stored at -80^{o}C for up to six months)[13]. These data support the findings of earlier small observational studies[35,41]. Frozen FMT is preferable to fresh FMT on logistical and cost grounds[16]. Banked frozen FMT also enables the window period for donor screening to be minimised, allowing centres to more closely to meet regulatory requirements (also see **Section 5.3.5**).

Recommendation:

We recommend that the use of banked frozen FMT material should be considered preferable to fresh preparations for CDI (GRADE of evidence: high; strength of recommendation: strong).

5.4.3. Use of frozen FMT:

Frozen FMT has been used up to six months after storage at -80°C[17,41,74], with high efficacy rates (>70%) observed in the cases treated. However, there have been no comparative trials investigating storage durations. A trend towards decrease in the viability of certain gut microbiota taxa was noted when faecal aliquots were frozen in 10% glycerol for six months[74], and as such, the working group agreed that six months was the acceptable limit for freezing of an FMT in glycerol. Storage at -80°C is recommended rather than -20°C to minimise sample degradation.

Warm water baths have been recommended to speed thawing[6]; however, the working group thought that this should be strongly discouraged, as this may introduce risks of cross contamination by *Pseudomonas* species (and other contaminants) from the water bath[107,108], and may reduce bacterial viability in the FMT. Repetitive freeze thawing of FMT samples should be avoided as bacterial numbers will be reduced during this process[109].

Recommendations:

i. We recommend that FMT material stored frozen at -80°C should be regarded as having a maximum shelf life of six months from preparation (GRADE of evidence: low; strength of recommendation: strong).

ii. We suggest consideration of thawing frozen FMT at ambient temperature, and using within six hours of thawing (GRADE of evidence: low; strength of recommendation: weak).

iii. We suggest not thawing FMT in warm water baths, due to the risks of cross contamination with Pseudomonas (and other contaminants) and reduced bacterial viability (GRADE of evidence: very low; strength of recommendation: weak).

5.5. What factors related to administration of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

5.5.1. Use of specific medications in the period around FMT administration:

5.5.1.1. General principles of FMT administration:

Bowel purgatives have been proposed pre-FMT as a means of removing residual antibiotics that may affect engraftment of transplanted microorganisms, and as a means of removing any residual *C. difficile* toxin, spores and vegetative cells[110–114]. Furthermore, bowel purgatives pre-colonoscopic FMT delivery facilitate safe endoscopy. Various bowel purgatives have been used in colonoscopic FMT studies, including polyethylene glycol (PEG) (often 4 litres)[14,17,115–117,35,41,43,46,54–56,100], MoviPrep®[35,41], and macrogol[13,15,18,59]. In those studies that used an upper GI route for FMT, PEG[54,55,84] and Klean-Prep®[15,61] were used. FMT without bowel preparation has also been used as treatment for recurrent CDI without any apparent reduction in efficacy, including in randomised studies[16].

The rationale for the use of proton pump inhibitors (PPI) prior to upper GI FMT is to minimise acidity which may impair engraftment of transplanted microorganisms; however, PPIs have been shown to alter the gut microbiota[118,119], and have also been associated with primary and recurrent CDI[120,121]. Some studies advocate the use of PPI prior to receiving FMT via the upper GI route[37,39,45,84,85,122,123], but there appears to be comparable efficacy data in studies where it has not been used. Certain studies have also given recipients PPI prior to receiving colonoscopic FMT[17,87].

The use of prokinetics (such as metoclopramide) has been described prior to FMT delivery via the upper GI tract route, but only in a very small number of studies[85]. Given the potential risk of regurgitation/aspiration associated with upper GI administration of FMT, the working group felt that its use should be considered where appropriate.

A single dose/ short course of loperamide has been used following FMT (predominantly for lower GI administration) in an attempt to prolong the exposure of the FMT to the mucosa, and to aid retention of the FMT within the GI tract[13,46,49,55,84,123]. One study utilised diphenoxylate with atropine[54] instead. However, no studies have compared FMT with and without anti-motility drugs.

The working group also discussed infection control aspects as they apply to FMT administration. Specifically, they agreed that recipients should ideally be cared for in a single room with en-suite bathroom facilities and, where appropriate, be placed at the end of an endoscopy list, to facilitate enhanced environmental decontamination and prevention of transmission of *C. difficile* spores. Protocols for decontamination of endoscopes should follow national guidance[124,125], using a sporicidal agent. Best practice for prevention of transmission of healthcare-associated infections, as described in national guidelines[126], should also be applied throughout.

Recommendations:

i. We recommend that bowel lavage should be administered prior to FMT via the lower GI route, and bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred (GRADE of evidence: low; strength of recommendation: strong).

ii. For upper GI FMT administration, we suggest that a proton pump inhibitor should be considered, e.g. the evening before and morning of delivery (GRADE of evidence: low; strength of recommendation: weak).

iii. We suggest that a single dose of loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery (GRADE of evidence: low; strength of recommendation: weak).

iv. We suggest that prokinetics (such as metoclopramide) should be considered prior to FMT via the upper GI route (GRADE of evidence: low; strength of recommendation: weak).

v. We recommend that best practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc) (GRADE of evidence: high; strength of recommendation: strong).

5.5.1.2. Additional antibiotics pre-FMT:

Many studies have given further courses of conventional antimicrobial *C. difficile* treatment prior to FMT. Regimens have included vancomycin alone[12,14,18,35,39,55,59,86,117], metronidazole or

vancomycin[40,41,43,122], or alternatively vancomycin, fidaxomicin or metronidazole[56], with one study using a range of regimens which included rifaximin[123]. The length of treatment was also variable, ranging from 24 hours[54] up to four days prior to receiving FMT[39,45]; however, comparative studies have not been undertaken.

Recommendation:

We recommend the administration of further antimicrobial treatment for CDI for at least 72 hours prior to FMT (GRADE of evidence: low; strength of recommendation: strong).

5.5.1.3. Washout period between antibiotic use and FMT:

Nearly all studies specified a washout period after completing anti-CDI antibiotics and before administration of FMT. However, this time period appeared to be arbitrarily selected and varied from as little as four[46] or 12 hours[51], up to 72 hours[36]. The majority of studies specified either 24 hours[15,37,39,40,45,54,127] or 48 hours[41,42,49,60], however some allowed a range from 1-3 days[16,44,52,53,55]. One study appeared to allow co-administration of vancomycin with bowel preparation, without a washout period[18].

The working group discussed the challenging scenario of providing FMT to patients with recurrent CDI, but who also had a strong indication for long-term non-anti-CDI antibiotics (e.g. splenectomy, osteomyelitis, or infective endocarditis), or patients who develop an indication for antibiotics for a reason other than CDI shortly after receiving FMT. The concern in this instance is that the use of antibiotics may limit engraftment of microbial communities derived from the FMT, and therefore reduce its effectiveness. The working group discussed a recent retrospective study demonstrating that exposure to non-anti-CDI antimicrobials within eight weeks of FMT is associated with an approximate threefold risk of FMT failure (*n*=8/29 failures with antibiotic exposure *vs* 36/320 failures without antibiotic exposure)[128]. Similarly, the experience of the large pan-Netherlands stool bank[129] was that ~50% of their failures of FMT in the treatment of recurrent CDI occurred in patients who had received antibiotics within one month of their FMT. For patients requiring long-term antibiotics, the working group's expert opinion was that such patients should still be eligible for FMT, but that the regimen for the use of non-anti-CDI antibiotics should be decided on a case-by-case basis, based on factors including response to FMT and/or strength of indication of antibiotics. Both in this scenario, and the scenario in which antibiotics are required shortly after receiving FMT, the working

party agreed that infectious diseases specialists/medical microbiologists should be involved in making decisions regarding the choice of agents used.

Recommendations:

iii. To minimise any deleterious effect of antimicrobials on the FMT material, we recommend that there should be a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT (GRADE of evidence: low; strength of recommendation: strong).

iv. We suggest considering consultation with infectious disease specialists or medical microbiologists for advice whenever FMT recipients also have an indication for long-term antibiotics, or have an indication for non-CDI antibiotics within eight weeks of FMT (GRADE of evidence: very low; strength of recommendation: weak).

5.5.2. Route of FMT delivery:

5.5.2.1. Introduction:

FMT can be delivered via the lower GI route (retention enema, colonoscopy), upper GI route (endoscopically, or via nasogastric tube, nasoduodenal or nasojejenal tube), or via capsules (containing either frozen FMT or lyophilised faecal material). Systematic reviews with meta-analysis suggest that FMT for recurrent CDI via colonoscopy may have slightly higher efficacy compared to upper GI administration[127,130–132] with similar safety profiles, but also note the trend towards using larger amounts of stool or 'higher concentration' FMT in lower GI administration. One systematic review (reviewing principally case series, and including only one randomised study) compared remission rates for CDI using FMT delivered to different areas of the GI tract, and reported that for FMT infused into the stomach, duodenum/jejunum, caecum/ascending colon, and rectum the rates of cure rate were 81%, 86%, 93%, and 84%, respectively[131].

In the only randomised study that directly compared upper and lower GI administration, there was no significant difference in overall cure rate ($p = 0.53$)[17].

5.5.2.2. Upper gastrointestinal tract administration of FMT:

FMT has been shown to be safe and efficacious in the treatment of *C. difficile* when administered via nasogastric tube[37,39,45,61,83,123], nasoduodenal tube[15,84,85], enteroscopy[122,123], or via the infusion channel on a gastroscope[40,45]. In a randomised trial, nasoduodenal donor FMT has been shown to be more efficacious than vancomycin in treating recurrent CDI[15]. Furthermore, it has been shown that FMT can also be safely and effectively delivered via a percutaneous endoscopic gastrectomy tube[45,83]. The working group noted that upper GI administration of FMT may be particularly suitable for certain patient groups, such as those in whom there are contraindications or who would find it difficult to tolerate lower GI endoscopy, and/ or patients unlikely to be unable to retain enemas.

Typically, smaller volumes of faecal suspension are administered to the upper GI tract compared to lower GI administration, with quoted volumes ranging from 25ml[39] up to 150ml[84]- 250ml[37,85]. Up to 500ml of suspension has been given safely and effectively via the upper GI route[15,77]. However, the working group expressed concerns regarding the risk of regurgitation and aspiration if large volumes of FMT are administered to the upper GI tract, and also discussed cases in which this has been described with adverse outcomes[80]. This included a reported death from aspiration, after 100-150ml of FMT was delivered by enteroscope into the distal duodenum under general anaesthetic as attempted treatment for recurrent CDI[133]. A further reported case described a case of fatal aspiration pneumonitis likely related to a 500ml FMT via nasoduodenal tube; this patient had a swallowing disorder following oropharyngeal radiation after surgical removal of a maxillary carcinoma two years previously[77]. Based on their expert opinion, the working group recommended that upper GI FMT should be used with caution in those at risk of regurgitation (e.g. known large hiatus hernia, severe gastro-oesophageal reflux disease, etc) and/ or with swallowing disorders (although administration via a gastrostomy tube would be acceptable). They also recommended that no more than 100ml of FMT should be administered to the upper GI tract to minimise these risks.

Recommendations:

i. We recommend that upper GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate (GRADE of evidence: high; strength of recommendation: strong).

ii. Where upper GI administration is considered most appropriate, we recommend that FMT administration should be via nasogastric, nasoduodenal, or nasojejunal

tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate (GRADE of evidence: high; strength of recommendation: strong).

v. We recommend that no more than 100ml of FMT is administered to the upper GI tract (GRADE of evidence: low; strength of recommendation: strong).

vi. We recommend that upper GI administration of FMT should be used with caution in those at risk of regurgitation and/ or those with swallowing disorders (GRADE of evidence: low; strength of recommendation: strong).

5.5.2.3. Lower gastrointestinal tract administration of FMT:

FMT via enema: Successful treatment of *C. difficile* with FMT enema has been demonstrated[16,38,42,53,55,83,86] but enema appears to have a lower efficacy than other routes of FMT administration. Specifically, in a randomised study primarily comparing the efficacy of fresh and frozen FMT in the treatment of recurrent CDI, only 52.8% of patients in the 'frozen' arm and 50.5% of patients in the 'fresh' arm of the study (*n*=57/108 and 56/111 respectively) experienced resolution of symptoms after a single enema, by modified intention to treat analysis[16]. However, resolution rates in both arms only reached >80% after at least three enemas[16]. A recent randomised study demonstrated similar rates of recurrence of CDI in patients with recurrent CDI treated with either a single FMT enema or a six week vancomycin taper (*n*=9/16 patients with recurrence vs 5/12 respectively)[12]. Notwithstanding this, enemas do have specific advantages, such as being a treatment option where full colonoscopy is contraindicated. It is also possible to give multiple infusions relatively easily and outside a hospital setting.

FMT via colonoscopy: Randomised study evidence has demonstrated that colonoscopic FMT has higher efficacy in treating recurrent CDI than vancomycin[18]**.** Efficacy is similar whether FMT is fresh or frozen, but modestly reduced when using a lyophilised FMT product[13]. Colonoscopic delivery of donor FMT into the ileum or caecum was associated with a 91% cure rate for recurrent CDI[14]. Observational studies highlighted similar success, describing cure rates of 88% (*n*=14/16)[74] and 91%[46] (*n*=21/23) in response to infusion of donor FMT into the caecum or terminal ileum. A further advantage of using colonoscopy to administer FMT has been to allow assessment for the presence of pseudomembranes; in certain reviewed studies, the presence or absence of pseudomembranes has influenced the FMT regimen used[18,73]. However, the working group noted that that many patients

with CDI are frail and elderly, and as such it will not always be safe or feasible to undertake colonoscopy in this particular group of patients. Flexible sigmoidoscopy appears to be an feasible option where full colonoscopy cannot be performed e.g. unable to tolerate colonoscopy, severity of colitis[56,60].

The amount of faecal suspension via enema has varied between 150-500mls[16,38,42,55,86]. The amount of faecal suspension delivered via colonoscopy has been similarly variable, with some studies suggesting as little as 100ml can be used with success rates of 94%[43]. 250ml-400ml had a success rate of 100%[36], whereas infusions of up to 500-700ml were associated with cure rates of 92%[46]. However, the working group noted that it is difficult to compare 'concentration' of FMT in different studies as different protocols used varied starting amounts of faecal material. Currently, there are no randomised studies that compare concentration/ volume of colonoscopic or enema FMT. As such, no recommendation was made to this regard.

Recommendations:

i. We recommend that colonoscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate (GRADE of evidence: high; strength of recommendation: strong).

ii. Where colonoscopic administration is used, we suggest considering preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate (GRADE of evidence: low; strength of recommendation: weak).

iii. We recommend that FMT via enema should be used as a lower GI option when delivery using colonoscopy or flexible sigmoidoscopy is not possible (GRADE of evidence: high; strength of recommendation: strong).

5.5.2.4. Capsulised FMT:

Capsulised FMT aims to remove some of the concerns regarding conventional FMT, such as the invasive means of administration and palatability. The largest case series describing the use of capsules as treatment for recurrent CDI[72,89] noted clinical resolution at eight weeks off antibiotics for CDI in 82% of cases (*n*=147/180) after one course of capsules, and 91% (*n*=164/180) after two courses. The capsules contained frozen FMT prepared in a diluent of saline with 10% glycerol; 15

capsules were administered each day for two consecutive days (equating to a mean 48g of original crude stool). Other smaller case series have demonstrated comparable results[87,123,134], including when lyophilised stool is used instead of frozen whole FMT[134].

The working group reviewed two randomised studies which have examined the efficacy of capsulised FMT in treating recurrent CDI. In one study, published in abstract form[94], a 'high dose' regimen of frozen FMT capsules (30 capsules each day for two days) was compared to 'low dose' (30 capsules in one day). CDI resolution was comparably high in both arms with one treatment course (77% (*n*=7/9) in the 'high dose' arm vs 70% (*n*=7/10) in the 'low dose arm'). 4/5 initial non-responders entered remission after a second capsule course with the 'high dose' regimen[94]. In a recent large randomised trial, patients with recurrent CDI were randomised to receive either thawed frozen FMT either via colonoscopy or via capsules (one treatment of 40 capsules)[11]. On per protocol analysis, remission at 12 weeks after a single treatment occurred in 96% in both arms (*n*=51/53 by capsule, *n*=50/52 by colonoscopy).

The working group discussed certain unresolved issues regarding capsules. Specifically, capsules are often large, and swallowing 30 capsules in a single day may be a significant undertaking for patients with CDI, such as the frail elderly with an existing high pill burden. They also noted that follow-up data post-capsule administration is relatively short compared to other modalities of FMT.

Recommendation:

Capsulised FMT holds promise as a treatment option for recurrent CDI and we recommend that this should be offered to patients as a potential treatment modality where available. Capsule preparations should follow a standard protocol. Further evidence regarding optimal dosing and formulation is required (GRADE of evidence: high; strength of recommendation: strong).

5.6. What is the clinical effectiveness of FMT in treating conditions other than *Clostridium difficile* infection?

5.6.1. Introduction:

In current clinical practice, FMT is used predominantly in the treatment of recurrent CDI. Its success has led to exploration of its efficacy in other GI diseases, primarily ulcerative colitis (UC), where perturbation of the gut microbiota has been observed and implicated in disease pathogenesis[135]. Due to variability of the quality, methodology and cohorts of patients recruited in trials of FMT for non-CDI indications, and in order to control for significant confounding factors, the working group only included randomised trials involving patients with well-defined conditions and in which there was a primary clinical outcome. To date, there have been a total of 71 such studies investigating the role of FMT in IBD; of these, only four are prospective randomised controlled trials, limited to patients with ulcerative colitis[136–139]. Five other reviewed randomised studies investigated the use of FMT in irritable bowel syndrome[140], slow transit constipation[141], hepatic encephalopathy[142] and metabolic syndrome[143,144].

5.6.2. Use of FMT for ulcerative colitis:

5.6.2.1. Efficacy:

All four RCTs, with a total of 277 subjects, included patients with mild to moderate UC (Mayo score 3-11 and endoscopic sub-score of at least 1). Participants were aged between 27 and 56 years and largely included patients on stable immunosuppressive therapy (only one study excluded patients using biologic treatments and methotrexate within the preceding two months)[136]. Three studies included patients on oral corticosteroids at the time of FMT, however only two required a mandatory wean of these to meet eligibility. Studies generally included patients with all disease distributions found in UC. Time to evaluation of response to FMT in these studies varied between seven and twelve weeks. Two studies used autologous FMT as placebo[136,139]. Three of the four studies demonstrated that patients receiving donor FMT were significantly more likely to achieve clinical and endoscopic remission compared to placebo[137–139]. The pooled rate of combined clinical and endoscopic remission was 27.9% for donor FMT and 9.5% for placebo. A pooled risk ratio for failure of FMT to achieve these combined outcomes was 0.8 (95% CI: 0.7-0.9). Deep remission (histological) was only reported in one RCT: 18.4% of patients receiving FMT achieved this outcome compared to 2.7% of those receiving placebo[137].

5.6.2.2. Characteristics of FMT preparation and delivery:

The four RCTs varied in their FMT preparation and delivery methodology. Two RCTs delivered frozen FMT, one fresh FMT, and one used a combination. Three RCTs with a positive outcome delivered the FMT via the lower GI route; these studies used a high intensity protocol ranging from a total of three

infusions in one week to 40 FMTs over an eight week period[137–139]. The other RCT (that failed to show efficacy of FMT for UC) had adopted a low intensity protocol of two nasoduodenal infusions given three weeks apart[136]. Interestingly, the only RCT that prepared stool in anaerobic conditions demonstrated the highest rate of steroid-free clinical remission and steroid-free clinical response with donor FMT[139]. A further interesting observation in one study was a trend towards higher rates of remission with one particular donor[137].

5.6.2.3. Adverse events:

Short-lived GI symptoms such as abdominal bloating, cramps, diarrhoea and fever were reported in patients receiving FMT for UC. There were no significant differences in serious adverse events between patients receiving FMT compared to placebo (10 *vs* 7 respectively). Most of the serious adverse events were a consequence of worsening colitis: one patient who received FMT required a colectomy[136]. In addition, one patient developed concurrent CDI[137]. No deaths were reported in any of the studies.

5.6.3. Use of FMT in functional bowel disorders:

Two RCTs have investigated the role of FMT in functional bowel disorders. In a double-blind placebo controlled RCT that recruited 90 patients with IBS with diarrhoea or with diarrhoea and constipation[140], the primary endpoint only just reached statistical significance in inducing symptom relief (as assessed by 75 point reduction in IBS-severity scoring system at three months following a single infusion FMT by colonoscopy) (p=0·049). The second RCT randomised 60 patients with slow transit constipation to either six consecutive days of nasogastric-delivered FMT or conventional treatment[141]. This demonstrated that a significant proportion of patients achieved the primary endpoint of a mean of at least three complete spontaneous bowel movements per week (53.3% vs. 20.0%, p= 0.009) along with improvement in stool consistency score and colonic transit time. However, the intervention group had more treatment-related adverse events than did the control group (total of 50 *vs* 4 cases).

5.6.4. Use of FMT in hepatic encephalopathy:

One small study has investigated the role of FMT in the management of hepatic encephalopathy (HE)[142]. This RCT randomised 20 male patients with cirrhosis with refractory HE to receive either five days of broad-spectrum antibiotic pre-treatment followed by a single FMT enema or standard of

care. Patients in the FMT arm had a significantly lower incidence of serious adverse events and improved cognition. The Model for End-Stage Liver Disease (MELD) score, however, transiently worsened post-antibiotics in the FMT arm. The study was potentially confounded as patients in the FMT arm continued to receive lactulose and/or rifaximin for treatment of their HE.

5.6.5. Use of FMT for metabolic syndrome:

Two randomised studies[143,144], with a combined total of 56 patients, demonstrated an improvement in peripheral (but not hepatic) insulin sensitivity in Caucasian male obese patients with metabolic syndrome following one or two infusions via nasoduodenal tube of FMT obtained from lean donors. This improvement was observed at six weeks post-FMT, but was no longer present by 18 weeks. No improvement in insulin sensitivity was identified in patients transplanted with autologous FMT (i.e. patients transplanted with their own collected faeces). The improvement in peripheral insulin sensitivity in the lean donor FMT group was accompanied by a small but significant improvement in HbA1c at six weeks[144], but no improvements in other metabolic parameters, such as weight. Whilst these data are of interest, the working group felt that the limited, transient nature of the benefits seen and small size of the studies meant that FMT could not be recommended as treatment for metabolic syndrome.

5.6.6. Future directions for randomised trials of FMT for non-CDI indications:

Currently there are a large number of randomised trials (including RCTs) being undertaken globally, to evaluate the potential role of FMT as treatment for a wide range of conditions. The working group concluded that until there are more reliable data to inform decision-making, the best practice principles described in this document for the governance of an FMT service for recurrent CDI should also be applied to FMT clinical trials for other conditions. However, specific adaptations may be considered depending on the condition being studied, e.g. consideration of using anaerobic conditions for the preparation of FMT in trials for the treatment of UC, as described above.

In conclusion, FMT has the potential to be an effective treatment option for mild to moderate ulcerative colitis, and appears to be safe despite the use of immunosuppressive therapy. FMT may also have a potential role in the treatment of functional bowel disorders. However, recommendations for clinical use for both these indications cannot be made until there is clearer evidence of the most appropriate patient characteristics, preparation methodology, route of delivery

and intensity of administration of FMT. The evidence for the use of FMT in hepatic encephalopathy and metabolic syndrome is currently limited, and further well-designed RCTs are needed to evaluate its potential role here.

Recommendation:

We do not currently recommended FMT as treatment for inflammatory bowel disease. Apart from CDI, there is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease (GRADE of evidence: moderate; strength of recommendation: strong).

6. Basic requirements for implementing a FMT service:

As discussed above, there is an absence of published studies to support the recommendations in this section (although the experience of setting up a nationwide stool bank has recently been reported from the Netherlands[129]). This section is therefore based on the working group's expert opinion and experience of developing FMT services. The working group considered best practice in this area as it applied to legal and clinical governance aspects, the relevant professionals required to establish an FMT service, the infrastructure of a service, and appropriate practices for FMT manufacturing and quality control monitoring where relevant. The full text of this section is in **Supplementary Material 3.**

7. Key performance indicators:

- All donors to have completed initial screening questionnaires and blood and stool screening results, as well as final health check prior to each stool donation processed to FMT. Results from each subsequent serial round of screening also to be documented.
- All FMT recipients to have clear documentation of details of their disease course and preparation prior to FMT, including whether recurrent or refractory disease, previous antimicrobial courses, and use of bowel purgatives/other preparatory medications pre-FMT.
- All FMT recipients to have sufficient documentation to allow clear traceability of the exact FMT aliquot transfused. Records should include identification of the donor, as well as a frozen FMT aliquot (and original faecal sample) - as well as serum - from that donor (see **Supplementary Material 3**).

- All FMT recipients for recurrent or refractory CDI to have documentation during follow-up of treatment success or failure (and subsequent treatment plan if failure), together with clear documentation of any adverse events that may be attributable to FMT.

8. Further research:

- As described within this guideline, many aspects of the terminology of CDI are used variably between studies, and end-points in FMT trials are inconsistent. The working group noted the need to standardise this terminology to allow more robust comparisons between studies.
- Given the relative novelty of FMT as a procedure, any potential long-term adverse events associated with its use are poorly-defined. The establishment of formal FMT registries should be considered. Whilst this would primarily act as an important tool for defining the safety and efficacy of FMT, it would also be a valuable database for researchers within the field. Standardisation of other key documentation related to FMT administration (e.g. establishment of a proforma for assessing eligibility for FMT and/or follow-up after FMT) would also be advantageous for the same reasons.
- The working group noted the lack of consistency in definitions related to the severity of CDI disease and to response or failure to FMT. This limited interpretation of the published studies. As such, the working group thought that standardisation of these definitions would allow more accurate delineation of the factors influencing the efficacy of FMT for CDI. The working group also noted that only one reviewed study had reported the relationship between *C difficile* ribotype and FMT outcome, and that recording of this information should be encouraged better to evaluate its influence.
- Further well-designed clinical trials (in particular, RCTs) are required to identify the optimal means of administration of FMT as treatment for recurrent and/or refractory CDI.
- The working group noted that even capsulised FMT may be associated with potential drawbacks. They also noted that there are many patients with recurrent CDI for whom FMT (or any form of 'bacteriotherapy') may be inappropriate, including those with very marked immunosuppression, and/or multi-organ disease. Despite high levels of efficacy, there is a small but appreciable FMT failure rate and it is not currently understood whether this is due to underlying donor or recipient factors. Therefore, a research priority should be in basic and translational studies better to define the mechanisms underlying the efficacy of FMT in CDI. This includes comparing the structure and function of the microbiota of donors to patients pre-FMT and post-FMT, via techniques including next-generation microbial sequencing, metabolic profiling, and

immunological assays. This would allow the refinement of FMT from its current state to a more targeted therapy, removing the concerns associated with FMT.

- The working group identified a need for further well-designed RCTs to investigate the potential role of FMT for non-CDI indications.

9. Conclusions:

FMT has become an accepted, efficacious treatment for recurrent and/or refractory CDI. In developing this guideline, the evidence for the technique has been reviewed in the context of other available treatments. Specific guidance for best practice for an FMT service is provided.

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11.Competing interests:

- THI: Acted as consultant, advisor or speaker for Pharmacosmos and Shield Therapeutics.
- ALH: Acted as consultant, advisory board member or speaker for AbbVie, Atlantic, Bristol-Myers Squibb, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. ALH also serves on the Global Steering Committee for Genentech.
- SDG: Received consultancy fees, speaker fees and research grant support from Astellas between 2015-2017; received consultancy fees and speaker fees from MSD between 2015-2017; and received consultancy fees in 2017 from Pfizer.
- All other authors declared no conflict of interest.

12.Provenance and peer review:

Commissioned. Peer review through stakeholder consultation, HIS (SDC and Council), BSG (CSSC and Council) and externally.

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15. Figure legends and tables:

Figure 1: Proposed summary pathway for donor screening for centres preparing frozen FMT from recurring donors.

Table 1: Recommended donor history/ questionnaire: A positive response to any of these questions would usually result in exclusion from further consideration as a donor, although this would depend upon the particular circumstances/ answers given.

1. Receipt of antimicrobials within the past three months.
2. Known prior exposure to HIV and/ or viral hepatitis, and known previous or latent tuberculosis.
3. Risk factors for blood-borne viruses - including high risk sexual behaviours, use of illicit drugs, any tattoo/ body piercing/ needlestick injury/ blood transfusion/ acupuncture, all within the previous six months.
4. Receipt of a live attenuated virus within the past six months.
5. Underlying gastrointestinal conditions/ symptoms (e.g. history of IBD, IBS, chronic diarrhoea, chronic constipation, coeliac disease, bowel resection or bariatric surgery) - also including acute diarrhoea/ gastrointestinal symptoms within the past two weeks.
6. Family history of any significant gastrointestinal conditions (e.g. family history of IBD, or colorectal cancer).
7. History of atopy (e.g. asthma, eosinophilic disorders).
8. Any systemic autoimmune conditions.
9. Any metabolic conditions, including diabetes and obesity.
10. Any neurological or psychiatric conditions, or known risk of prion disease.
11. History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia.
12. History of any malignancy.
13. Taking particular regular medications, or such medications within the past three months, i.e. antimicrobials, proton pump inhibitors, immunosuppression, chemotherapy
14. History of receiving growth hormone, insulin from cows, or clotting factor concentrates.
15. History of receiving an experimental medicine or vaccine within the past six months.
16. History of travel to tropical countries within the past six months.

Table 2: Recommended blood screening for stool donors: *EBV and CMV testing is 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 if exposed to CMV and EBV.

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

General/ metabolic screening:

- Full blood count with differential.
- Creatinine and electrolytes
- Liver enzymes (including albumin, bilirubin, aminotransferases, gamma-glutamyltransferase and alkaline phosphatase).
- C-reactive protein

Table 3: Recommended stool screening for stool donors: *Whilst CPE and ESBL are the only multi-drug resistant bacteria that are recommended to be screened for universally, consider testing for other resistant organisms (including vancomycin-resistant *Enterococci* (VRE) and/ or methicillin-resistant *Staphylococcus aureus* (MRSA)) based upon risk assessment and local prevalence.

- *Clostridium difficile* PCR
- *Campylobacter, Salmonella,* and *Shigella* by standard stool culture and/ or PCR
- Shiga toxin-producing *Escherichia coli* by PCR.
- Multi-drug resistant bacteria, at least carbapenemase-producing *Enterobacteriaceae* (CPE) and extended-spectrum beta-lactamases (ESBL)*.
- Stool ova, cysts and parasite analysis, including for *Microsporidia.*
- Faecal antigen for *Cryptosporidium* and *Giardia.*
- Acid fast stain for *Cyclospora* and *Isospora.*
- *Helicobacter pylori* faecal antigen.
- Norovirus, Rotavirus PCR.

Table 4: A summary of the GRADE system:

GRADE - strength of evidence:	GRADE - strength of recommendation:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.	*The trade-offs:* Taking into account the estimate size of the effect for main outcomes, the confidence limits around those estimates and the relative value placed on each outcome.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	*The quality of the evidence.*
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	*Translation of the evidence into practice in a particular setting:* Taking into consideration important factors that could be expected to modify the size of expected effects.
Very low quality: Any estimate of effect is very uncertain.	*Uncertainty about the baseline risk for the population of interest.*

Table 5: Criteria for stool collection:

Clear instructions should be given to donors regarding hand hygiene.
Collect stool donations in a sealable clean container. A number of specifically designed devices are available commercially.
Stool should ideally be passed directly into the clean container for collection; alternatively, it may be collected in clean tissue and transferred to the clean container.
Stool should be transported to the FMT production site as soon as possible post defaecation (and within six hours); however, if a short period of storage is necessary, this should be at 4°C.

HIS/ BSG FMT Guideline: Main Document, *Gut* version.

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

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HIS/ BSG FMT Guideline: Main Document, *Gut* version.

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Abbreviations:

FMT	faecal microbiota transplant
CDI	*Clostridium difficile* infection
EBV	Epstein-Barr virus
CMV	cytomegalovirus
BMI	body mass index
GI	gastrointestinal
RCT	randomised controlled trial
NAAT	nucleic acid amplification test
GDH	glutamate dehydrogenase
EIA	enzymes immunoassay
PCR	polymerase chain reaction
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome

HIV	human immunodeficiency virus
AIDS	acquired immune deficiency syndrome
CPE	carbapenemase-producing *Enterobacteriaceae*
ESBL	extended-spectrum beta-lactamase
VRE	vancomycin-resistant *Enterococci*
MRSA	methicillin-resistant *Staphylococcus aureus*
PPI	proton pump inhibitor
UC	ulcerative colitis
HE	hepatic encephalopathy
MELD	Model for End-Stage Liver Disease

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1. Abstract:

Interest in the therapeutic potential of faecal microbiota transplant (FMT) has been increasing globally in recent years, particularly as a result of randomised studies in which it has been used as an intervention. The main focus of these studies has been the treatment of recurrent or refractory *Clostridium difficile* infection (CDI), but there is also an emerging evidence base regarding potential applications in non-CDI settings. The key clinical stakeholders for the provision and governance of FMT services in the United Kingdom (UK) have tended to be in two major specialty areas: gastroenterology and microbiology/infectious diseases. Whilst the National Institute for Health and Care Excellence (NICE) guidance (2014) for use of FMT for recurrent or refractory CDI has become accepted in the UK, clear evidence-based UK guidelines for FMT have been lacking. This resulted in discussions between the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS), and a joint BSG/HIS FMT working group was established. This guideline document is the culmination of that joint dialogue.

2. Executive summary:

2.1. Overview:

The remit of the British Society of Gastroenterology (BSG)/ Healthcare Infection Society (HIS) working group was to provide recommendations as to best practice in the provision of a faecal microbiota transplant (FMT) service. This guideline considers the use of FMT for the treatment of *Clostridium difficile* infection (CDI) – as well as for potential non-CDI indications – in adults. The working group have primarily targeted their report at clinicians involved in the use and provision of FMT services, but have also aimed it to be of interest to patients and their relatives.

2.2. Summary of recommendations:

2.2.1. Which patients with *Clostridium difficile* infection should be considered for faecal microbiota transplant, and how should they be followed up after treatment?

2.2.1.1. Prior to faecal microbiota transplant. Patient selection:

2.2.1.1.1. Recurrent *Clostridium difficile* infection:

We recommend that FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.1.1.2. Refractory *Clostridium difficile* infection:

We recommend that FMT should be considered in cases of refractory CDI *(GRADE of evidence: moderate; strength of recommendation: strong).*

2.2.1.1.3. FMT as initial therapy for *Clostridium difficile* infection:

We recommend that FMT should not be administered as initial treatment for CDI *(GRADE of evidence: low; strength of recommendation: strong)*.

2.2.1.1.4. Antimicrobial/ antitoxin therapy prior to considering FMT for patients with CDI:

i. We recommend that FMT for recurrent CDI should only be considered after recurrence of symptoms following resolution of an episode of CDI that was treated with appropriate antimicrobials for at least 10 days *(GRADE of evidence: low; strength of recommendation: strong).*

ii. We recommend consideration of treatment with extended/ pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI *(GRADE of evidence: low; strength of recommendation: strong).*

iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, we recommend that consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.1.2. Post-FMT follow-up, outcomes and adverse events:

2.2.1.2.1. Management of FMT failure:

We recommend that FMT should be offered after initial FMT failure *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.1.2.2. General approach to follow-up post-FMT:

We recommend that all FMT recipients should routinely receive follow-up. Clinicians should follow-up FMT recipients for long enough to fully establish efficacy/adverse events, and for at least eight weeks in total *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.1.2.3. Management of the FMT recipient:

i. We recommend that immediate management after endoscopic administration of FMT should be as per endoscopy unit protocol *(GRADE of evidence: very low: strength of recommendation: strong).*

ii. We recommend that patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare *(GRADE of evidence: very low; strength of recommendation: strong).*

iii. After enteral tube administration, we recommend that patients may have the tube removed and oral water given from 30 minutes post-administration *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.1.2.4. Definition of cure post-FMT for CDI:

We recommend that a decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.1.2.5. Definition of treatment failure post-FMT for CDI:

We recommend that treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for *C. difficile* toxin after FMT is not recommended, but it is appropriate to consider in the case of persistent CDI symptoms/suspected relapse *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.2. What recipient factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

2.2.2.1. General approach to co-morbidities and FMT:

i. We recommend that FMT should be avoided in those with anaphylactic food allergy *(GRADE of evidence: very low; strength of recommendation: strong).*

ii. We suggest that FMT should be offered with caution to patients with CDI and decompensated chronic liver disease *(GRADE of evidence: very low; strength of recommendation: weak).*

2.2.2.2. Immunosuppression and FMT:

i. We recommend that FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects *(GRADE of evidence: moderate; strength of recommendation: strong).*

ii. We recommend that immunosuppressed FMT recipients at risk of severe infection if exposed to EBV or CMV should only receive FMT from donors negative for EBV and CMV *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.2.3. Other comorbidities and FMT:

i. We recommend that FMT should be offered to those with recurrent CDI and inflammatory bowel disease, but patients should be counselled about a small but recognised risk of exacerbation of IBD *(GRADE of evidence: moderate; strength of recommendation: strong).*

ii. We recommend that FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities *(GRADE of evidence: moderate; strength of recommendation: strong).*

2.2.3. What donor factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

2.2.3.1. General approach to donor selection:

We recommend that related or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.3.2. Age and BMI restrictions for potential donors:

We suggest that people should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of ≥18 and ≤30 kg/m^2 *(GRADE of evidence: low; strength of recommendation: weak).*

2.2.3.3. General approach to the donor screening assessment:

It is mandatory to screen potential donors by questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota (**Table 1**) *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.3.4. Laboratory screening of potential donors:

Blood and stool screening of donors is mandatory (**Tables 2 and 3**) *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.3.5. Repeat donor checks, and donation pathway:

i. In centres using frozen FMT, before FMT may be used clinically, we recommend that donors should have successfully completed a donor health questionnaire and laboratory screening assays both before and after the period of stool donation. This is the preferred means of donor screening *(GRADE of evidence: low; strength of recommendation: strong).*

ii. In centres using fresh FMT, we recommend that a repeat health questionnaire should be assessed at the time of each stool donation. To ensure ongoing suitability for inclusion as a donor, the donor health questionnaire and laboratory screening should be repeated regularly *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.4. What factors related to the preparation of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

2.2.4.1. General principles of FMT preparation:

i. We recommend that stool collection should follow a standard protocol *(GRADE of evidence: low; strength of recommendation: strong).*

ii. We recommend that donor stool should be processed within 6 hours of defaecation *(GRADE of evidence: low; strength of recommendation: strong).*

iii. We recommend that both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI *(GRADE of evidence: moderate; strength of recommendation: strong).*

iv. We recommend that sterile 0.9% saline should be considered as an appropriate diluent for FMT production, and cryoprotectant such as glycerol should be added for frozen FMT *(GRADE of evidence: moderate: strength of recommendation: strong).*

v. We recommend using ≥50g of stool in each FMT preparation *(GRADE of evidence: moderate: strength of recommendation: strong).*

vi. We suggest that stool should be mixed 1:5 with diluent to make the initial faecal emulsion *(GRADE of evidence: low; strength of recommendation: weak).*

vii. We suggest that homogenisation and filtration of FMT should be undertaken in a closed disposable system *(GRADE of evidence: low; strength of recommendation: weak).*

2.2.4.2. Fresh vs frozen FMT:

We recommend that the use of banked frozen FMT material should be considered preferable to fresh preparations for CDI *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.4.3. Use of frozen FMT:

i. We recommend that FMT material stored frozen at -80^{o}C should be regarded as having a maximum shelf life of six months from preparation *(GRADE of evidence: low; strength of recommendation: strong).*

ii. We suggest consideration of thawing frozen FMT at ambient temperature, and using within six hours of thawing *(GRADE of evidence: low; strength of recommendation: weak).*

iii. We suggest not thawing FMT in warm water baths, due to the risks of cross contamination with *Pseudomonas* (and other contaminants) and reduced bacterial viability *(GRADE of evidence: very low; strength of recommendation: weak).*

2.2.5. What factors related to administration of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

2.2.5.1. Use of specific medications in the period around FMT administration:

2.2.5.1.1. General principles of FMT administration:

i. We recommended that bowel lavage should be administered prior to FMT via the lower GI route, and that bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred *(GRADE of evidence: low; strength of recommendation: strong).*

ii. For upper GI FMT administration, we suggest that a proton pump inhibitor should be considered, e.g. the evening before and morning of delivery *(GRADE of evidence: low; strength of recommendation: weak).*

iii. We suggest that a single dose of loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery *(GRADE of evidence: low; strength of recommendation: weak).*

iv. We suggest that prokinetics (such as metoclopramide) should be considered prior to FMT via the upper GI route *(GRADE of evidence: low; strength of recommendation: weak).*

v. We recommend that best practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc) *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.5.1.2. Additional antibiotics pre-FMT:

We recommend the administration of further antimicrobial treatment for CDI for at least 72 hours prior to FMT *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.5.1.3. Washout period between antibiotic use and FMT:

i. To minimise any deleterious effect of antimicrobials on the FMT material, we recommend that there should be a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT *(GRADE of evidence: low; strength of recommendation: strong).*

ii. We suggest considering consultation with infectious disease specialists or medical microbiologists for advice whenever FMT recipients also have an indication for long-term antibiotics, or have an indication for non-CDI antibiotics within eight weeks of FMT *(GRADE of evidence: very low; strength of recommendation: weak).*

2.2.5.2. Route of FMT delivery:

2.2.5.2.1. Upper gastrointestinal tract administration of FMT:

i. We recommend that upper GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate *(GRADE of evidence: high; strength of recommendation: strong).*

ii. Where upper GI administration is considered most appropriate, we recommend that FMT administration should be via nasogastric, nasoduodenal, or nasojejunal tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate *(GRADE of evidence: high; strength of recommendation: strong).*

iii. We recommend that no more than 100ml of FMT is administered to the upper GI tract *(GRADE of evidence: low; strength of recommendation: strong).*

iv. We recommend that upper GI administration of FMT should be used with caution in those at risk of regurgitation and/ or those with swallowing disorders *(GRADE of evidence: low; strength of recommendation: strong).*

2.2.5.2.2. Lower gastrointestinal tract administration of FMT:

i. We recommend that colonoscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate *(GRADE of evidence: high; strength of recommendation: strong).*

ii. Where colonoscopic administration is used, we suggest considering preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate *(GRADE of evidence: low; strength of recommendation: weak).*

iii. We recommend that FMT via enema should be used as a lower GI option when delivery using colonoscopy or flexible sigmoidoscopy is not possible *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.5.2.3. Capsulised FMT:

Capsulised FMT holds promise as a treatment option for recurrent CDI and we recommend that this should be offered to patients as a potential treatment modality where available. Capsule preparations should follow a standard protocol. Further evidence regarding optimal dosing and formulation is required *(GRADE of evidence: high; strength of recommendation: strong).*

2.2.6. What is the clinical effectiveness of FMT in treating conditions other than *Clostridium difficile* infection?

We do not currently recommended FMT as treatment for inflammatory bowel disease. Apart from CDI, there is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease *(GRADE of evidence: moderate; strength of recommendation: strong).*

2.2.7. Basic requirements for implementing a FMT service:

2.2.7.1. General considerations:

i. The development of FMT centres should be encouraged *(GRADE of evidence: very low; strength of recommendation: strong).*

ii. We suggest that FMT centres should work to raise awareness about FMT as a treatment option amongst clinicians caring for patients with CDI, and provide training to relevant healthcare professionals on the practicalities of delivering an FMT service *(GRADE of evidence: very low; strength of recommendation: weak).*

2.2.7.2. Legal aspects and clinical governance:

In the UK, FMT must be manufactured in accordance with MHRA guidance for human medicines regulation. When FMT is supplied on a named patient basis, within a single organisation, a pharmacy exemption may be used, subject to ensuring proper governance and traceability. All centres that are processing and distributing FMT should seek guidance from the MHRA and where necessary obtain appropriate licenses prior to establishing an FMT service. This is a legal requirement. In countries other than the UK, FMT should only be manufactured following appropriate approval from the national authority of that country *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.3. Multidisciplinary teams:

We recommend that a multidisciplinary team should be formed to deliver FMT services *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.4. Infrastructure:

We recommend utilisation of suitable laboratory facilities and infrastructure for FMT production *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.5. FMT manufacturing:

We recommend ensuring the traceability of supply *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.6. FMT production quality control:

We recommend monitoring, notification and investigation of all adverse events and reactions related to FMT *(GRADE of evidence: very low; strength of recommendation: strong).*

2.2.7.7. Donor screening governance:

We recommend ensuring the clinical governance of donor screening *(GRADE of evidence: very low; strength of recommendation: strong).*

3. Introduction:

The aim of the BSG/ HIS FMT working group was to establish a guideline that defined best practice in all aspects of a FMT service, by providing evidence-based recommendations wherever possible, and consensus multi-disciplinary expert opinion where specific published evidence is currently lacking. This included the evaluation of the use of FMT in the treatment of *Clostridium difficile* infection (CDI; also referred to as *Clostridioides difficile*[1]), and also in potential non-CDI indications. Relevant guidance published to date includes the interventional procedure guidance from the National Institute for Health and Care Excellence (NICE)[2], UK, European and US microbiological guidelines on the treatment of *Clostridium difficile* infection (CDI)[3–5], and recent expert consensus documents on FMT in clinical practice[6,7]. Furthermore, there have also been national recommendations regarding FMT produced by working groups in several different countries[8–10]. Principally as a result of randomised studies that have been published in recent years[11–18], FMT has become an accepted treatment for recurrent/refractory CDI.

The unique remit and objectives of this guideline when commissioned by the BSG and HIS was:

i. To review the rapidly-growing body of randomised trial evidence for the efficacy of FMT in the treatment of adults (≥18 years), both in CDI and in other clinical conditions, much of which has been published after the publication of current CDI treatment algorithms[3,4].

ii. To provide specific guidance about best practice for an FMT service within the context of the regulatory framework for the intervention as it currently exists in the UK[19,20].

The elucidation of the mechanisms underlying the efficacy of FMT in treating CDI remains an active area of global research, with the aim of rationalising FMT from its current crude form to a more targeted, refined therapeutic modality[21]. Previous research has demonstrated that commensal bacteria cultured from the stool of healthy donors[22], sterile faecal filtrate[23], and/ or spores of *Firmicutes* derived from ethanol-treated stool from healthy donors[24], may have similar efficacy to conventional FMT in treating CDI, although results of the latter approach produced disappointing outcome data when extended to a Phase II clinical trial[25]. For the purposes of this guideline, the BSG/HIS working group considered only studies that used the administration of manipulated whole stool (including encapsulated faeces). They deemed studies using cultured microorganisms (or their

proteins, metabolites or other components), or microbiota suspensions, to be in the pre-clinical research stage, without firm evidence.

FMT has been shown to be very acceptable to patients, both in the setting of CDI[11,26] and in non-CDI settings, e.g. ulcerative colitis[27]. However, the absence of appropriate protocols[28–31] specifically taking into account UK clinical practice and regulation of FMT has been perceived as a barrier to the use of FMT in the UK and Ireland; these guidelines seek to rectify this problem.

4. Guideline development:

4.1. Guideline development team

BSG and HIS commissioned the authors to undertake the Working Party Report. The authors represent the membership of both societies. The working group included gastroenterologists, infectious diseases/microbiology clinicians, a clinical scientist, a systematic reviewer, and patient representatives. The views expressed in this publication are those of the authors, and have been endorsed by BSG and HIS following consultation.

4.2. Scope of the guidelines

The main scope of the guidelines is to provide guidance for the optimal provision of an effective and safe FMT service, principally for recurrent or refractory CDI, but non-CDI indications are also considered. These guidelines only apply to adult patients (≥18 years); the working party did not consider the role of FMT in the treatment of either CDI or non-CDI indications in children or young people. The guidelines were written with a focus upon UK practice, but also with consideration of more global practice as it applied. The diagnosis and management of *Clostridium difficile* infection in general are outside the remit of these guidelines.

4.3. Evidence appraisal

Questions for review were derived from the Working Party Group, which included patient representatives in accordance with the PICO process[32]. To prepare these recommendations, the working group collectively reviewed relevant peer-reviewed research.

4.4. Data sources and search strategy

A systematic literature search was undertaken using MEDLINE, EMBASE databases and Cochrane Library for relevant articles published from 1st January 1980 to 1st January 2018. The MEDLINE and EMBASE strategy are shown in **Supplementary Material 1, Appendix 2ii**. Free text and MESH/ index terms for faecal microbial transplant and *Clostridium difficile* or other diseases of interest were combined. In addition, conference proceedings from microbiology, infectious disease, and gastroenterology conferences were also searched to identify additional studies.

4.5. Study eligibility and selection criteria

The members of the guideline group determined criteria for study inclusion. Two reviewers (BHM, MNQ) screened the titles and abstracts of each article for relevance independently; any disagreements were resolved by discussion with a third reviewer (JPS). Copies of relevant articles were obtained and assessed for inclusion as evidence in the guideline by all three reviewers. The reason for not selecting studies was recorded. Only articles published in English and human clinical studies were included. For evidence on FMT for CDI, both randomised studies (including randomised controlled trials (RCTs)) and case series with at least 10 patients were selected. Only randomised trials were included as evidence for FMT for non-CDI indications. Conference abstracts were only included for CDI and non-CDI indications if they reported a randomised trial; where abstracts were available reporting data from a randomised trial that was subsequently published, only the published paper was reviewed.

4.6. Data extraction and quality assessment

The initial search identified 2658 publications, and of these, 802 duplicates were excluded. 1856 studies were subsequently screened, from which 78 studies were assessed by reviewing the full text for eligibility (see **Supplementary Material 1, Appendix 2iii** and **Supplementary Material 2, Additional Appendix D**). Of these 78 studies, 58 studies were included as the basis of evidence for writing this guideline. In total, 39 were case studies in CDI including at least 10 patients (see **Supplementary Material 2, Additional Appendix C.1)**, and ten were randomised studies in CDI (see **Supplementary Material 2, Additional Appendix C.2**). Nine were randomised trials for non-CDI indications (see **Supplementary Material 2, Additional Appendix C.3**). Data were extracted for patient demographics, disease characteristics, donor screening characteristics, stool preparation and administration, clinical outcomes and adverse events. The quality of randomised studies was

assessed with the Cochrane Collaboration's risk of bias tool. Case series were assessed using the Centre for Reviews and Dissemination guidance.

4.7. Rating of evidence and recommendations

The BSG version of these guidelines was prepared in keeping with the BSG Clinical Services & Standards Committee (CSSC) advice document on the writing of clinical guidelines[33]. Evidence tables were presented and discussed by the working group, and guidelines were prepared according to the nature and applicability of the evidence regarding efficacy and patient preference and acceptability. For the BSG version of this guideline, the GRADE system (Grades of Recommendation Assessment, Development and Evaluation)[34] was used to assess the strength of evidence (high/ moderate/ low/ very low) and strength of recommendation (strong/ weak) (**Table 4**). The section entitled 'Basic requirements for implementing an FMT service' (**Supplementary Material 3**) was based on expert opinion, since this was a key area of the working party's remit but not one amenable to evaluation by the PICO process. Face-to-face meetings and group teleconferences were held to agree on recommendations. Any disagreements on recommendations or the strength of recommendation were resolved by discussion and, where necessary, voting by the members of the working group, with consensus achieved when >80% were in agreement.

4.8. Consultation process

Feedback on draft guidelines was received from the Scientific Development Committee (SDC) of HIS, and changes made. These guidelines were then opened to consultation with relevant stakeholders (see **Supplementary Material 1, Appendix 3** of this document). The draft report was available on the HIS website for one month. Views were invited on format, content, local applicability, patient acceptability, and recommendations. The working group reviewed stakeholder comments, and collectively agreed revisions. Final changes were made after repeat reviews from HIS (Chair of the SDC and HIS Council) and BSG (BSG CSSC and BSG Council), and after further external peer review.

4.9. Guideline accreditation and scheduled review

The guidelines will be reviewed at least every four years and updated if change(s) in the evidence are sufficient to require a change in practice.

4.0. Additional information:

Additional information related to this guideline (including a lay summary, background on the working party report, and information on the implementation of these guidelines) is contained within **Supplementary Material 1, Section 1**.

5. Rationale for recommendations:

5.1. Which patients with *Clostridium difficile* infection should be considered for faecal microbiota transplant, and how should they be followed up after treatment?

5.1.1. Prior to faecal microbiota transplant. Patient selection:

5.1.1.1. Recurrent *Clostridium difficile* infection:

As already described, there is widespread consensus that FMT is an efficacious treatment for recurrent CDI. In defining recurrent CDI, some studies have relied on a minimum threshold of return of clinical symptoms (e.g. at least three unformed bowel movements within 24 hours, for at least two consecutive days)[12,18] following previous successful CDI treatment; most studies have also included a requirement for a positive microbiological test[12,14,18,35–45]. Other studies explicitly state that a positive test was not required[46]. Recommendations for CDI testing are beyond the scope of this guideline, and there are already well-established evidence-based guidelines[47]. These recommend testing with either a nucleic acid amplification test (NAAT) or GDH assay, followed by detection of free toxin (either by toxin A/B enzyme immunoassay (EIA) or cytotoxin neutralisation assay), which allows differentiation of patients with active disease as well as those who are likely colonised[47]. However, the working group discussed the importance of the accurate diagnosis of true recurrent CDI prior to consideration of FMT; in particular, they noted a study which observed that of 117 patients with presumed recurrent CDI referred for work-up for FMT, 25% (*n*=29/117) were determined to have a non-CDI diagnosis, with irritable bowel syndrome (*n*=18) and inflammatory bowel disease (*n*=3) being the most common alternative diagnoses, and younger patients more likely to be misdiagnosed[48].

All of the reviewed studies have included patients with recurrent CDI, however some studies offered FMT to patients at the first recurrence (second episode)[12,15,16,18,35,37,42,43,46,49], whereas others offered FMT after the second recurrence (third episode)[13,14,39,41,44,45,50,51]. Some protocols offered FMT after three or more recurrences[52], whilst others did not define the point at which it was adminstered[40,53].

The severity of infection has been used as a parameter to decide at which stage FMT is offered. Youngster *et al.* offered FMT to patients with at least three episodes of mild to moderate CDI, or at least two episodes of severe CDI resulting in hospitalisation and associated with significant morbidity[17]. Another study selected patients for FMT using four categories of severity, which also accounted for prior anti-CDI therapy and requirement for hospitalisation[54].

None of the studies directly compared the efficacy of FMT according to the stage at which it was offered (i.e. first recurrence vs. ≥ two recurrences). A small number of studies[55–57] included patients with severe CDI (defined as hypoalbuminaemia with increased peripheral white cell count and/or abdominal tenderness) or complicated CDI (defined as admission to Intensive Care, altered mental status, hypotension, fever, ileus, white blood cell count > 30 x 10^9/l, lactate > 2.2mmol/l, or evidence of end organ damage). A single study described an apparent lower rate of treatment success when FMT was used to treat patients with recurrent CDI with disease caused by ribotype 027[43], but this is the case for all anti-CDI treatment modalities for this ribotype in comparison to others. The working group agreed that there was insufficient evidence to suggest that *C. difficile* ribotype should influence whether or not FMT is offered.

A lower primary cure rate was reported for complicated CDI (66%) compared with recurrent CDI (82%) and severe CDI (91%) in one study[55]; in a case series of 17 patients who all had severe and/or complicated CDI, a primary cure rate of 88% was described[57]. A cohort of 328 patients was analysed to determine which factors were associated with failure of FMT[58]. Higher early (one month) failure rates were found in patients with severe (72%, *n*=19/25) or severe-complicated (52.9%, *n*=9/17) CDI than for recurrent CDI (11.9%, *n*=34/286). This study also identified that patients who were treated with FMT as an inpatient were nearly four times more likely to fail as those who had FMT as an outpatient; however, the working group noted that the authors of this study themselves identified that inpatient status is likely a proxy of severity of CDI and/or co-morbidities. A further similar study, including 64 patients treated with FMT as treatment for recurrent CDI, also identified severe CDI as the strongest independent risk factor for FMT failure on multivariate analysis[59].

The working group discussed their experience of treating patients with CDI whose disease fitted an intermediate pattern to the typical descriptions given of recurrent or refractory CDI, e.g. patients with CDI who have some (but incomplete) symptomatic improvement with anti-CDI antibiotics and worsening of disease when these are stopped. The experience of the working group was that such

patients experienced excellent responses to FMT, and that these patients should be considered for FMT.

As FMT is currently an unlicensed medicine with poorly-studied long term sequelae, the working group considered that it should generally be reserved for patients who have had three or more episodes of infection. There are no studies directly comparing its effectiveness with some of the newer agents such as fidaxomicin or bezlotoxumab, hence this recommendation is made on the basis of safety. However, the working group agreed that it may be reasonable in certain patient groups with ongoing risk factors for further recurrence to offer FMT after the second episode.

Recommendation:

<u>We recommend that</u> FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI (GRADE of evidence: high; strength of recommendation: strong).

5.1.1.2. Refractory *Clostridium difficile* infection:

Two randomised trials allowed the recruitment of patients with refractory CDI. The first defined this as at least three weeks of ongoing severe symptoms despite standard antimicrobial therapy for CDI[17]. The second required persistent or worsening diarrhoea and one of the following: ongoing abdominal pain, fever > 38^{o}C, or white blood cell count > 15x 10^{9}/l despite oral vancomycin at a dose of 500mg four times daily for at least five days[16]. Both studies included only small numbers of patients with refractory CDI (*n*=4/20 (20%) and *n*=15/219 (6.8%), respectively). There did not appear to be any significant difference in primary outcome measure (clinical cure) in patients with recurrent or refractory CDI, although neither study was designed to assess this difference. There are also a number of case series in which FMT was given to patients with refractory CDI; however, outcome measures were not reported for these groups individually in these studies[37,38,54,60].

Overall, the working group concluded that there is little consensus on the definition of refractory CDI, with some studies using the terms 'refractory' and 'recurrent' interchangeably (as well as other terms, e.g. 'salvage therapy'). Consequently, the quality of evidence for the utility of FMT in

refractory cases of CDI is lower than for recurrent CDI. The standardisation of definitions will allow more robust comparison between patient cohorts.

Recommendation:

<u>We recommend that</u> FMT should be considered in cases of refractory CDI (GRADE of evidence: moderate; strength of recommendation: strong).

5.1.1.3. FMT as initial therapy for *Clostridium difficile* infection:

Experience of the use of FMT as initial therapy for CDI is very limited. In a case series of patients with CDI with ribotype 027, use of anti-CDI antibiotics together with nasogastric FMT within a week of diagnosis during an initial episode of CDI was associated with reduced mortality when compared to using FMT only after the failure of three courses of antibiotics (mortality of 18.75% (*n*=3/16 patients) vs 64.4% (*n*=29/45 patients))[61]. However, 37.5% (*n*=6/16) of the patients treated with FMT within a week of CDI diagnosis required further antibiotics and a second FMT within one month of the first FMT because of relapse[61]. In a small pilot randomised trial, patients were randomised to either vancomycin or multi-donor FMT (administered either via upper or lower GI routes) as initial therapy for CDI; CDI resolution occurred in 88.9% (*n*=8/9) patients with vancomycin, compared to 57.1% of patients (n=4/7) patients with one FMT, and 71.4% of patients (n=5/7) after two FMTs[62]. Given the small size of these studies and equivocal results, the working group concluded that the reviewed studies did not support FMT as initial therapy for CDI.

Recommendation:

<u>We recommend that</u> FMT should not be administered as initial treatment for CDI (GRADE of evidence: low; strength of recommendation: strong).

5.1.1.4. Antimicrobial/ antitoxin therapy prior to considering FMT for patients with CDI:

There are now at least two licensed agents (fidaxomicin and bezlotoxumab) which have been shown to significantly reduce the risk of recurrence compared with vancomycin[63,64]. There is also some evidence that pulsed/tapered dosing of vancomycin and fidaxomicin (including pulsed fidaxomicin[65]) results in fewer recurrences than with standard dosing of these agents[66,67] (although this finding has

not been replicated in all studies[68]). Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, *n*=12/92) than when treated with vancomycin (26.6%, *n*=29/209)[63]; this finding was replicated in another randomised controlled trial, with 8.3% (*n*=4/48) and 32.6% (*n*=14/43) experiencing a recurrence respectively[69]. In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared to standard of care antibiotics alone (10.9% (*n*=6/55) vs 20% (*n*=13/65) respectively)[64].

As discussed above, the working group noted that there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT[12]. The working group agreed that in the absence of this evidence, on the balance of safety and potential risks, consideration should be given to using antimicrobial/antitoxin therapy associated with reduced CDI recurrence prior to considering the use of FMT.

Several studies specify that patients should be treated with anti-*C. difficile* antibiotics for a minimum period of 10 days before diagnosing recurrent CDI and offering FMT[12,15,16,18].

Recommendations:

i. ***We recommend that FMT for recurrent CDI should only be considered after recurrence of symptoms following resolution of an episode of CDI that was treated with appropriate antimicrobials for at least 10 days (GRADE of evidence: low; strength of recommendation: strong).***

ii. ***We recommend consideration of treatment with extended/ pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI (GRADE of evidence: low; strength of recommendation: strong).***

iii. ***For those with severe or complicated CDI, which appears to be associated with reduced cure rates, we recommend that consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT (GRADE of evidence: low; strength of recommendation: strong).***

5.1.2. Post-FMT follow-up, outcomes and adverse events:

5.1.2.1. Management of FMT failure:

Where patients were deemed not to have responded to an initial FMT, many studies have offered repeat FMT and success rates have been excellent even in patients with modest response to a first FMT[14,15,17,18,35,43,46,51,54,70,71]. The success of a second FMT appears to be high whether treatment failure represents non-response to the first FMT, or a late failure (i.e. further relapse of CDI after an initial response); however, these terms have been defined variably between different studies (also see **Section 5.1.2.5**). Second FMTs have been offered as soon as 24-72 hours after an initial FMT for presumed non-response[37,72,73]. For FMT failure in patients with pseudomembranous colitis, repeat FMT every three days until resolution of pseudomembranes has been a successful approach[18]. Good outcomes in pseudomembranous disease have also been achieved through a protocol that routinely restarted five days of vancomycin if FMT failed, before offering another FMT[73]. Other studies have demonstrated potential success in treating initial FMT failure with further antibiotics, including repeat FMT with vancomycin between procedures[42], or anti-CDI antibiotics alone[35,42,43,45,51,70,71]. Patients unresponsive to two FMTs have been offered further FMT or antibiotic therapy[16], or even the administration of intravenous immunoglobulin[35]. Whilst the working group collectively agreed that there was strong evidence to recommend repeat FMT after initial FMT failure, they were not able to recommend a specific protocol for administering repeat FMT and/ or maximum number of FMTs, given the wide heterogeneity of approach described within the reviewed literature.

Recommendation:

<u>We recommend that</u> FMT should be offered after initial FMT failure (GRADE of evidence: high; strength of recommendation: strong).

5.1.2.2. General approach to follow-up post-FMT:

Follow-up post-FMT (in terms of duration, modality and regimen for follow-up) varies considerably between studies, and is largely dependent upon study design. Follow-up regimens vary not only between studies but within them too, reflecting the retrospective nature of many early FMT studies in CDI, where follow-up mostly reflected pragmatic routine clinical care.

Modalities of follow-up have included outpatient review[14,43,58,71,74–76], telephone interview[17,39,43,46,58,71,74] and case note/ database review[35,39,70,71,74,40,42,43,45,46,49,51,54]. Follow-up duration has varied from 60 days[45] to 8 years[36], with very different durations used in each study. Once again, however, this variability in follow-up largely reflects the retrospective analysis of case

series rather than being justified by any specific methodology. The working group decided by consensus that at least eight weeks of follow-up was appropriate post-FMT to fully assess efficacy and potential adverse events; this figure was also influenced by discussions regarding the timepoint after FMT at which a decision could be made regarding cure/ remission of CDI (see **Section 5.1.2.4**).

Recommendation:

<u>We recommend that all</u> FMT recipients should routinely receive follow-up. Clinicians should follow-up FMT recipients for long enough to fully establish efficacy/adverse events, and for at least eight weeks in total (GRADE of evidence: low; strength of recommendation: strong).

5.1.2.3. Management of the FMT recipient:

Procedural adverse events during administration of FMT have predominantly occurred with colonoscopic administration of FMT. These have included mild nausea and vomiting attributed to sedation for the colonoscopy, minor mucosal tears during colonoscopy[49,60], and microperforation following biopsy of an area of presumed ischaemic small bowel injury in a patient with chronically dilated small bowel (which resolved with conservative management[46]). One death occurred due to witnessed aspiration at the time of colonoscopy[60]. Faecal regurgitation and vomiting with temporal association to upper GI FMT administration has also been described (discussed further in **Section 5.5.2.2**)[77].

The predominant short term adverse events post-FMT for CDI are mild: self-limiting GI symptoms have been the most frequently reported adverse events. These may be related to the route of administration and include belching[15], nausea[15,16,49,60], abdominal cramps/ discomfort/ bloating/ pain[15,18,49,60,72], and diarrhoea[15,16,18,60]. One patient with a history of autonomic dysfunction experienced dizziness with diarrhoea after FMT[15]. These symptoms are typically short-lived, resolving in hours to days[15,16,18,49,72]. Minor subsequent adverse events have included a range of GI side effects including self-limiting abdominal discomfort[14,17,57,76], nausea[14,49,70], flatulence[14,16,17,41,42,49,57], self-limiting irregular bowel movements[41], *C. difficile*-toxin negative diarrhoea[52,55], constipation[14,15,42,55,70] and constitutional symptoms/ temperature disturbance[14,17].

As such, immediately post-endoscopic administration of FMT, most FMT centres typically manage patients using standard protocols for an endoscopic procedure[41,49], without any specific adaptations (apart from to reiterate advice about the possibility of self-limiting GI side effects, and the use of departmental infection control protocols). There is often a relatively short period of post-procedural observation[15,18]. Most studies allow patients to leave the administration site after the period of observation, although overnight observation was the protocol used for a cohort of very elderly patients with multiple comorbidities[51]. Where enteral tube administration is used, post-procedure management has ranged between removal of the tube after 30 minutes (following nasoenteral administration of 500ml of FMT[15]) to prompt post-procedure removal and oral water administration (after nasogastric administration of 90ml of FMT[72]), with no direct adverse outcomes in either case. The working group felt that removal of the tube at 30 minutes, with administration of water at this point, was a pragmatic approach.

The definition of post-FMT serious adverse events has varied between studies, but has included significant morbidity necessitating hospital admission and death in the follow up period. Many of these events are described as not directly caused by the FMT, including the scenario of post-FMT severe CDI recurrences[72] and probable or certain CDI-related deaths[16,60,70] occurring in the context of FMT failure, or deaths related to patient comorbidities[17,55]. One patient was admitted to hospital with self-limiting abdominal pain post-FMT[60], and four patients with flares of inflammatory bowel disease[60]. Three patients underwent colectomy during the post-FMT follow-up period, with all related to ulcerative colitis and not believed to be due to CDI[60]. Other reported serious adverse events include recurrent urinary tract infection[15], fever during haemodialysis[15] and upper gastrointestinal haemorrhage after nasogastric FMT (in a patient taking NSAIDs[51]), none of which were thought to be strongly linked to FMT. There have also been a number of new onset autoimmune, inflammatory and metabolic conditions described post-FMT, although these have been described from single centres only, with these findings not replicated elsewhere. Such conditions include microscopic colitis, Sjögren's syndrome, follicular lymphoma, peripheral neuropathy, immune thrombocytopenia and rheumatoid arthritis[53,55].

Significant adverse events are therefore rare but well-described. Furthermore, the procedure is relatively novel, and longer-term follow-up data regarding safety are required. Therefore, the working group opined that formal follow-up post-FMT to assess outcome and possible adverse events is essential.

The use of questionnaires to compare symptoms pre- and post-FMT is common. Specifically, data collected have included clinical response to symptom severity[55], stool frequency[15,17,46,55,57,72], stool consistency[14,15,72], abdominal pain or tenderness[55,57], rating of gastrointestinal symptoms[72], general well-being[55,72], days to improvement post-FMT[57], weight change[72], functional status[55], and changes in medication/use of antibiotics[57,72]. Additionally, certain patients have been given specific advice post-FMT to contact their clinical team if there is recurrence of diarrhoea or symptoms[14,35,41,43]. Where patients underwent outpatient clinical evaluation, this was generally undertaken relatively early post-FMT[39,52,76]. In one study, patients were additionally given instructions for cleaning and disinfection at home, with the aim of reducing the possibility of *C. difficile* reinfection[43], and counselling on the risk of recurrent CDI with future antibiotic courses[76].

Recommendations:

i. ***<u>We recommend that immediate</u> management after endoscopic administration of FMT should be as per endoscopy unit protocol (GRADE of evidence: very low: strength of recommendation: strong).***

ii. ***<u>We recommend that patients</u> should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare (GRADE of evidence: very low; strength of recommendation: strong).***

iii. ***After enteral tube administration, <u>we recommend that</u> patients may have the tube removed and oral water given from 30 minutes post-administration (GRADE of evidence: very low; strength of recommendation: strong).***

5.1.2.4. Definition of cure post-FMT for CDI:

It is recognised that symptoms of CDI resolve relatively promptly post-successful FMT, although this has been variably described (within hours in some studies[52], at an average of 4-5 days in others[57,71]). Treatment success post-FMT for CDI has no uniformly-agreed definition, with the time point at which cure/ remission is defined on clinical grounds varying between 3-5 days[36] up to six months[42]. A consensus document from the USA recommends 'resolution of symptoms as a primary end point; absence within eight weeks of FMT as a secondary end point'[78]. The working group recommended that this definition should be made on a case-by-case basis; however, they agreed that an

assessment for cure/ remission of CDI within eight weeks post-FMT was reasonable in most cases, and therefore that this was also a reasonable minimum length of time to undertake follow-up post-FMT (see **Section 5.1.2.2**).

Recommendation:

<u>We recommend that a</u> decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis (GRADE of evidence: very low; strength of recommendation: strong).

5.1.2.5. Definition of treatment failure post-FMT for CDI:

There is no uniformly-agreed definition of treatment failure/recurrence post-FMT for CDI, with varied definitions used in studies. The use of *C. difficile* toxin as a marker of treatment success or failure is variable, with some studies opting not to test for CDT unless symptoms consistent with CDI recurred[49,52–54,60,72,74]. Some studies have routinely performed CDT testing without specifying any action taken after a positive result[14,15,18,36,39,41], whilst others have tested for *C. difficile* PCR but relied on clinical criteria (even if PCR was positive) post-FMT for evaluating FMT efficacy[14]. A recent prospective study from the USA identified that only 3% (3/129) of patients who were asymptomatic at four weeks post-FMT for recurrent CDI had positive *C. difficile* PCR, again emphasising that symptoms rather than laboratory assays are more useful contributors to establishing FMT success[79].

Recommendation:

<u>We recommend that treatment</u> failure/recurrence should be defined on a case-by-case basis. Routine testing for C. difficile toxin after FMT is not recommended, but it is appropriate to consider in the case of persistent CDI symptoms/suspected relapse (GRADE of evidence: low; strength of recommendation: strong).

5.2. <u>What recipient factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?</u>

5.2.1. General approach to co-morbidities and FMT:

Most published studies had a core set of general recipient exclusions which included: significant/ anaphylactic food allergy[14,17], pregnancy[12–15,17,18], breastfeeding[14], admission to Intensive Care or the

requirement for vasopressors[12,15,18], chronic diarrhoea or other infectious cause of diarrhoea[12,14,18,50], inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS)[14,36], immunodeficiency due to recent chemotherapy and/ or neutropenia[12,14–18,50], HIV/AIDS[14,17,18], prolonged use of corticosteroids[15,17,18], graft versus host disease[12], and decompensated cirrhosis[14,15,17,18].

The working group discussed the reported practice of several centres of treating patients with recurrent CDI and food allergies through the use of FMT prepared from a patient-directed donor instructed to avoid trigger foods before stool donation. They agreed that this seemed reasonable for patients with true adverse immunological reactions to defined food groups (e.g. gluten-free diet donor for a recipient with coeliac disease). However, the working group noted that food allergies are often poorly-defined clinically, and also expressed concerns that there was no means to verify how closely a donor had followed an exclusion diet; as such, they felt unable to make any specific recommendation about FMT in patients with food allergies in general. In contrast, whilst the working group were unaware of any reports in the literature of anaphylaxis attributable to FMT, they felt that the theoretical risk of a serious adverse outcome in patients with anaphylactic food allergy merited a specific recommendation that such individuals should not be offered FMT. Similarly, the working group expressed concern about the theoretical risk of adverse outcomes when administering FMT to patients with advanced decompensated chronic liver disease (including translocation of microbial material from the intestinal tract into the portal and systemic circulations, and theoretical risk of sepsis), and felt that FMT should be used with caution in this patient group.

Recommendations:

i. ***<u>We recommend that</u> FMT should be avoided in those with anaphylactic food allergy (GRADE of evidence: very low; strength of recommendation: strong).***

ii. ***<u>We suggest that</u> FMT should be offered with caution to patients with CDI and decompensated chronic liver disease (GRADE of evidence: very low; strength of recommendation: weak).***

5.2.2. Immunosuppression and FMT:

One randomised study[16] included patients with immunodeficiency (treatment with immunosuppressive therapy (azathioprine, ciclosporin, infliximab, methotrexate alone, or in combination with corticosteroids) (*n*=18), renal transplant (*n*=5), chronic haemodialysis (*n*=5), solid organ tumours (*n*=3) and haematological malignancy (*n*=4)) at the time of FMT. Clinical resolution

rates after up to two FMTs were high: 27/29 (93%) for immunocompromised individuals, 5/6 (83%) for patients with IBD.

There are also limited data from case series and single case reports describing the use of FMT in patients with immunocompromise. Agrawal and colleagues[55] included 46/146 (32%) patients with a history of cancer, and an additional 15/146 (10%) patients with non-cancer-related immunologic dysfunction, although primary outcome measures were not specifically reported for these groups. Overall cure at 12 weeks in a case series of 80 patients with immunocompromise was reported in 71 (89%) of patients[60]. Adverse events occurred in 12 (15%) immunocompromised patients; this included two deaths (one due to respiratory failure and another due to pneumonia resulting from aspiration at the time of FMT administration)[60]; however, such adverse events have also been reported in non-immunocompromised patient populations[80]. Hefazi and coauthors described high efficacy rates in a case series of FMT for recurrent CDI and a range of haematological or solid organ malignancies (remission after one FMT in 11/12 with haematological patients, and 8/10 in solid organ malignancy patients). No significant FMT-related complications were reported[81]. A further case series[45] reported FMT treatment for 75 patients with recurrent CDI and found no significant difference in primary cure rates for patients with diabetes mellitus, malignancy, or steroid use in the preceding three months.

The working group discussed the potential impact of donor EBV and CMV status for the immunocompromised FMT recipient at risk of severe infection if exposed to these viruses. Their opinion was that such recipients should only receive FMT from donors with negative EBV and CMV status.

Recommendations:

i. ***<u>We recommend that</u> FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (GRADE of evidence: moderate; strength of recommendation: strong).***

ii. ***<u>We recommend that immunocompromised</u> FMT recipients at risk of severe infection if exposed to EBV or CMV should only receive FMT from donors negative for EBV and CMV (GRADE of evidence: very low; strength of recommendation: strong).***

5.2.3. Other comorbidities and FMT:

Only a limited number of cited studies included specific detail about the presence of comorbidities in patients receiving FMT. However, several studies reported median Charlson comorbidity scores[12,14,15,18,50]. One randomised study reported the presence of IBD in 10/17 (59%) FMT recipients[16], and there did not appear to be any significant difference in primary outcome measures in this group. Another randomised trial included 14/72 (33%) patients with IBD and reported clinical cure of CDI in 12/14 (86%) of these patients[13]. This study also included 64/72 (89%) patients with cardiac, respiratory, renal, central nervous system or multi-organ system comorbidities[13]; however outcomes were not stratified according to co-morbidity. Kelly and coauthors[60] reported an overall cure rate of 94% in a subset of CDI patients with IBD. A meta-analysis of studies in which patients with IBD received FMT (either primarily as treatment for concurrent recurrent CDI, or with the aim of treating IBD) noted a small risk of exacerbation of IBD in association with the use of FMT[82]. The working group noted the complexity of the relationship between IBD and CDI, given that IBD is itself a risk factor for CDI.

Other exclusions have been more directly related to the mode of administration. For upper gastrointestinal delivery, exclusion criteria have included delayed gastric emptying, chronic aspiration, 'swallow dysfunction', and dysphagia[17,50]. Exclusions for lower GI administration have included colostomy/ileostomy[16,50], significant bleeding disorders[12], untreated colorectal cancer[14,36,54], and ileus/small bowel obstruction[50].

In summary, the working group noted that co-morbidities amongst patients with recurrent CDI are common. Most studies did not analyse primary outcome measures according to co-morbidity; however, a small number of studies have analysed primary outcome measures (clinical cure) for patients with IBD receiving FMT for recurrent CDI and have found no significant difference compared to those without IBD, along with no overall significant worsening of IBD activity.

Recommendations:

i. <u>We recommend that</u> FMT should be offered to those with recurrent CDI and inflammatory bowel disease, but <u>patients</u> should be counselled about a small but recognised risk of exacerbation of IBD (GRADE of evidence: moderate; strength of recommendation: strong).

ii. ***<u>We recommend that</u> FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities (GRADE of evidence: moderate; strength of recommendation: strong).***

5.3. <u>What donor factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?</u>

5.3.1. General approach to donor selection:

Excellent efficacy has been shown in treating recurrent CDI using FMT derived from both related[14,36,54,57,59,61,83,38,40,41,43,45,46,49,53] and unrelated[14,15,57,59,61,72,74,83–87,16,17,35,37,38,41,43,53] donors. To date, there have been no randomised studies comparing differences in efficacy. Case series have tended to rely more on donation of stool from healthy family members. In randomised studies using FMT, all donors were healthy unrelated individuals[12–18,88]. Three case series used donor stool from healthcare professionals[39,61,85]; no randomised studies have used stool from this cohort. However, the working group noted that there were clear advantages to using FMT from a screened anonymous donor, in particular with regards to monitoring and traceability, as discussed further later.

Recommendation:

<u>We recommend that related</u> or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor (GRADE of evidence: low; strength of recommendation: strong).

5.3.2. Age and BMI restrictions for potential donors:

There are no well-defined age restrictions on donors. Randomised studies have used donors of ≥18[12,72] and ≤60 years old[15,17,18] with satisfactory outcomes. Two of the case series defined age limitations for donors as ≥18 and ≤ 50 years[72,89]. A recent study demonstrated that *Bacteroides: Firmicutes* ratio and microbial diversity was similar for donors above and below 60 years, and their stool donations had similar clinical efficacy as FMT; however, there were loss of the phylum *Actinobacteria* and family *Bifidobactericeae* from donors older than 60 years[90]. On balance, the working group agreed that an age range of 18 – 60 years was appropriate for donors.

A widely-reported case study noted apparent weight gain in a recipient of FMT for treatment of CDI when an overweight donor was used[91], but any association between a donor with a raised BMI and weight gain post-FMT has not been replicated elsewhere in the literature[92]. Whereas most randomised studies did not report donor-specific BMIs, some have excluded those without a 'normal' BMI[13,17]. The working group considered an acceptable BMI for donors as between ≥18 to ≤30 kg/m^2.

Recommendation:

<u>We suggest that people</u> should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of ≥18 and ≤30 kg/m^2 (GRADE of evidence: low; strength of recommendation: weak).

5.3.3. General approach to the donor screening assessment:

There is a clear theoretical risk of the transmission of infection by FMT; furthermore, given the large number of conditions in which perturbation of the gut microbiota has been described[93], there is a concern regarding a risk of transmission of microbiota associated with vulnerability to disease. Whilst FMT is efficacious for recurrent CDI, adverse events may be associated with its use (discussed further later), and long-term safety follow-up is lacking. The aim of a donor screening questionnaire and interview is to minimise post-FMT adverse events by excluding potential donors from whom FMT may be associated with risk to recipients. Randomised studies performed to date used various pre-screening questionnaires, including self-screening questionnaires which focused on high risk behaviours for blood-borne infections[12–16], questionnaires that focused on previous potential transferable medical conditions[18], and adaptations from the American Association of Blood Banks Donor Questionnaire[14,17]. One randomised study used the OpenBiome questionnaire as a screening questionnaire[94]. Some studies have suggested excluding potential donors who have recently travelled to defined regions (typically tropical areas), varying between 3-6 months prior to donation[38,39,49,52,55,59,74,87]; this is also the protocol employed in randomised studies[14,16,18]. Another important point for assessment is recent use of medications by potential donors. In particular, given the profound effects of antimicrobials on the gut microbiota[95–98] (along with the theoretical concern that recent antimicrobials might precipitate gut colonisation with antimicrobial-resistant bacteria that could be transferred during FMT), studies advocate either a three month[14,46,53–55,57,61,74] or six month[16–18,35,38,39,43,49,85,99,100] period without antimicrobial use prior to FMT donation.

The working group agreed that, given the growing evidence for the contribution of the gut microbiota to the aetiopathogenesis of colorectal carcinoma, patients with a significant personal or family history of (or risk factors for) this condition should be excluded as donors (**Table 1**). However, the working group noted an added complexity, in that their recommendation was that potential donors may be up to 60 years of age, but bowel scope screening for colorectal carcinoma currently begins within the UK at 55 years of age, and formal NHS bowel cancer screening starts at the age of 60 years[101]. The working group agreed that potential donors living in countries with bowel cancer screening programmes that start before the age of 60 years should have therefore completed appropriate screening with negative/ normal tests before they are considered further as donors.

The working group was of the opinion that a screening process is mandatory; any positive responses should usually result in exclusion from donation, although this will depend upon the particular circumstances/ answers given. A donor screening questionnaire should be performed both prior to considering a person as a donor, and also at a further point in time (discussed further in **Section 5.3.5**).

Recommendation:

It is mandatory to screen potential donors by questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota (Table 1) (GRADE of evidence: low; strength of recommendation: strong).

5.3.4. Laboratory screening of potential donors:

Currently, there are no known confirmed cases of blood-borne pathogens being transmitted by FMT, but strict preventative measures are important, as the potential risk of transmission is unknown. Many of the suggestions are extended from established blood screening guidelines[102]. Case series almost universally screen for HIV, hepatitis B and hepatitis C as a minimum[35,36,52–55,59,61,72,74,84,86,37,87,103,39–43,46,49]; other studies (including the randomised trials) have a more thorough blood screening process[14–18]. Many studies have also included a 'metabolic/general blood screen', to select out donors with hitherto undiagnosed chronic illness. **Table 2** shows the suggested blood screening protocol of the BSG/HIS working group.

The working group specifically discussed the role of screening donors for their EBV and CMV status; the importance of the rationale for this is discussed in **Section 5.2.2.** They agreed that EBV and CMV testing was only required where there is the potential that the FMT prepared from that donor would be administered to immunosuppressed patients at risk of severe infection if exposed to CMV and EBV.

The primary aim of stool screening of potential donors is to minimise the risk of transmission of pathogens; again, the relative novelty of FMT for CDI means that these risks are not currently well-defined. Stool screening protocols are universal amongst published studies, though widely-variable protocols have been used. **Table 3** displays the suggested stool screening protocol of the working group. The working group discussed stool screening for multi-drug resistant bacteria carriage, and agreed that carbapenemase-producing *Enterobacteriaceae* (CPE) should be screened for. Although these bacteria are carried only by a minority of the UK population, transfer into debilitated patients with CDI is clearly undesirable given that CPE are potentially so difficult to treat. They also agreed that extended-spectrum beta-lactamase (ESBL)-producing organisms could also potentially cause severe disease (with limited antimicrobial options) if transplanted into patients with CDI, and so should also be screened for. Whilst vancomycin-resistant *Enterococci* (VRE) carriage is relatively common in the community (probably related to food consumption)[104], community strains of VRE are genetically distinct from (and generally of much lower pathogenicity than) those found nosocomially[105]; as such, the working group thought that routine screening was not justified. The working group also noted that methicillin-resistant *Staphylococcus aureus* (MRSA) carriage is very rare in healthy adults in non-healthcare settings (with significant intestinal carriage even rarer), so did not justify routine screening. However, the working group acknowledged that the potential infection risk from VRE and MRSA would vary regionally dependent upon local prevalence and pathogenicity, and as such recommended that a risk assessment is performed to assess whether screening for these organisms should be considered.

A donor laboratory screening should be performed both prior to considering a person as a donor, and also at a further point in time (discussed further in **Section 5.3.5**).

Recommendation:

Blood and stool screening of donors is mandatory (Tables 2 and 3) (GRADE of evidence: low; strength of recommendation: strong).

5.3.5. Repeat donor checks, and donation pathway:

Almost all reviewed studies have repeated at least some elements of the initial donor screening process either at the time of donation of each stool sample used to prepare FMT, or at the end of a period of donation to assess ongoing suitability for inclusion. However, protocols have differed widely between studies.

The opinion of the working group was that when a donor had met criteria for donation (both with an acceptable health questionnaire and satisfactory laboratory tests), they were suitable to begin donation of stool that may be prepared into FMT. Repeat donor screening was also deemed necessary. In centres where frozen FMT is being prepared, stool may be collected and processed immediately after the first donor screen is successfully completed, but should be stored in 'quarantine' pending further donor screening, rather than used immediately for clinical use. At the end of the locally-defined period of donation, potential donors should undergo repeat testing, with a further health questionnaire and laboratory screening. If the donor's health questionnaire remains acceptable and repeat laboratory screening is negative at this point, then the frozen FMT may be released from 'quarantine', and used. The working group thought that donor screening both before and after donation was the safest route possible, and that this represented the preferred scenario. A proposed summary pathway for donor screening in this scenario is provided in **Figure 1.**

In centres using fresh FMT, the working group agreed that a repeat health questionnaire should be completed at the time of donation of each stool sample used to prepare FMT. Formal repetition of both the personal interview/ health questionnaire and laboratory screening tests should occur at regular intervals to ensure ongoing suitability for inclusion as a donor. The working group's opinion was that this repetition of the screening process should occur at least once every four months.

Recommendations:

i. In centres using frozen FMT, before FMT may be used clinically, <u>we recommend that</u> donors should have successfully completed a donor health questionnaire and

laboratory screening assays both before and after the period of stool donation. This is the preferred means of donor screening (GRADE of evidence: low; strength of recommendation: strong).

ii. ***In centres using fresh FMT, we recommend that a repeat health questionnaire should be assessed at the time of each stool donation. To ensure ongoing suitability for inclusion as a donor, the donor health questionnaire and laboratory screening should be repeated regularly (GRADE of evidence: low; strength of recommendation: strong).***

5.4. What factors related to the preparation of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

5.4.1. General principles of FMT preparation:

There is very little evidence or guidance on the collection of donor stool. Critical steps during this process centre on the reduction of environmental cross-contamination risk, so the use of clean collection devices and clean collection procedures is advocated. To promote standardised practice and a safe and effective product, clear instructions should be provided to the donor for stool collection (**Table 5)**.

Regardless of the methods used to prepare FMT, stool donations should be processed within six hours of defaecation. The period of six hours has been generally applied across many successful studies of FMT treatment in CDI[14,18,35,39,43,52], although no formal comparative study has been undertaken. This strategy aims to minimise sample degradation and alteration over time, which may occur due to the complex metabolic and environmental requirements of the faecal microbiota.

There are no comparative trials of anaerobically versus aerobically prepared FMT in the treatment of recurrent CDI. With the exception of small observational studies[41,74], the vast majority of FMT preparation has been undertaken aerobically for the treatment of CDI and has proved highly efficacious. There appears to be no clear need to process anaerobically, a method which introduces complexity and cost for the treatment of CDI.

The reviewed randomised studies reported variable amounts of stool used in the preparation of each FMT aliquot, and the lack of comparative data means that it is not possible to link stool mass to outcome from these studies. However, a previous systematic review of case series using FMT as treatment for recurrent CDI reported similar rates of treatment efficacy, but an approximate fourfold increase in recurrence rates, if <50g of stool was used compared to ≥50g[106]. Similarly, the initial volume of diluent used to create the faecal emulsion is variable between studies, although the most common practice appears to be creation of a stool: diluent ratio of approximately 1:5. The overwhelming majority of the reviewed studies used stool from only a single donor per FMT (rather than stool pooled from a mixture of donors), and there are no comparative studies of outcomes of CDI from single donor vs pooled donor FMT; as such, the working group found no justification to recommend donor stool pooling for FMT for CDI.

The majority of studies have used preservative-free sterile 0.9% saline as the diluent for FMT production, although there have been a handful of reports of other diluents including potable water[16,35,43]. There have been no comparative studies of FMT diluent. In cases where frozen FMT is prepared, an appropriate cryoprotective substance should be added prior to freezing. Most studies use glycerol at a final concentration of ~10%[16,41]. It has been demonstrated that storing stool at -80°C for up to six months in saline without glycerol decreases viable aerobic and anaerobic bacterial counts; the reduction was statistically significant in all bacterial groups with the exception of *E. coli* and total anaerobes. When stored with glycerol, no significant reduction in viable counts was observed[74].

A variety of homogenisation and open filtration systems have been used, with no apparent major variation in efficacy. Open filtration systems such as gauze[16,37,40,55], filter paper[39] and strainers/ sieves[17,41] are unpleasant to use and pose a risk of external contamination. In order to best comply with GMP standards, a sterile, single-use closed homogenisation and filtration system is recommended. An example of such a system includes the use of sterile filter bags inside a laboratory paddle homogeniser.

Recommendations:

i. We recommend that donor stool collection should follow a standard protocol (GRADE of evidence: low; strength of recommendation: strong).

ii. ***We recommend that donor stool should be processed within 6 hours of defaecation (GRADE of evidence: low; strength of recommendation: strong).***

iii. ***We recommend that both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI (GRADE of evidence: moderate; strength of recommendation: strong).***

iv. ***We recommend that sterile 0.9% saline should be considered as an appropriate diluent for FMT production, and cryoprotectant such as glycerol should be added for frozen FMT (GRADE of evidence: moderate: strength of recommendation: strong).***

v. ***We recommend using ≥50g of stool in each FMT preparation (GRADE of evidence: moderate: strength of recommendation: strong).***

vi. ***We suggest that stool should be mixed 1:5 with diluent to make the initial faecal emulsion (GRADE of evidence: low; strength of recommendation: weak).***

vii. ***We suggest that homogenisation and filtration of FMT should be undertaken in a closed disposable system (GRADE of evidence: low; strength of recommendation: weak).***

5.4.2. Fresh vs frozen FMT:

Two randomised studies have examined this area. One double-blind randomised study concluded that enema frozen FMT (*n*=91) was non-inferior for clinical resolution of diarrhoea to fresh FMT (*n*=87) for the treatment of recurrent or refractory CDI[16] (with frozen FMT in this study stored at -20°C for up to 30 days). A further randomised study demonstrated statistically comparable remission rates for recurrent CDI with fresh or frozen FMT delivered colonoscopically (*n*=25/25 vs 20/24 respectively, *p*=0.233) (using frozen FMT stored at -80°C for up to six months)[13]. These data support the findings of earlier small observational studies[35,41]. Frozen FMT is preferable to fresh FMT on logistical and cost grounds[16]. Banked frozen FMT also enables the window period for donor screening to be minimised, allowing centres to more closely to meet regulatory requirements (also see **Section 5.3.5**).

Recommendation:

We recommend that the use of banked frozen FMT material should be considered preferable to fresh preparations for CDI (GRADE of evidence: high; strength of recommendation: strong).

5.4.3. Use of frozen FMT:

Frozen FMT has been used up to six months after storage at -80°C[17,41,74], with high efficacy rates (>70%) observed in the cases treated. However, there have been no comparative trials investigating storage durations. A trend towards decrease in the viability of certain gut microbiota taxa was noted when faecal aliquots were frozen in 10% glycerol for six months[74], and as such, the working group agreed that six months was the acceptable limit for freezing of an FMT in glycerol. Storage at -80°C is recommended rather than -20°C to minimise sample degradation.

Warm water baths have been recommended to speed thawing[6]; however, the working group thought that this should be strongly discouraged, as this may introduce risks of cross contamination by *Pseudomonas* species (and other contaminants) from the water bath[107,108], and may reduce bacterial viability in the FMT. Repetitive freeze thawing of FMT samples should be avoided as bacterial numbers will be reduced during this process[109].

Recommendations:

i. We recommend that FMT material stored frozen at -80°C should be regarded as having a maximum shelf life of six months from preparation (GRADE of evidence: low; strength of recommendation: strong).

ii. We suggest consideration of thawing frozen FMT at ambient temperature, and using within six hours of thawing (GRADE of evidence: low; strength of recommendation: weak).

iii. We suggest not thawing FMT in warm water baths, due to the risks of cross contamination with Pseudomonas (and other contaminants) and reduced bacterial viability (GRADE of evidence: very low; strength of recommendation: weak).

5.5. What factors related to administration of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

5.5.1. Use of specific medications in the period around FMT administration:

5.5.1.1. General principles of FMT administration:

Bowel purgatives have been proposed pre-FMT as a means of removing residual antibiotics that may affect engraftment of transplanted microorganisms, and as a means of removing any residual *C. difficile* toxin, spores and vegetative cells[110–114]. Furthermore, bowel purgatives pre-colonoscopic FMT delivery facilitate safe endoscopy. Various bowel purgatives have been used in colonoscopic FMT studies, including polyethylene glycol (PEG) (often 4 litres)[14,17,115–117,35,41,43,46,54–56,100], MoviPrep®[35,41], and macrogol[13,15,18,59]. In those studies that used an upper GI route for FMT, PEG[54,55,84] and Klean-Prep®[15,61] were used. FMT without bowel preparation has also been used as treatment for recurrent CDI without any apparent reduction in efficacy, including in randomised studies[16].

The rationale for the use of proton pump inhibitors (PPI) prior to upper GI FMT is to minimise acidity which may impair engraftment of transplanted microorganisms; however, PPIs have been shown to alter the gut microbiota[118,119], and have also been associated with primary and recurrent CDI[120,121]. Some studies advocate the use of PPI prior to receiving FMT via the upper GI route[37,39,45,84,85,122,123], but there appears to be comparable efficacy data in studies where it has not been used. Certain studies have also given recipients PPI prior to receiving colonoscopic FMT[17,87].

The use of prokinetics (such as metoclopramide) has been described prior to FMT delivery via the upper GI tract route, but only in a very small number of studies[85]. Given the potential risk of regurgitation/aspiration associated with upper GI administration of FMT, the working group felt that its use should be considered where appropriate.

A single dose/ short course of loperamide has been used following FMT (predominantly for lower GI administration) in an attempt to prolong the exposure of the FMT to the mucosa, and to aid retention of the FMT within the GI tract[13,46,49,55,84,123]. One study utilised diphenoxylate with atropine[54] instead. However, no studies have compared FMT with and without anti-motility drugs.

The working group also discussed infection control aspects as they apply to FMT administration. Specifically, they agreed that recipients should ideally be cared for in a single room with en-suite bathroom facilities and, where appropriate, be placed at the end of an endoscopy list, to facilitate enhanced environmental decontamination and prevention of transmission of *C. difficile* spores. Protocols for decontamination of endoscopes should follow national guidance[124,125], using a sporicidal agent. Best practice for prevention of transmission of healthcare-associated infections, as described in national guidelines[126], should also be applied throughout.

Recommendations:

i. <u>We recommend that bowel</u> lavage should be administered prior to FMT via the lower GI route, and bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred (GRADE of evidence: low; strength of recommendation: strong).

ii. For upper GI FMT administration, <u>we suggest that a</u> proton pump inhibitor should be considered, e.g. the evening before and morning of delivery (GRADE of evidence: low; strength of recommendation: weak).

iii. <u>We suggest that a</u> single dose of loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery (GRADE of evidence: low; strength of recommendation: weak).

iv. <u>We suggest that prokinetics</u> (such as metoclopramide) should be considered prior to FMT via the upper GI route (GRADE of evidence: low; strength of recommendation: weak).

v. <u>We recommend that best</u> practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc) (GRADE of evidence: high; strength of recommendation: strong).

5.5.1.2. Additional antibiotics pre-FMT:

Many studies have given further courses of conventional antimicrobial *C. difficile* treatment prior to FMT. Regimens have included vancomycin alone[12,14,18,35,39,55,59,86,117], metronidazole or

vancomycin[40,41,43,122], or alternatively vancomycin, fidaxomicin or metronidazole[56], with one study using a range of regimens which included rifaximin[123]. The length of treatment was also variable, ranging from 24 hours[54] up to four days prior to receiving FMT[39,45]; however, comparative studies have not been undertaken.

Recommendation:

<u>We recommend the administration of</u> further antimicrobial treatment for CDI for at least 72 hours prior to FMT (GRADE of evidence: low; strength of recommendation: strong).

5.5.1.3. Washout period between antibiotic use and FMT:

Nearly all studies specified a washout period after completing anti-CDI antibiotics and before administration of FMT. However, this time period appeared to be arbitrarily selected and varied from as little as four[46] or 12 hours[51], up to 72 hours[36]. The majority of studies specified either 24 hours[15,37,39,40,45,54,127] or 48 hours[41,42,49,60], however some allowed a range from 1-3 days[16,44,52,53,55]. One study appeared to allow co-administration of vancomycin with bowel preparation, without a washout period[18].

The working group discussed the challenging scenario of providing FMT to patients with recurrent CDI, but who also had a strong indication for long-term non-anti-CDI antibiotics (e.g. splenectomy, osteomyelitis, or infective endocarditis), or patients who develop an indication for antibiotics for a reason other than CDI shortly after receiving FMT. The concern in this instance is that the use of antibiotics may limit engraftment of microbial communities derived from the FMT, and therefore reduce its effectiveness. The working group discussed a recent retrospective study demonstrating that exposure to non-anti-CDI antimicrobials within eight weeks of FMT is associated with an approximate threefold risk of FMT failure (*n*=8/29 failures with antibiotic exposure *vs* 36/320 failures without antibiotic exposure)[128]. Similarly, the experience of the large pan-Netherlands stool bank[129] was that ~50% of their failures of FMT in the treatment of recurrent CDI occurred in patients who had received antibiotics within one month of their FMT. For patients requiring long-term antibiotics, the working group's expert opinion was that such patients should still be eligible for FMT, but that the regimen for the use of non-anti-CDI antibiotics should be decided on a case-by-case basis, based on factors including response to FMT and/or strength of indication of antibiotics. Both in this scenario, and the scenario in which antibiotics are required shortly after receiving FMT, the working

party agreed that infectious diseases specialists/medical microbiologists should be involved in making decisions regarding the choice of agents used.

Recommendations:

iii. To minimise any deleterious effect of antimicrobials on the FMT material, we recommend that there should be a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT (GRADE of evidence: low; strength of recommendation: strong).

iv. We suggest considering consultation with infectious disease specialists or medical microbiologists for advice whenever FMT recipients also have an indication for long-term antibiotics, or have an indication for non-CDI antibiotics within eight weeks of FMT (GRADE of evidence: very low; strength of recommendation: weak).

5.5.2. Route of FMT delivery:

5.5.2.1. Introduction:

FMT can be delivered via the lower GI route (retention enema, colonoscopy), upper GI route (endoscopically, or via nasogastric tube, nasoduodenal or nasojejenal tube), or via capsules (containing either frozen FMT or lyophilised faecal material). Systematic reviews with meta-analysis suggest that FMT for recurrent CDI via colonoscopy may have slightly higher efficacy compared to upper GI administration[127,130–132] with similar safety profiles, but also note the trend towards using larger amounts of stool or 'higher concentration' FMT in lower GI administration. One systematic review (reviewing principally case series, and including only one randomised study) compared remission rates for CDI using FMT delivered to different areas of the GI tract, and reported that for FMT infused into the stomach, duodenum/jejunum, caecum/ascending colon, and rectum the rates of cure rate were 81%, 86%, 93%, and 84%, respectively[131].

In the only randomised study that directly compared upper and lower GI administration, there was no significant difference in overall cure rate ($p = 0.53$)[17].

5.5.2.2. Upper gastrointestinal tract administration of FMT:

FMT has been shown to be safe and efficacious in the treatment of *C. difficile* when administered via nasogastric tube[37,39,45,61,83,123], nasoduodenal tube[15,84,85], enteroscopy[122,123], or via the infusion channel on a gastroscope[40,45]. In a randomised trial, nasoduodenal donor FMT has been shown to be more efficacious than vancomycin in treating recurrent CDI[15]. Furthermore, it has been shown that FMT can also be safely and effectively delivered via a percutaneous endoscopic gastrectomy tube[45,83]. The working group noted that upper GI administration of FMT may be particularly suitable for certain patient groups, such as those in whom there are contraindications or who would find it difficult to tolerate lower GI endoscopy, and/ or patients unlikely to be unable to retain enemas.

Typically, smaller volumes of faecal suspension are administered to the upper GI tract compared to lower GI administration, with quoted volumes ranging from 25ml[39] up to 150ml[84]- 250ml[37,85]. Up to 500ml of suspension has been given safely and effectively via the upper GI route[15,77]. However, the working group expressed concerns regarding the risk of regurgitation and aspiration if large volumes of FMT are administered to the upper GI tract, and also discussed cases in which this has been described with adverse outcomes[80]. This included a reported death from aspiration, after 100-150ml of FMT was delivered by enteroscope into the distal duodenum under general anaesthetic as attempted treatment for recurrent CDI[133]. A further reported case described a case of fatal aspiration pneumonitis likely related to a 500ml FMT via nasoduodenal tube; this patient had a swallowing disorder following oropharyngeal radiation after surgical removal of a maxillary carcinoma two years previously[77]. Based on their expert opinion, the working group recommended that upper GI FMT should be used with caution in those at risk of regurgitation (e.g. known large hiatus hernia, severe gastro-oesophageal reflux disease, etc) and/ or with swallowing disorders (although administration via a gastrostomy tube would be acceptable). They also recommended that no more than 100ml of FMT should be administered to the upper GI tract to minimise these risks.

Recommendations:

i. <u>We recommend that upper</u> GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate (GRADE of evidence: high; strength of recommendation: strong).

ii. Where upper GI administration is considered most appropriate, <u>we recommend that</u> FMT administration should be via nasogastric, nasoduodenal, or nasojejunal

tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate (GRADE of evidence: high; strength of recommendation: strong).

v. We recommend that no more than 100ml of FMT is administered to the upper GI tract (GRADE of evidence: low; strength of recommendation: strong).

vi. We recommend that upper GI administration of FMT should be used with caution in those at risk of regurgitation and/ or those with swallowing disorders (GRADE of evidence: low; strength of recommendation: strong).

5.5.2.3. Lower gastrointestinal tract administration of FMT:

FMT via enema: Successful treatment of *C. difficile* with FMT enema has been demonstrated[16,38,42,53,55,83,86] but enema appears to have a lower efficacy than other routes of FMT administration. Specifically, in a randomised study primarily comparing the efficacy of fresh and frozen FMT in the treatment of recurrent CDI, only 52.8% of patients in the 'frozen' arm and 50.5% of patients in the 'fresh' arm of the study (*n*=57/108 and 56/111 respectively) experienced resolution of symptoms after a single enema, by modified intention to treat analysis[16]. However, resolution rates in both arms only reached >80% after at least three enemas[16]. A recent randomised study demonstrated similar rates of recurrence of CDI in patients with recurrent CDI treated with either a single FMT enema or a six week vancomycin taper (*n*=9/16 patients with recurrence vs 5/12 respectively)[12]. Notwithstanding this, enemas do have specific advantages, such as being a treatment option where full colonoscopy is contraindicated. It is also possible to give multiple infusions relatively easily and outside a hospital setting.

FMT via colonoscopy: Randomised study evidence has demonstrated that colonoscopic FMT has higher efficacy in treating recurrent CDI than vancomycin[18]**.** Efficacy is similar whether FMT is fresh or frozen, but modestly reduced when using a lyophilised FMT product[13]. Colonoscopic delivery of donor FMT into the ileum or caecum was associated with a 91% cure rate for recurrent CDI[14]. Observational studies highlighted similar success, describing cure rates of 88% (*n*=14/16)[74] and 91%[46] (*n*=21/23) in response to infusion of donor FMT into the caecum or terminal ileum. A further advantage of using colonoscopy to administer FMT has been to allow assessment for the presence of pseudomembranes; in certain reviewed studies, the presence or absence of pseudomembranes has influenced the FMT regimen used[18,73]. However, the working group noted that that many patients

with CDI are frail and elderly, and as such it will not always be safe or feasible to undertake colonoscopy in this particular group of patients. Flexible sigmoidoscopy appears to be an feasible option where full colonoscopy cannot be performed e.g. unable to tolerate colonoscopy, severity of colitis[56,60].

The amount of faecal suspension via enema has varied between 150-500mls[16,38,42,55,86]. The amount of faecal suspension delivered via colonoscopy has been similarly variable, with some studies suggesting as little as 100ml can be used with success rates of 94%[43]. 250ml-400ml had a success rate of 100%[36], whereas infusions of up to 500-700ml were associated with cure rates of 92%[46]. However, the working group noted that it is difficult to compare 'concentration' of FMT in different studies as different protocols used varied starting amounts of faecal material. Currently, there are no randomised studies that compare concentration/ volume of colonoscopic or enema FMT. As such, no recommendation was made to this regard.

Recommendations:

i. <u>We recommend that colonoscopic</u> administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate (GRADE of evidence: high; strength of recommendation: strong).

ii. Where colonoscopic administration is used, <u>we suggest considering</u> preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate (GRADE of evidence: low; strength of recommendation: weak).

iii. <u>We recommend that FMT</u> via enema should be used as a lower GI option when delivery using colonoscopy or flexible sigmoidoscopy is not possible (GRADE of evidence: high; strength of recommendation: strong).

5.5.2.4. Capsulised FMT:

Capsulised FMT aims to remove some of the concerns regarding conventional FMT, such as the invasive means of administration and palatability. The largest case series describing the use of capsules as treatment for recurrent CDI[72,89] noted clinical resolution at eight weeks off antibiotics for CDI in 82% of cases (*n*=147/180) after one course of capsules, and 91% (*n*=164/180) after two courses. The capsules contained frozen FMT prepared in a diluent of saline with 10% glycerol; 15

capsules were administered each day for two consecutive days (equating to a mean 48g of original crude stool). Other smaller case series have demonstrated comparable results[87,123,134], including when lyophilised stool is used instead of frozen whole FMT[134].

The working group reviewed two randomised studies which have examined the efficacy of capsulised FMT in treating recurrent CDI. In one study, published in abstract form[94], a 'high dose' regimen of frozen FMT capsules (30 capsules each day for two days) was compared to 'low dose' (30 capsules in one day). CDI resolution was comparably high in both arms with one treatment course (77% (*n*=7/9) in the 'high dose' arm vs 70% (*n*=7/10) in the 'low dose arm'). 4/5 initial non-responders entered remission after a second capsule course with the 'high dose' regimen[94]. In a recent large randomised trial, patients with recurrent CDI were randomised to receive either thawed frozen FMT either via colonoscopy or via capsules (one treatment of 40 capsules)[11]. On per protocol analysis, remission at 12 weeks after a single treatment occurred in 96% in both arms (*n*=51/53 by capsule, *n*=50/52 by colonoscopy).

The working group discussed certain unresolved issues regarding capsules. Specifically, capsules are often large, and swallowing 30 capsules in a single day may be a significant undertaking for patients with CDI, such as the frail elderly with an existing high pill burden. They also noted that follow-up data post-capsule administration is relatively short compared to other modalities of FMT.

Recommendation:

Capsulised FMT holds promise as a treatment option for recurrent CDI and we recommend that this should be offered to patients as a potential treatment modality where available. Capsule preparations should follow a standard protocol. Further evidence regarding optimal dosing and formulation is required (GRADE of evidence: high; strength of recommendation: strong).

5.6. What is the clinical effectiveness of FMT in treating conditions other than *Clostridium difficile* infection?

5.6.1. Introduction:

In current clinical practice, FMT is used predominantly in the treatment of recurrent CDI. Its success has led to exploration of its efficacy in other GI diseases, primarily ulcerative colitis (UC), where perturbation of the gut microbiota has been observed and implicated in disease pathogenesis[135]. Due to variability of the quality, methodology and cohorts of patients recruited in trials of FMT for non-CDI indications, and in order to control for significant confounding factors, the working group only included randomised trials involving patients with well-defined conditions and in which there was a primary clinical outcome. To date, there have been a total of 71 such studies investigating the role of FMT in IBD; of these, only four are prospective randomised controlled trials, limited to patients with ulcerative colitis[136–139]. Five other reviewed randomised studies investigated the use of FMT in irritable bowel syndrome[140], slow transit constipation[141], hepatic encephalopathy[142] and metabolic syndrome[143,144].

5.6.2. Use of FMT for ulcerative colitis:

5.6.2.1. Efficacy:

All four RCTs, with a total of 277 subjects, included patients with mild to moderate UC (Mayo score 3-11 and endoscopic sub-score of at least 1). Participants were aged between 27 and 56 years and largely included patients on stable immunosuppressive therapy (only one study excluded patients using biologic treatments and methotrexate within the preceding two months)[136]. Three studies included patients on oral corticosteroids at the time of FMT, however only two required a mandatory wean of these to meet eligibility. Studies generally included patients with all disease distributions found in UC. Time to evaluation of response to FMT in these studies varied between seven and twelve weeks. Two studies used autologous FMT as placebo[136,139]. Three of the four studies demonstrated that patients receiving donor FMT were significantly more likely to achieve clinical and endoscopic remission compared to placebo[137–139]. The pooled rate of combined clinical and endoscopic remission was 27.9% for donor FMT and 9.5% for placebo. A pooled risk ratio for failure of FMT to achieve these combined outcomes was 0.8 (95% CI: 0.7-0.9). Deep remission (histological) was only reported in one RCT: 18.4% of patients receiving FMT achieved this outcome compared to 2.7% of those receiving placebo[137].

5.6.2.2. Characteristics of FMT preparation and delivery:

The four RCTs varied in their FMT preparation and delivery methodology. Two RCTs delivered frozen FMT, one fresh FMT, and one used a combination. Three RCTs with a positive outcome delivered the FMT via the lower GI route; these studies used a high intensity protocol ranging from a total of three

infusions in one week to 40 FMTs over an eight week period[137–139]. The other RCT (that failed to show efficacy of FMT for UC) had adopted a low intensity protocol of two nasoduodenal infusions given three weeks apart[136]. Interestingly, the only RCT that prepared stool in anaerobic conditions demonstrated the highest rate of steroid-free clinical remission and steroid-free clinical response with donor FMT[139]. A further interesting observation in one study was a trend towards higher rates of remission with one particular donor[137].

5.6.2.3. Adverse events:

Short-lived GI symptoms such as abdominal bloating, cramps, diarrhoea and fever were reported in patients receiving FMT for UC. There were no significant differences in serious adverse events between patients receiving FMT compared to placebo (10 *vs* 7 respectively). Most of the serious adverse events were a consequence of worsening colitis: one patient who received FMT required a colectomy[136]. In addition, one patient developed concurrent CDI[137]. No deaths were reported in any of the studies.

5.6.3. Use of FMT in functional bowel disorders:

Two RCTs have investigated the role of FMT in functional bowel disorders. In a double-blind placebo controlled RCT that recruited 90 patients with IBS with diarrhoea or with diarrhoea and constipation[140], the primary endpoint only just reached statistical significance in inducing symptom relief (as assessed by 75 point reduction in IBS-severity scoring system at three months following a single infusion FMT by colonoscopy) (p=0·049). The second RCT randomised 60 patients with slow transit constipation to either six consecutive days of nasogastric-delivered FMT or conventional treatment[141]. This demonstrated that a significant proportion of patients achieved the primary endpoint of a mean of at least three complete spontaneous bowel movements per week (53.3% vs. 20.0%, p= 0.009) along with improvement in stool consistency score and colonic transit time. However, the intervention group had more treatment-related adverse events than did the control group (total of 50 *vs* 4 cases).

5.6.4. Use of FMT in hepatic encephalopathy:

One small study has investigated the role of FMT in the management of hepatic encephalopathy (HE)[142]. This RCT randomised 20 male patients with cirrhosis with refractory HE to receive either five days of broad-spectrum antibiotic pre-treatment followed by a single FMT enema or standard of

care. Patients in the FMT arm had a significantly lower incidence of serious adverse events and improved cognition. The Model for End-Stage Liver Disease (MELD) score, however, transiently worsened post-antibiotics in the FMT arm. The study was potentially confounded as patients in the FMT arm continued to receive lactulose and/or rifaximin for treatment of their HE.

5.6.5. Use of FMT for metabolic syndrome:

Two randomised studies[143,144], with a combined total of 56 patients, demonstrated an improvement in peripheral (but not hepatic) insulin sensitivity in Caucasian male obese patients with metabolic syndrome following one or two infusions via nasoduodenal tube of FMT obtained from lean donors. This improvement was observed at six weeks post-FMT, but was no longer present by 18 weeks. No improvement in insulin sensitivity was identified in patients transplanted with autologous FMT (i.e. patients transplanted with their own collected faeces). The improvement in peripheral insulin sensitivity in the lean donor FMT group was accompanied by a small but significant improvement in HbA1c at six weeks[144], but no improvements in other metabolic parameters, such as weight. Whilst these data are of interest, the working group felt that the limited, transient nature of the benefits seen and small size of the studies meant that FMT could not be recommended as treatment for metabolic syndrome.

5.6.6. Future directions for randomised trials of FMT for non-CDI indications:

Currently there are a large number of randomised trials (including RCTs) being undertaken globally, to evaluate the potential role of FMT as treatment for a wide range of conditions. The working group concluded that until there are more reliable data to inform decision-making, the best practice principles described in this document for the governance of an FMT service for recurrent CDI should also be applied to FMT clinical trials for other conditions. However, specific adaptations may be considered depending on the condition being studied, e.g. consideration of using anaerobic conditions for the preparation of FMT in trials for the treatment of UC, as described above.

In conclusion, FMT has the potential to be an effective treatment option for mild to moderate ulcerative colitis, and appears to be safe despite the use of immunosuppressive therapy. FMT may also have a potential role in the treatment of functional bowel disorders. However, recommendations for clinical use for both these indications cannot be made until there is clearer evidence of the most appropriate patient characteristics, preparation methodology, route of delivery

and intensity of administration of FMT. The evidence for the use of FMT in hepatic encephalopathy and metabolic syndrome is currently limited, and further well-designed RCTs are needed to evaluate its potential role here.

Recommendation:

<u>We do not currently recommended FMT</u> as treatment for inflammatory bowel disease. Apart from CDI, there is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease (GRADE of evidence: moderate; strength of recommendation: strong).

6. <u>Basic requirements for implementing a FMT service:</u>

As discussed above, there is an absence of published studies to support the recommendations in this section (although the experience of setting up a nationwide stool bank has recently been reported from the Netherlands[129]). This section is therefore based on the working group's expert opinion and experience of developing FMT services. The working group considered best practice in this area as it applied to legal and clinical governance aspects, the relevant professionals required to establish an FMT service, the infrastructure of a service, and appropriate practices for FMT manufacturing and quality control monitoring where relevant. The full text of this section is in **Supplementary Material 3.**

7. <u>Key performance indicators:</u>

- All donors to have completed initial screening questionnaires and blood and stool screening results, as well as final health check prior to each stool donation processed to FMT. Results from each subsequent serial round of screening also to be documented.
- All FMT recipients to have clear documentation of details of their disease course and preparation prior to FMT, including whether recurrent or refractory disease, previous antimicrobial courses, and use of bowel purgatives/other preparatory medications pre-FMT.
- All FMT recipients to have sufficient documentation to allow clear traceability of the exact FMT aliquot transfused. Records should include identification of the donor, as well as a frozen FMT aliquot (and original faecal sample) - as well as serum - from that donor (see **Supplementary Material 3**).

- All FMT recipients for recurrent or refractory CDI to have documentation during follow-up of treatment success or failure (and subsequent treatment plan if failure), together with clear documentation of any adverse events that may be attributable to FMT.

8. Further research:

- As described within this guideline, many aspects of the terminology of CDI are used variably between studies, and end-points in FMT trials are inconsistent. The working group noted the need to standardise this terminology to allow more robust comparisons between studies.
- Given the relative novelty of FMT as a procedure, any potential long-term adverse events associated with its use are poorly-defined. The establishment of formal FMT registries should be considered. Whilst this would primarily act as an important tool for defining the safety and efficacy of FMT, it would also be a valuable database for researchers within the field. Standardisation of other key documentation related to FMT administration (e.g. establishment of a proforma for assessing eligibility for FMT and/or follow-up after FMT) would also be advantageous for the same reasons.
- The working group noted the lack of consistency in definitions related to the severity of CDI disease and to response or failure to FMT. This limited interpretation of the published studies. As such, the working group thought that standardisation of these definitions would allow more accurate delineation of the factors influencing the efficacy of FMT for CDI. The working group also noted that only one reviewed study had reported the relationship between *C difficile* ribotype and FMT outcome, and that recording of this information should be encouraged better to evaluate its influence.
- Further well-designed clinical trials (in particular, RCTs) are required to identify the optimal means of administration of FMT as treatment for recurrent and/or refractory CDI.
- The working group noted that even capsulised FMT may be associated with potential drawbacks. They also noted that there are many patients with recurrent CDI for whom FMT (or any form of 'bacteriotherapy') may be inappropriate, including those with very marked immunosuppression, and/or multi-organ disease. Despite high levels of efficacy, there is a small but appreciable FMT failure rate and it is not currently understood whether this is due to underlying donor or recipient factors. Therefore, a research priority should be in basic and translational studies better to define the mechanisms underlying the efficacy of FMT in CDI. This includes comparing the structure and function of the microbiota of donors to patients pre-FMT and post-FMT, via techniques including next-generation microbial sequencing, metabolic profiling, and

immunological assays. This would allow the refinement of FMT from its current state to a more targeted therapy, removing the concerns associated with FMT.

- The working group identified a need for further well-designed RCTs to investigate the potential role of FMT for non-CDI indications.

9. Conclusions:

FMT has become an accepted, efficacious treatment for recurrent and/or refractory CDI. In developing this guideline, the evidence for the technique has been reviewed in the context of other available treatments. Specific guidance for best practice for an FMT service is provided.

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11.Competing interests:

- THI: Acted as consultant, advisor or speaker for Pharmacosmos and Shield Therapeutics.
- ALH: Acted as consultant, advisory board member or speaker for AbbVie, Atlantic, Bristol-Myers Squibb, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. ALH also serves on the Global Steering Committee for Genentech.
- SDG: Received consultancy fees, speaker fees and research grant support from Astellas between 2015-2017; received consultancy fees and speaker fees from MSD between 2015-2017; and received consultancy fees in 2017 from Pfizer.
- All other authors declared no conflict of interest.

12.Provenance and peer review:

Commissioned. Peer review through stakeholder consultation, HIS (SDC and Council), BSG (CSSC and Council) and externally.

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15. Figure legends and tables:

Figure 1: Proposed summary pathway for donor screening for centres preparing frozen FMT from recurring donors.

Table 1: Recommended donor history/ questionnaire: A positive response to any of these questions would usually result in exclusion from further consideration as a donor, although this would depend upon the particular circumstances/ answers given.

1. Receipt of antimicrobials within the past three months.
2. Known prior exposure to HIV and/ or viral hepatitis, and known previous or latent tuberculosis.
3. Risk factors for blood-borne viruses - including high risk sexual behaviours, use of illicit drugs, any tattoo/ body piercing/ needlestick injury/ blood transfusion/ acupuncture, all within the previous six months.
4. Receipt of a live attenuated virus within the past six months.
5. Underlying gastrointestinal conditions/ symptoms (e.g. history of IBD, IBS, chronic diarrhoea, chronic constipation, coeliac disease, bowel resection or bariatric surgery) - also including acute diarrhoea/ gastrointestinal symptoms within the past two weeks.
6. Family history of any significant gastrointestinal conditions (e.g. family history of IBD, or colorectal cancer).
7. History of atopy (e.g. asthma, eosinophilic disorders).
8. Any systemic autoimmune conditions.
9. Any metabolic conditions, including diabetes and obesity.
10. Any neurological or psychiatric conditions, or known risk of prion disease.
11. History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia.
12. History of any malignancy.
13. Taking particular regular medications, or such medications within the past three months, i.e. antimicrobials, proton pump inhibitors, immunosuppression, chemotherapy
14. History of receiving growth hormone, insulin from cows, or clotting factor concentrates.
15. History of receiving an experimental medicine or vaccine within the past six months.
16. History of travel to tropical countries within the past six months.

Table 2: Recommended blood screening for stool donors: *EBV and CMV testing is 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 if exposed to CMV and EBV.

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

General/ metabolic screening:

- Full blood count with differential.
- Creatinine and electrolytes
- Liver enzymes (including albumin, bilirubin, aminotransferases, gamma-glutamyltransferase and alkaline phosphatase).
- C-reactive protein

Table 3: Recommended stool screening for stool donors: *Whilst CPE and ESBL are the only multi-drug resistant bacteria that are recommended to be screened for universally, consider testing for other resistant organisms (including vancomycin-resistant *Enterococci* (VRE) and/ or methicillin-resistant *Staphylococcus aureus* (MRSA)) based upon risk assessment and local prevalence.

- *Clostridium difficile* PCR
- *Campylobacter, Salmonella,* and *Shigella* by standard stool culture and/ or PCR
- Shiga toxin-producing *Escherichia coli* by PCR.
- Multi-drug resistant bacteria, at least carbapenemase-producing *Enterobacteriaceae* (CPE) and extended-spectrum beta-lactamases (ESBL)*.
- Stool ova, cysts and parasite analysis, including for *Microsporidia.*
- Faecal antigen for *Cryptosporidium* and *Giardia.*
- Acid fast stain for *Cyclospora* and *Isospora.*
- *Helicobacter pylori* faecal antigen.
- Norovirus, Rotavirus PCR.

Table 4: A summary of the GRADE system:

GRADE - strength of evidence:	GRADE - strength of recommendation:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.	*The trade-offs:* Taking into account the estimate size of the effect for main outcomes, the confidence limits around those estimates and the relative value placed on each outcome.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	*The quality of the evidence.*
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	*Translation of the evidence into practice in a particular setting:* Taking into consideration important factors that could be expected to modify the size of expected effects.
Very low quality: Any estimate of effect is very uncertain.	*Uncertainty about the baseline risk for the population of interest.*

Table 5: Criteria for stool collection:

Clear instructions should be given to donors regarding hand hygiene.
Collect stool donations in a sealable clean container. A number of specifically designed devices are available commercially.
Stool should ideally be passed directly into the clean container for collection; alternatively, it may be collected in clean tissue and transferred to the clean container.
Stool should be transported to the FMT production site as soon as possible post defaecation (and within six hours); however, if a short period of storage is necessary, this should be at 4°C.

Supplementary Material 1 for *Gut*

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

Supplementary Material 1: General additional information:

1. Additional information:

1.1. Lay summary:

Faecal microbiota transplant (FMT) involves the transfer of a sample of faeces from a healthy donor to a recipient. There are several different ways to administer the transplant, including via endoscopy, rectally as an enema, via nasogastric/ nasoenteral tube (tube passed through the nose into the stomach/ upper part of the small intestine), or via oral ingestion of capsules that contain faecal material. The transplant may either be administered fresh (i.e. immediately after preparation), or may be prepared in advance, stored in a freezer and thawed when required. FMT is an accepted and effective treatment for recurrent infection by *Clostridium difficile*, a bacterium which can cause severe illness with diarrhoea, most commonly in frail elderly populations as a complication of antibiotic use. Despite adequate treatment, *Clostridium difficile* infection recurs in about 25% of patients, and some may suffer multiple recurrences.

This guideline reviews the evidence for FMT as a treatment for *Clostridium difficile* infection (CDI) and other conditions. Recommendations are made for: which patients are most likely to benefit, how donors should be selected and screened, how FMT should be prepared and administered, how patients should be followed up, and how FMT services should be configured.

1.2. Working Party Report

1.2.1. What is the Working Party Report?

The report is a set of recommendations covering key aspects of safe and efficacious delivery of a FMT service for recurrent/ refractory *Clostridium difficile* infection (CDI). The guidelines also review the evidence for the use of FMT for non-CDI indications.

The working group recommendations have been developed systematically through multi-disciplinary discussions based on published evidence. They should be used in the development of local protocols for all relevant healthcare settings.

1.2.2. Why do we need a Working Party Report for this topic?

There is widespread and growing interest in the use of FMT as a treatment for recurrent CDI. The previous absence of randomised trials and lack of evidence-based guidelines describing best practice related to its use has led to uncertainty as to how to establish an FMT service. Existing services may be providing suboptimal clinical care. There is now a developing portfolio of randomised study evidence (including randomised controlled trial data) regarding the use of FMT in CDI and non-CDI indications, providing the opportunity to develop an evidence-based guideline for its use. There have also been recent changes to the UK regulatory framework for FMT (see **Supplementary Material 3**), which are not well-understood by clinicians.

1.2.3. What is the purpose of the Working Party Report's recommendations?

The main purpose is to inform clinicians about the use of FMT (and about the establishment of this service) for the treatment of recurrent and refractory CDI, and other possible future indications. The recommendations provide an evidence-based approach to a high quality clinical service, with appropriate governance structures. This document also serves to illustrate areas in which there are current gaps in knowledge, which will help to direct future areas of research.

1.2.4. Who are these guidelines for?

Any healthcare practitioner may use these guidelines and adapt them for their use. It is anticipated that users will include clinical staff, as well as healthcare infection prevention and control teams. It is expected that these guidelines will raise awareness of FMT amongst clinicians who care for patients with recurrent or refractory CDI, but who may be unaware that it is a feasible and accessible treatment option. The guidelines are also designed to be read by patients with CDI, helping them to understand whether FMT may be an appropriate treatment option for them.

1.2.5. How are the guidelines structured?

Each section comprises an introduction, a summary of the evidence base with levels, and a recommendation graded according to the available evidence.

1.2.6. Aim

The primary aim of this report was to assess the current evidence for all aspects relating to provision of an FMT service as treatment for recurrent or refractory CDI. A secondary aim was to review the current evidence for the efficacy of FMT in treating non-CDI conditions.

1.3. Implementation of these guidelines:

1.3.1. How can these guidelines be used to improve clinical effectiveness?

Primarily, these guidelines will inform the development of local FMT services and appropriate local operational protocols, and will guide clinical decision-making. They also provide a framework for clinical audit, a tool for improving clinical effectiveness. In addition, the future research priorities identified by the working group will allow researchers to refine applications to funding bodies.

1.3.2. How much will it cost to implement these guidelines?

Where FMT is being provided under a MHRA license according to Good Manufacturing Practice (GMP) standards, there are significant costs associated with initial setup and maintenance of the service. These include the cost of obtaining the relevant license, laboratory design and equipment to enable quality assurance, storage facilities for samples, etc. However, there is counterbalance to this, as the expectation of the working group is that the publication of this guideline may encourage provision of FMT as treatment for recurrent or refractory CDI. This has consistently been shown to be cost effective in comparison with anti-*C. difficile* antimicrobial therapy[1–4], so overall costs associated with treating the condition may actually decrease. Furthermore, there may be changes to the practice of clinicians already offering the service. For example, encouraging the use of healthy unrelated donors (who can provide multiple stool donations after one screening) reduces the cost of screening when compared to the use of an FMT recipient's relative as donor, who is likely to provide one donation only.

1.3.3. E-learning tools:

Supplementary Material 1 for *Gut*

Continuing Professional Development questions and their answers are provided for self-assessment in **Appendix 4** of this document**.**

2. Appendices

Appendix 1: Glossary

Clostridium difficile infection (CDI) - Symptomatic infection caused by the spore-forming, toxin-secreting bacterium, *Clostridium difficile*. It is the most common cause of antibiotic-associated diarrhoea, and symptoms include watery stools, fever, nausea, and abdominal pain.

Refractory CDI – Failure of an episode of CDI to respond to metronidazole and oral vancomycin, although no uniform definition.

Recurrent CDI – Defined in ESMID guidelines as 'when CDI re-occurs within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment'[4]; however, defined more variably within the reviewed literature within this guideline.

Faecal microbiota transplant – A procedure in which faecal matter (stool) is collected from a healthy screened donor, homogenised, strained, and introduced into the gastrointestinal tract of a patient.

Donor – In the context of FMT, this is a healthy screened individual that provides stool for the use in preparation of FMT.

Nasogastric – A means of reaching/ supplying the stomach via the nose for the purpose of treatment or investigation. This is usually achieved by the insertion of a tube.

Enema – A procedure in which liquid (or gas) is infused into the rectum as means for treatment or investigation.

Gut microbiota - Population of microorganisms that live in the gastrointestinal tract including bacteria, viruses and fungi.

Inflammatory bowel disease – Describes a group of chronic disorders (ulcerative colitis and Crohn's diseases) in which the gastrointestinal tract becomes inflamed. The exact cause is unknown but it is thought to result from a combination of factors that trigger the body's immune system to produce an inflammatory reaction in the gastrointestinal tract.

Supplementary Material 1 for *Gut*

Medicines and Healthcare Products Regulatory Agency - An executive agency of the Department of Health in the United Kingdom which is responsible for ensuring that medicines and medical devices are efficacious and are acceptably safe.

Appendix 2: Guideline Development

Introduction

The need for a guideline within this area was agreed at a HIS guideline scoping day, and a BSG Gut Microbiota for Health (GMfH) panel teaching/ meeting day, both in September 2015, and further meetings between both bodies confirmed the establishment of a working group. Members were chosen to reflect the range of stakeholders, but were not limited to members of BSG or HIS. Feedback from the HIS guideline scoping day (including patient representatives) was used to establish a basis for PICO questions, with the final structure of PICO questions agreed collectively by teleconference in July 2017. No payment was made to anyone involved in this guideline.

Conflict of interest

Conflict of interest was registered from all working group members and underwent ongoing review up until the point of completion. In the event of a potential conflict being identified, the working group agreed that the member should not contribute to the section affected.

Search Strategy & Results

i. Literature search strategy: PICO Review Questions:

Review Question 1: Which patients with *Clostridium difficile* infection should be considered for faecal microbiota transplant, and how should they be followed up after treatment?

Populations: Adults (18 years and over) with *Clostridium difficile* infection

Intervention: Faecal microbiota transplant

Comparison: Placebo

Vancomycin

Metronidazole

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Fidaxomicin

Intravenous immunoglobulin

Bezlotoxumab

Probiotics

Cessation of antibiotics for alternative indication

Outcomes: **Critical:** Cessation of diarrhoea and other symptoms/ relapse

Quality of life

Serious adverse events

Important: Negative tests for *Clostridium difficile* infection

Adverse events

Study design: Randomised trials

If no randomised trials identified – prospective cohort studies and retrospective case series

Review Question 2: What recipient factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

Populations: Adults (18 years and over) with *Clostridium difficile* infection

Intervention: Faecal microbiota transplant

Comparison: **Preparation of patient:**

Use of bowel purgatives vs no bowel purgatives

For upper GI administration - use of PPI/ acid suppression prior to procedure vs no acid suppression

Use of agents affecting GI motility (e.g. metoclopramide for upper GI/ loperamide for lower GI) vs no use

Time before procedure that anti-CDI antibiotics are used and stopped (comparing time courses)

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Comorbidities:

Severe CDI/ toxic megacolon vs non-severe disease

Co-existing inflammatory bowel disease (IBD) vs no IBD

Immunosuppression vs no immunosuppression

Chronic liver disease/ cirrhosis vs no chronic liver disease

Outcomes: **Critical:** Cessation of diarrhoea and other symptoms/ relapse

Quality of life

Serious adverse events

Important: Negative tests for *Clostridium difficile* infection

Adverse events

Study design: Randomised trials

If no randomised trials identified – prospective cohort studies, retrospective case series

Review Question 3: What donor factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

Populations: Adults (18 years and over) with *Clostridium difficile* infection

Intervention: Faecal microbiota transplant

Comparison: Related vs unrelated donor

Donor working in healthcare setting vs donor not from healthcare setting

BMI (comparing cut-offs used)

Age (comparing ages)

Length of time since donor had antibiotics (comparing cut-offs used)

Outcomes: **Critical :** Cessation of diarrhoea and other symptoms/ relapse

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		Quality of life
		Serious adverse events
	Important:	Negative tests for *Clostridium difficile* infection
		Adverse events
Study design:	Randomised trials	
	If no randomised trials identified – prospective cohort studies and retrospective case series	

Review Question 4: What factors related to the preparation of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

Populations:	Adults (18 years and over) with *Clostridium difficile* infection	
Intervention:	Faecal microbiota transplant	
Comparison:	Time after delivery when transplant is prepared (comparing time points)	
	Anaerobic preparation vs preparation in ambient air	
	Manual preparation vs use of blender/ homogeniser	
	Diluent used (comparing normal saline, phosphate-buffered saline, water, milk/ yoghurt and others)	
	Amount of stool/ transplant administered (comparing amounts)	
	Fresh preparation vs frozen preparation:	
	-comparing glycerol vs other cryopreservative	
	-comparing concentration of cryopreservative used	
	-comparing length of time that frozen for before use	
Outcomes:	**Critical:**	Cessation of diarrhoea and other symptoms/ relapse
		Quality of life
		Serious adverse events
	Important:	Negative tests for *Clostridium difficile* infection

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Adverse events

Study design: Randomised trials

If no randomised trials identified – prospective cohort studies and retrospective case series

Review Question 5: What factors related to administration of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

Populations: Adults (18 years and over) with *Clostridium difficile* infection

Intervention: Faecal microbiota transplant

Comparison: Upper GI administration (nasogastric, nasoduodenal or nasojejunal tube; upper GI endoscopy) *vs* lower GI administration (enema, rectal catheter, colonoscopy)

Encapsulated vs full transplant

Outcomes: **Critical:** Cessation of diarrhoea and other symptoms/ relapse

Quality of life

Serious adverse events

Important: Negative tests for *Clostridium difficile* infection

Adverse events

Study design: Randomised trials

If no randomised trials identified – prospective cohort studies, and retrospective case series

Review Question 6: What is the clinical effectiveness of faecal microbiota transplant in treating conditions other than *Clostridium difficile* infection?

Populations: Adults (18 years and over) with conditions of interest (e.g. inflammatory bowel disease)

Intervention: Faecal microbiota transplant

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Comparison: Standard care for the condition of interest

Autologous faecal microbiota transplant

Outcomes: **Critical:** Clinical improvement

Improvement in laboratory/ radiological/ endoscopic tests

Quality of life

Serious adverse events

Important: Adverse events

Study design: Randomised trials

ii. Literature search terms:

Review Questions 1 – 5:

EMBASE

1. exp Clostridium difficile infection/ or exp Clostridium difficile toxin B/ or exp Clostridium difficile toxin A/

2. clostridium difficile.ti,ab.

3. c diff*.ti,ab.

4. (CDAD or RCDI or CDI).ti,ab.

5. pseudomembranous.ti,ab.

6. exp pseudomembranous colitis/

7. (antibiotic* adj2 (diarrhea or diarrhoea or colitis)).ti,ab.

8. (FMT or HPI).ti,ab.

9. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant* or infus* or transfus* or implant* or instil* or donat* or donor* or reconstitut* or therap* or bacteriotherapy or encapsulated* or capsul*)).ti,ab.

10. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.

11. transplant*.ti,ab.

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12. exp transplantation/

13. 8 or 9

14. 10 and (11 or 12)

15. 13 or 14

16. or/1-7

17. 15 and 16

MEDLINE

1. Clostridium difficile/

2. clostridium difficile.ti,ab.

3. c diff$.ti,ab.

4. Enterocolitis, Pseudomembranous/

5. (antibiotic$ adj2 (diarrhoea or colitis)).ti,ab.

6. (antibiotic$ adj2 (diarrhea or colitis)).ti,ab.

7. pseudomembranous.ti,ab.

8. (CDAD or CDI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

9. RCDI.ti,ab.

10. Clostridium Infections/

11. FMT.mp. or HPI.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant$ or infus$ or transfus$ or implant$ or instil$ or donat$ or donor or reconstitut$ or therap$ or bacteriotherapy or encapsulated$ or capsul$)).ti,ab.

13. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.

Supplementary Material 1 for *Gut*

14. (transplant$ or infus$ or transfus$ or implant$ or instil$ or donat$ or donor or reconstitut$ or therap$ or bacteriotherapy or encapsulated$ or capsul$).ti,ab.

15. Transplantation/

16. Transplants/

17. 11 or 12

18. 14 or 15 or 16

19. 13 and 18

20. 17 or 19

21. or/1-10

22. 20 and 21

Limits:

1. After 1980.
2. Studies in English only.
3. Human studies only.
4. Exclude case reports.
5. Exclude case series with less than 10 patients.

Review Question 6:

EMBASE

1. (FMT or HPI).ti,ab.

2. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant* or infus* or transfus* or implant* or instil* or donat* or donor* or reconstitut* or therap* or bacteriotherapy)).ti,ab.

3. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.

4. transplant*.ti,ab.

5. exp transplantation/

6. 1 or 2

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7. 3 and (4 or 5)

8. 6 or 7

9. (clostridium difficile or CDAD or RCDI or CDI).ti.

10. 8 not 9

11. limit 10 to (clinical trial or randomized controlled trial or controlled clinical trial)

MEDLINE

1. FMT.mp. or HPI.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

2. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant$ or infus$ or transfus$ or implant$ or instil$ or donat$ or donor or reconstitut$ or therap$ or bacteriotherapy)).ti,ab.

3. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.

4. Transplantation/

5. Transplants/

6. transplant$.ti,ab.

7. Fecal Microbiota Transplantation/

8. 4 or 5 or 6

9. 3 and 8

10. 1 or 2 or 7 or 9

11. (clostridium difficile or cdiff or CDAD or RCDI or CDI or pseudomembranous).ti.

12. 10 not 11

13. limit 12 to (clinical trial or randomized controlled trial or controlled clinical trial)

Limits:

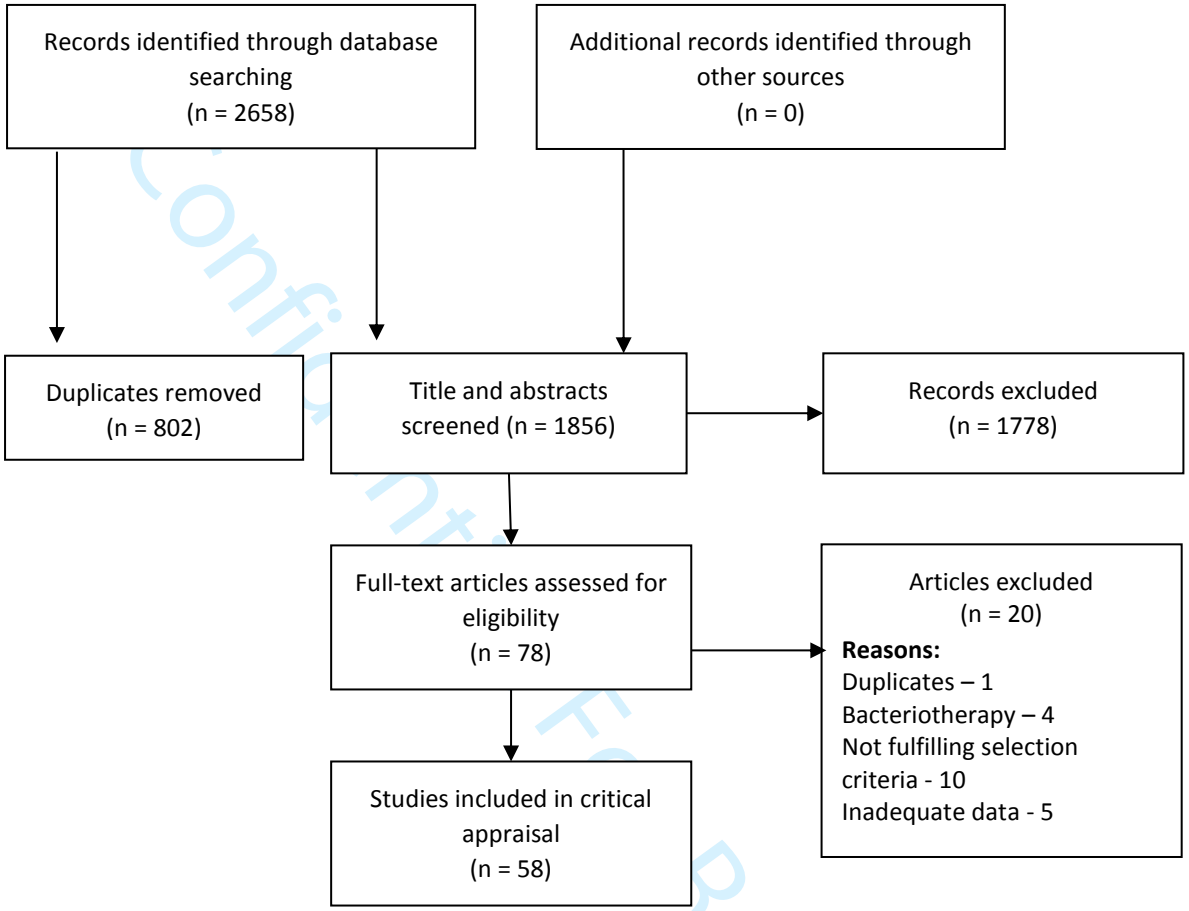
1. After 1980.
2. Studies in English only.

Supplementary Material 1 for *Gut*

3. Human studies only.
4. Randomised trials only.

Supplementary Material 1 for *Gut*

iii. ***Summary of the data extraction and literature review process (includes Q1-6):***



Appendix 3: Consultation Stakeholders:

Individuals or organisation who were invited to and/ or attended the scoping day for these guidelines (as well as to provide feedback in stakeholder consultation) included:

- HRPA (Ireland) (Dr Eadaoin Griffin attended)
- Human Tissue Authority (Dr Robert Watson attended)
- NHS Wales
- NHS Scotland
- ECDC
- Royal College of Pathologists
- Royal College of General Practitioners
- Infection Prevention Society

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- Public Health England
- Royal College of Physicians
- Royal College of Nursing
- Royal College of Surgeons
- ESCMID
- MRSA Action
- HSCNI
- Institute of Microbiology and Infection, University of Birmingham (Prof Peter Hawkey and Dr Victoria McCune attended)
- Microbiology, Royal Devon and Exeter NHS Foundation Trust (Dr Ray Sheridan, Dr Alaric Colville, Dr Robert Porter and Dr Melissa Baxter attended)
- C diff support (Ms Graziella Kontkowski attended)
- OpenBiome (Dr Majdi Osman and Dr Carolyn Edelstein attended)
- Dr Sally Cudmore (University College Cork) attended
- Dr Ngozi Elumogo attended (Microbiology, Norfolk & Norwich University NHS Trust)
- Dr Vanya Gant (University College London Hospitals)
- Dr Simon Goldenberg attended (Guy's and St Thomas' NHS Foundation Trust)
- Dr Bram Goorguis attended (Academic Medical Centre, Amsterdam)
- Dr Geraldine Moloney attended (Microbiology, Trinity College Dublin)
- Dr Benjamin Mullish attended (Imperial College Healthcare NHS Trust)
- Dr Laura Prtak attended (Sheffield Teaching Hospitals NHS Trust)
- Mr Glenn Taylor attended (Taymount Clinic)
- Dr Mark Wilks attended (Microbiology, Barts and The London NHS Trust)

Appendix 4. Continuing Professional Development material

1) In which of the following settings would you **most strongly** avoid giving a patient FMT?
   a) Immunocompromised patients
   b) Decompensated liver disease
   c) Heart failure
   d) History of anaphylactic food allergy
   e) A previous failed FMT

Supplementary Material 1 for *Gut*

Answer: d

2) Where is FMT best sourced, if available?
   a) Related healthy donor
   b) Health care professional
   c) Centralised stool bank
   d) Pooled from multiple donors
   e) Any of above

Answer: c

3) What is the maximum recommended length of time between stool donation and stool processing?
   a) 6 hours
   b) 7 hours
   c) 8 hours
   d) 9 hours
   e) 10 hours

Answer: a

4) For which non-CDI condition is FMT currently recommended?
   a) Irritable bowel syndrome
   b) Obesity and metabolic syndrome
   c) Parkinson's disease
   d) Ulcerative colitis
   e) None of the above

Answer: e

5) When considering setting up an FMT service in the UK, which organisation should be contacted to seek guidance in establishing the service?
   a) Medicines and Healthcare Products and Regulatory Agency
   b) Medicines and Healthcare Products Regulatory Authority
   c) Medical Drugs and Healthcare Products and Regulatory Agency

d) Medical Drugs and Healthcare Products Regulatory Authority

e) None of the above

Answer: b

3. References:

1. Varier RU, Biltaji E, Smith KJ, et al. Cost-Effectiveness Analysis of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. *Infect Control Hosp Epidemiol*. 2015;36(4):438-444. doi:10.1017/ice.2014.80.

2. Konijeti GG, Sauk J, Shrime MG, Gupta M, Ananthakrishnan AN. Cost-effectiveness of competing strategies for management of recurrent Clostridium difficile infection: a decision analysis. *Clin Infect Dis*. 2014;58(11):1507-1514. doi:10.1093/cid/ciu128.

3. Baro E, Galperine T, Denies F, et al. Cost-Effectiveness Analysis of Five Competing Strategies for the Management of Multiple Recurrent Community-Onset Clostridium difficile Infection in France. Green J, ed. *PLoS One*. 2017;12(1):e0170258. doi:10.1371/journal.pone.0170258.

4. Lapointe-Shaw L, Tran KL, Coyte PC, et al. Cost-Effectiveness Analysis of Six Strategies to Treat Recurrent Clostridium difficile Infection. Deshpande A, ed. *PLoS One*. 2016;11(2):e0149521. doi:10.1371/journal.pone.0149521.

Supplementary Material 2 for *Gut*

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

Supplementary Material 2: Additional Appendices

Appendix A. Scope

1. Guideline title

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

1.1. Short title

The use of faecal microbiota transplant

2. The remit

i. To review the evidence (include randomised trial evidence) for the efficacy of faecal microbiota transplant (FMT) in the treatment of adults (≥18 years), both in *Clostridium difficile* infection (CDI) and in other clinical conditions, and use this to make recommendations about optimal recipient selection and management, donor assessment, material preparation and administration, and other key elements of FMT delivery.

ii. To provide specific guidance about best practice for an FMT service within the context of the regulatory framework for the intervention as it currently exists in the UK and beyond.

Whilst this is not a guideline specifically addressing the management of *Clostridium difficile* infection (CDI), the working group will include consideration of where FMT should be considered within the conventional treatment algorithm of patients with CDI (specifically, in which patients it should be considered, and at which point in their care).

The working group agreed that for the purposes of this guideline, faecal microbiota transplant would be defined as treatment that involves the administration of manipulated whole stool.

There is a growing literature of the use of 'bacteriotherapy' originally deriving from healthy donor stool as a potential alternative to FMT (including commensal bacteria, spores, bacteriophages and/ or bacterial proteins or metabolites). However, the working group considered this to still be at the research stage, and would not be considered further.

2.1. Population

2.1.1. Groups that will be covered

Adults (≥18 years) in whom:
i. FMT has been used as treatment for CDI.
ii. FMT has been used as treatment for a non-CDI indication.

Given the variability in the means used to diagnose CDI within different studies, the working group agreed to consider the suitability of the definition used on a study-by-study basis.

2.1.2. Groups that will not be covered

Children and young people (<18 years).

2.2. Healthcare setting

All settings in which National Health Service care is received, and/ or clinical trials are undertaken.

2.3. Clinical management

2.3.1. Key clinical issues that will be covered

a) Appropriate selection of patients with CDI for FMT, and best practice in their management post-FMT.
b) Optimal selection of donors of faecal material, and maintenance of a donor pool.
c) Identification of the preferred means of preparation and administration of FMT to recipients.
d) Evaluation of the safety and efficacy of FMT in treating non-CDI indications.
e) Best practice in the development and delivery of an FMT service.

2.3.2. Clinical issues that will not be covered

a) General management of CDI.

b) General management of non-CDI conditions in which FMT may have a role in therapy.

2.4. Main outcomes

Recommendations for practice

a) Patient/ recipient selection, and peri-FMT management
b) Donor selection
c) Preparation and administration of FMT
d) Efficacy and safety of FMT for non-CDI indications
e) Provision of an FMT service

2.5. Economic aspects

Where FMT is being provided under a MHRA license according to Good Manufacturing Practice (GMP) standards, there are significant costs associated with initial setup and maintenance of the service. These include the cost of obtaining the relevant license, laboratory design and equipment to enable quality assurance, storage facilities for samples, etc. However, there is counterbalance to this, as the expectation of the working group is that the publication of this guideline may encourage provision of FMT as treatment for recurrent or refractory CDI. This has consistently been shown to be cost effective in comparison with anti-*C. difficile* antimicrobial therapy[31–34], so overall costs associated with treating the condition may actually decrease. Furthermore, there may be changes to the practice of clinicians already offering the service. For example, encouraging the use of healthy unrelated donors (who can provide multiple stool donations after one screening) reduces the cost of screening when compared to the use of an FMT recipient's relative as donor, who is likely to provide one donation only.

2.6. Status

2.6.1. Scope

This is the final scope.

2.6.2. Timing

The development of the guideline recommendation will begin in July 2017.

Supplementary Material 2 for *Gut*

3. Related NICE guidance

National Institute for Health and Care Excellence. *Faecal microbiota transplant for recurrent Clostridium difficile infection.* NICE Interventional Procedures Guidance IPG485. London: NICE; 2014. Available at: https://www.nice.org.uk/guidance/ipg485 [last accessed 19th December 2017].

4. Further information

Guideline development process

Scottish Intercollegiate Guidelines Network. *SIGN 50: a guideline developer's handbook.* Revised edition. Edinburgh: Healthcare Improvement Scotland; 2014. Available at: http://www.sign.ac.uk [last accessed December 2017].

Appendix B. Declarations of interest

B.1. *Introduction*

All members of the Working Group were required to make formal declarations of interest at the outset, and these were updated throughout the development process. No interests were declared that required any actions.

B.2. *Tariq Iqbal*

First meeting 19/07/17: no declarations of interest; second meeting 04/10/17: no change.

Third meeting 19/10/17: consultant, advisor or speaker for: Pharmacosmos and Shield Therapeutics.

B.3. *Simon Goldenberg (co-chair)*

First meeting 19/07/17

Advisory board and/ or consultancy and/ or speaker fees: Astellas, MSD, Pfizer.

Second meeting 04/10/17; third meeting 19/10/17: no change.

No action required.

B.4. *Ailsa Hart*

First meeting 19/07/17

Advisory board and/ or consultancy and/ or speaker fees: AbbVie, Atlantic, Bristol-Myers Squibb, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. Global steering committee for Genentech.

Second meeting 04/10/17; third meeting 19/10/17: no change.

No action required.

No declared conflict of interests for the other participants.

Supplementary Material 2 for *Gut*

Appendix C. Clinical evidence tables

C.1. Reviewed case series of FMT for recurrent or refractory CDI

Supplementary Material 2 for *Gut*

Paper	Study and patient characteristics	Donor characteristics	FMT characteristics	Outcomes	Adverse events	CRD
Aas *et al, Clinical Infectious Diseases,* 2003	Case series. Number of patients: 18. Female: male 13:5. Age (mean): 73+/-9 (range 53-88) years. Comorbidities: x1 patient with Crohn's colitis, x1 with leukaemia. CDI features: Recurrent (at least 2 x laboratory-confirmed CDI after initial antibiotic treatment). CDI diagnosis confirmation: Cytotoxin A and B positivity. Pre-FMT antibiotics: Metronidazole +/- vancomycin (not defined).	Donors were 15 family members, and 3 clinical volunteers. Working in healthcare: Yes - for 3 donors. Donor demographics: Not defined. Donor screening: Questionnaire not explicitly stated. Travel and antibiotic exclusion period: No antibiotics for 6 months prior; nil stated regarding travel. Screening blood tests: Hepatitis A, B and C, HIV-1/-2, syphilis. Screening stool tests: C.*difficile*, enteric pathogens, ova, cysts and parasites.	Amount of stool per transplant / administered to patients: 30g stool in 50-70ml normal saline; only 25ml of total administered to patient. Diluent used to prepare: Normal saline. Diluent used to store if frozen: N/A – fresh. Preparation methods: Homogenised in domestic blender, then coffee filter. Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: all nasogatric (18); lower GI: nil; capsules: nil. Number of infusions: Single infusion for all patients. Bowel purgative: Not described. PPI: 20mg omeprazole on day prior to FMT and day of FMT. Antimotility: Not described. Prokinetics: Not described.	Overall cure within stated follow up period: 83.3% (n=15/18). Cure with one infusion alone: 83.3% (n=15/18). Total follow-up period: 90 days.	Minor GI adverse events: Nil stated. Minor non-GI adverse events: Nil stated. Serious adverse events: Nil stated. Deaths: x2 - one related to ESRF, one related to COPD.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: No - 89%.

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			Time before CDI treatment was stopped before FMT: Continued until day of FMT.			

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Agrawal *et al, Journal of Clinical Gastroenterology,* 2016	Case series. Number of patients: 146. Female: male: 100: 46. Age(mean): 78.6 (range 65-97) years. Comorbidities: Immunosupression in 15 patients (x3 Crohn's, x2 UC, x1 renal transplant) CDI features: 89 with recurrent CDI. CDI diagnosis confirmation: As per ACG guidelines. Pre-FMT antibiotics: All had prior metronidazole, vancomycin and/ or fidaxomicin.	Donors were identified by the patient or - if not available - provided by the physician. Working in healthcare: Not stated. Donor demographics: No antibiotics for last three months. Excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, and/ or high risk lifestyle in last three months. Donor screening: Questionnaire - excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, high risk lifestyle in last three months. Travel and antibiotic exclusion period: Exclusion if travel to an area of high incidence of infectious diarrhoea, and/ or antibiotics within past three months. Screening blood tests: Hepatitis A, B and C, HIV-1/-2, syphilis. Screening stool tests: *C difficile*, enteric pathogens, ova, cysts	Amount of stool per transplant / administered to patients: 60-100g of fresh stool. Diluent used to prepare: Normal saline, upper GI: 75-200ml; lower GI: 250-400ml; enema: 150-200ml. Diluent used to store if frozen: N/A – fresh. Preparation methods: Handstirred and blender, sifted through gauze. Time from preparation to transplant (fresh): Not stated. Time period for storage (frozen): N/A. Route administered: upper GI (16); lower GI (130); capsules: nil. Number of infusions: 1 routinely; 2nd infusion given with vancomycin so data unable to be extracted. Bowel purgative: PEG on day prior to FMT. PPI: Not stated. Antimotility: Loperamide on day of FMT. Prokinetics: Not stated.	Overall cure within stated follow-up period: 83% (n=121/146) . Cure with one infusion alone: 83% (n=121/146) . Total follow up period: mean follow up was 12.3 months (range 1-48 months).	Minor GI adverse events: Nil stated. Minor non-GI adverse events: Nil stated. Serious adverse events: x2 microscopic colitis, x1 Sjögren's, x1 scalp follicular lymphoma, x1 contact dermatitis and idiopathic Bence-Jones gammaglobulinaemia. In addition, x1 SCC, x1 ileus (died two weeks after ileus), x1 colonic perforation secondary to CMV colitis and subsequent death after 1 year. Patients developing cancers had underlying risk factors. Deaths: x10 (x4 decompensated CCF, x3 malignancies, x1 dementia, x1	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: No. At least 90% followed up: No.

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		and parasites, *Giardia*, *Cryptosporidium*, *Isospora, H. pylori,* Rotavirus.	Time before CDI treatment was stopped before FMT: Between 3 days prior to FMT and one day prior to FMT.		stroke, x1 pneumonia); deaths between 19 days to 7 months post-FMT.	

Supplementary Material 2 for *Gut*

Alrabaa *et al, Transplant Infectious Diseases,* 2017	Case series. Number of patients: 13. Female: male: 8:5. Age (median): 69 (range 59-74) years. Comorbidities: Yes - x4 OLT, x1 kidney/ liver transplant, x1 lung transplant, x1 HIV+ with CD4 count of 453. x1 immunocompromised patients with IBS, x1 immunocompetent patient with IBS; no IBD patients. CDI features: Not clear if recurrent or refractory. Mean of 4 previous episodes of CDI prior to FMT. CDI diagnosis confirmation: PCR. Pre-FMT antibiotics: All patients had previously had oral vancomycin, x7 prev metronidazole (either with or without vancomycin). x5 received fidaxomicin	Donors were unrelated. Working in healthcare: Nox Donor demographics: As per OpenBiome protocolx Donor screening: Questionnaire - as per OpenBiome protocolx Travel and antibiotic exclusion period: As per OpenBiome protocolx Screening bloods: FBC, hepatitis A, B and C, LFTs, HIV, HTLV-1/-2, syphilis. Screening stools: C.*difficile* toxin, MC&S, ova, cysts and parasites, *H.pyl*ori stool antigen.	Amount of stool per transplant / administered to patients: 12.5g of stool in 28.5g of product. Diluent used to prepare: normal saline - diluted to approx 100-150ml to administer. Diluent used to store if frozen: Not clear. Preparation methods: As per OpenBiome protocol. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): As per OpenBiome protocol - not described in paper. Route administered: Upper GI (nasoduodenal): 13; lower GI: 0; capsules: nil. Number of infusions: One routinely, but retreated if relapsed after primary outcome. However - one renal transplant patient received 2 doses of FMT on consecutive days (with successful outcome). Bowel purgative: Bowel preparation used - GoLytely (PEG). PPI: 40mg pantoprazole night before and morning of procedure.	Overall cure within stated follow up period: 84.6% (*n*=11/13) at eight weeks post-FMT. Cure with one infusion alone: 100% (*n*=13/13) at 5 days. Total follow up period: Follow up up to 8 weeks described.	Minor GI adverse events: Several patients transient cramps and/ or diarrhoea. Minor non-GI adverse events: Nil noted. Serious adverse events: x1 patient had episode of CMV reactivation at the time of FMT - thought unrelated. X1 patient had episode of mild transplant rejection two months after FMT - thought unrelated. Deaths: None.	Selection/ eligibility reported: Yes. Consecutively recruited: Not clearly described. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	with or after oral vancomycin.		Antimotility: Loperamide 4mg 1 hour post FMT. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: See last box.			

Supplementary Material 2 for *Gut*

Brandt *et al, American Journal of Gastroenterology,* 2012	Case series. Number of patients: 77. Female: male: 56: 21. Age (mean): 65+/-17 (range 22-87) years. Comorbidities: Not stated. CDI features: All recurrent/ refractory. CDI diagnosis confirmation: Not clear. Pre-FMT antibiotics: 62 patients had had prior metronidazole, 76 vancomycin (25 tapered vancomycin), 17 rifaximin.	Donors were 45 spouses/ partners; 21 relatives; 1 unknown person. Working in healthcare: No. Donor demographics: No antibiotics within past 3 months. Donor screening: Questionnaire - not stated. Travel and antibiotic exclusion period: Excluded if travel to area of high incidence of infectious diarrhoea, or if antibiotics within past three months. Screening blood tests: HIV-1, HIV-2, hepatitis A, B and C, Syphillis. Screening stool tests: *Clostridium difficile toxin* (if unavailable then EIA), MC&S, *Giardia, Cryptosporidium*, ova, cysts and parasites, *H.pylori*, Acid Fast stain for *Cyclospora, Isospora*.	Amount of stool per transplant / administered to patients: 6 tablespoons of stool up to entire donation; 300-700ml of transplant administered. Diluent used to prepare: Normal saline. Diluent used to store if frozen: N/A – fresh. Preparation methods: Hand blender used to prep. Time from preparation to transplant (fresh): Within 8 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: 0; lower GI: all 77 colonoscopic. Number of infusions: 77 patients had one (patients that had second not included because given with concurrent vancomycin). Bowel purgative: All patients given prep but no details. PPI: Not described. Antimotility: Not described. Prokinetics: Not described.	Overall cure within stated follow up period: N/A. Cure with one infusion alone: 90.9% (*n*=70/77). Total follow up period: not clear, but some patients followed-up to 3 years.	Minor GI adverse events: Not stated. Minor non-GI adverse events: Not stated. Serious adverse events: Nil. Deaths: x7 deaths (cause unknown in one case, x1 metastatic colorectal cancer (present from pre-FMT), x1 metastatic ovarian cancer, x1 pneumonia (non-enteric organism), x1 MI, x1 stroke, x1 sepsis five months after FMT.	Selection/ eligibility reported: Yes. Consecutively recruited: Not clear. Prospectively recruited: No. Loss to follow up explained: Reported but not explained. At least 90% followed up: No - only 77%.

Supplementary Material 2 for *Gut*

			Time before CDI treatment was stopped before FMT: 3 days.			

Supplementary Material 2 for *Gut*

Brumbaugh *et al, Journal of Pediatrics,* 2017	Case series. Number of patients: 42. Female: male: 23: 19. Age (median): 9 (range 1 -18) years. Comorbidities: 31% had IBD (x4 Crohn's, x9 UC); 29% 'medically complex', including oncological, metabolic, cardiopulmonary or neurological diagnoses. CDI features: All children had had at least one course of vancomycin. Previously recurrent - at least 2 episodes. CDI diagnosis: Diarrhoea, haematochezia and/ or crampy abdominal pain in combination with positive *C. difficile* PCR. Pre-FMT antibiotics: Not stated.	Donor: OpenBiome-supplied FMT. Working in healthcare: No. Donor demographics: Not stated. Donor screening: Questionnaire: As per OpenBiome protocol. Travel and antibiotic exclusion period: As per OpenBiome protocol. Screening bloods: As per OpenBiome protocol. Screening stools: As per OpenBiome protocol.	Amount of stool per transplant / administered to patients: 30ml OpenBiome aliquot/ capsule, although not defined re stool quantity. Diluent used to prepare: As per OpenBiome protocol Diluent used to store if frozen: As per OpenBiome protocol Preparation methods: As per OpenBiome protocol Time from preparation to transplant (fresh): None given fresh Time period for storage (frozen): N/A Route administered: Upper GI: 41, nasogastric administration (some children used pre-existing gastrostomy); lower GI: 0; capsules: 1 (1 x 30 capsules). Number of infusions: 1 routinely Bowel purgative: Not stated PPI: Rantidine for 24hrs prior to FMT Antimotility: N/A Prokinetics: N/A Time before CDI treatment was stopped	Overall cure within stated follow up period: 71% (*n*=30/42). Cure with one infusion alone: 71% (*n*=30/42) - remission in 94% (*n* =16/17) otherwise healthy children, 54% (*n* =7/13) (54%) with IBD, 75% (*n*=9/12) medically complex. Success in 71% of children when via NGT, and 67% via gastrostomy (non-significant). Total follow up period: 5 patients with initial failure opted for 2nd and 2 cured, so total success of 76% (*n*=32/42).	Minor GI adverse events: 6/47 FMT administrations accompanied by vomiting within 24hrs; self-resolved. Minor non-GI adverse events: Nil reported. Serious adverse events: Nil reported. Deaths: Nil reported.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			before FMT: 48 hours, after minimum of 5 days of vancomycin.			

Supplementary Material 2 for *Gut*

Chin et al, *Clinical Gastroenterology & Hepatology,* 2016	Case series. Number of patients: 35. Female: male: 16: 19. Age (mean): 43 (range 8 -93) years. Comorbidities: IBD in all, 8 on corticosteroids, 3 on Immunomodulators, 11 on biologics. CDI features: Recurrent - at least 2 episodes. CDI diagnosis confirmation: Not stated. Pre-FMT antibiotics: Not stated.	Donors were age 18 - 50, no medications, BMI 18.5 – 25. Working in healthcare: Not stated. Donor demographics: Not stated. Donor screening: Questionnaire - adapted from US blood bank. Travel and antibiotic exclusion period: Excluded if antibiotic within past six months. Screening blood tests: FBC, U&E, LFTs, CRP, ANA, hepatitis A, B and C, HBV, HIV-1/-2, syphilis. Screening stool tests: Faecal occult blood, rotavirus, bacterial pathogens, ova, cysts and parasites, Acid fast stain for *Giardia* and *Cryptosporidium*, *C difficile*, *H. pylori.*	Amount of stool per transplant / administered to patients: 41g of stool on average. Diluent used to prepare: Normal saline. Diluent used to store if frozen: Frozen in 10% glycerol. Preparation methods: Ambient air. Time from preparation to transplant (fresh): N/A; given fresh. Time period for storage (frozen): Up to 156 days. Route administered: Upper GI: 5 via nasogastric tube; lower GI: 3 via colonoscopy; capsule: 27 patients. Number of infusions: Not stated. Bowel purgative: Not routinely - just for colonoscopy (4 litres of PEG). PPI: 7 on PPI not as premedications. Antimotility: Not described. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 2 days prior to FMT.	Overall cure within stated follow up period: N/A. Cure with one infusion alone: Not stated. Total follow up period: At least 2 months (range 2 to 6 months).	Minor GI adverse events: Not specified. Minor non-GI adverse events: Not specified. Serious adverse events: two required surgery (diverting colostomy and total proctectomy), two developed perianal disease with no prior history of it. Deaths: Ni.	Selection/ eligibility reported: No. Consecutively recruited: No. Prospectively recruited: No. Loss to follow up explained: No. At least 90% followed up: No.

Supplementary Material 2 for *Gut*

Cohen et al, *Israel Medical Association Journal,* 2016	Case series. Number of patients: 22. Female: male: 9: 13. Age (median): Median 71.5 (range 16-92) years. Comorbidities: x1 IBD (colonoscopic group), x2 patients on chemotherapy, unclear why. CDI features: Recurrent or refractory. CDI diagnosis confirmation: Diarrhoea and toxin testing. Pre-FMT antibiotics: 19 patients given previous metronidazole, 9 vancomycin (with 13 both together).	Donors were 13 unrelated, 9 related. Working in healthcare: Yes - for unrelated. Donor demographics: No details - just says screening similar to blood donors. Donor screening: Questionnaire - no details. Travel and antibiotic exclusion period: Excluded if antibiotics within past six months. Screening bloods: No details. Screening stools: No details.	Amount of stool per transplant / administered to patients: 60g stool average (35-75g), 250ml total once mixed with saline (100 - 300ml range). Diluent used to prepare: Normal saline. Diluent used to store if frozen: Not stated. Preparation methods: Some fresh, some frozen. Time from preparation to transplant (fresh): Not stated. Time period for storage (frozen): No details. Route administered: Upper GI: nasoduodenal in 10; lower GI: colonoscopic in 12. Number of infusions: 1 FMT. Bowel purgative: 3l of PEG if colonoscopic administration. PPI: PPI if upper GI administration. Antimotility: Not described. Prokinetics: Metoclopramide just prior to upper GI administration.	Overall cure within stated follow up period: 72.7% (*n*=16/22) at 2 months. Cure with one infusion alone: 72.7% (*n*=16/22) (5/10 upper GI (out of 7 analysed), 91.7% (*n*=11/12) for lower GI (out of 11 analysed)). Total follow up period: Results reported at two months, but followed up to six months (7 months in the upper GI arm and 5 in the lower GI arm followed up to 6 months).	Minor GI adverse events: x5 transient constipation/ abdominal discomfort. Minor non-GI adverse events: Not stated. Serious adverse events: See deaths. Deaths: x7 (x1 due to CDI, x1 chronic resp disease, x1 related to dialysis, x2 pneumonia, x1 sepsis at ten days post-FMT (aspiration of stool; had been gastroscopic administration), x1 died at home ?cause).	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Time before CDI treatment was stopped before FMT: 12-24hrs.			

Supplementary Material 2 for *Gut*

Costello *et al, Alimentary Pharmacology and Therapeutics,* 2015	Case series. Number of patients: 20. Female: male: not stated. Age(median): 69 years. Comorbidities: Not stated. CDI features: All recurrent. CDI diagnosis confirmation: Not stated. Pre-FMT antibiotics: Conventional therapy with metronidazole, vancomycin and/or fidaxomicin had failed in all.	Donors were 4 healthy volunteers. Working in healthcare: No. Donor demographics: No details. Donor screening: Questionnaire - adapted from US blood bank. Travel and antibiotic exclusion period: Excluded if travel to diarrhoea-endemic areas witihin 6 months and/ or used antibiotics for 3 months. Screening blood tests: HIV -1 and -2, hepatitis A, B and C, and syphillis. Screening stool tests: *C difficile* toxin B PCR, routine MC&S, faecal *Giardia* antigen, faecal *Cryptosporidium*, Acid-fast stain for *Cyclospora, Isospora*, ova, cysts and parasites, *H.pylori* fecal antigen.	Amount of stool per transplant / administered to patients: Not stated. Diluent used to prepare: Normal saline. Diluent used to store if frozen: 10% glycerol. Preparation methods: Anaerobically prepared. Time from preparation to transplant (fresh): all frozen. Time period for storage (frozen): 16 patients had stool stored for < 2 months. 4 patients had stool stored > 2 months. Route administered: Upper GI: 1; lower GI: 19; capsule: nil. Number of infusions: 17 patients had 1, 3 patients had 2. Bowel purgative: Not reported. PPI: Not reported. Antimotility: Not reported. Prokinetics: Not reported. Time before CDI treatment was stopped before FMT: Not reported.	Overall cure within stated follow up period: 85% (*n*=17/20). Cure with one infusion alone: 85% (*n*=17/20). Total follow up period: Minimum 3 months (but up to 14 months).	Minor GI adverse events: None. Minor non-GI adverse events: None. Serious adverse events: None. Deaths: None.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

Emanuelsson *et al, Scandanavian Journal of Infectious Diseases,* 2014	Case series. Number of patients: 23. Female: male: 14: 9. Age (median): 66 years (range 25-99) years (including 8 additional patients treated with 'bacteriotherapy'). Comorbidities: 3 with diabetes mellitus, 1 with microscopic colitis. CDI features: All recurrent. CDI diagnosis confirmation: Culture and/or toxin EIA. Pre-FMT antibiotics: Metronidazole and/or vancomycin used in all patients beforehand.	Donors were spouses or close relative. Donor working in healthcare: No. Donor demographics: Not stated. Donor screening: Questionnaire – asked regarding current and previous GI diagnoses/ symptoms. Travel and antibiotic exclusion period: Definitely an antibiotic use restriction but not clearly stated. Screening blood tests: HIV-1 and -2, hepatitis C virus, and hepatitis B surface antigen. Screening stool tests: *Salmonella, Shigella, Campylobacter,* enterohemolytic *Escherichia coli,* and *Clostridium difficile.*	Amount of stool per transplant / administered to patients: 50g in 500mls. Diluent used to prepare: Normal saline. Diluent used to store if frozen: N/A - fresh. Preparation methods: Anaerobically prepared. Time from preparation to transplant (fresh): Not stated. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; ower GI: 23 (enema/ rectal catheter); capsules: nil. Number of infusions: 22 patients eceived 1 FMT, 1 patient received 2 FMTs. Bowel purgative: Not stated. PPI: Not stated. Antimotility: Not stated. Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: Not stated.	Overall cure within stated follow up period: 65% (*n*=15/23). Cure with one infusion alone: 65% (*n*=15/23). Total follow up period: Median follow up of 18 months (range 0-201 months).	Minor GI adverse events: None. Minor non-GI adverse events: None. Serious adverse events: None. Deaths: None.	Selection/eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

Fischer *et al, Inflammatory Bowel Diseases,* 2016	Case series Number of patients: 67 Female: male: 39:28 Age (mean/ standard deviation): Mean 45.42 (+/-17.33) years. Comorbidities: x5 PSC, x4 liver transplant, x3 end stage liver disease, concurrent IBD in all (x35 Crohn's, x31 UC, x1 indeterminate colitis). CDI features: recurrent or refractory. CDI diagnosis confirmation: Return of diarrhoea and positive CDI testing within 12 weeks of FMT. Pre-FMT antibiotics: metrronidazole in 47 patients, vancomycin in 63, vancomycin taper in 38 patients,, fidaxomicin in 7, rifaxamin in 7.	Donors were patient-directed donor or unrelated healthy volunteers. Donors working in healthcare: not stated. Donor demographics: As per Bakken *et al, Clin Gastroenterol Hepatol,* 2011. Donor screening: Questionnaire - as per Bakken *et al, Clin Gastroenterol Hepatol,* 2011. Travel and antibiotic exclusion period: Excluded as donor if travel within last 6 months where diarrheal illnesses are endemic or risk of travelers diarrhea is high, and/ or use of antibiotics within 3 months. Screening blood tests: HIV -1&-2, hepatitis A, B and C, syphilis. Screening stool tests: As per Bakken *et al, Clin Gastroenterol Hepatol,* 2011.	Amount of stool per transplant / administered to patients: lower GI:-25-50ml; upper GI: 250-500ml. Diluent used to prepare: Preservative-free normal saline or 4% milk. Diluent used to store if frozen: N/A – fresh. Preparation methods: Household blender, homogenized and removal of particle matter with gauze/ urine strainers in a Biohazard Level 2 facility. Time from preparation to transplant (fresh): Certainly within 24 hours, and preferably within 6 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: 67 (colonoscopy or sigmoidoscopy); capsule: nil. Number of infusions: 53 patients received one infusion, 14 received 2 infusions. Bowel purgative: Standard bowel preparation, but not specified. PPI: If upper GI administration, PPI on the evening before and morning of the procedure.	Overall cure within stated follow up period: 90% (*n*=60/67) within 3 months. Cure with one infusion alone: 79% (*n*=53/67). Total follow up period: average length 10.4 (range 3-36) months.	Minor GI adverse events: x1 IBD flare, managed as outpatient. Minor non-GI adverse events: x4 pneumonia. Serious adverse events: x1 colectomy for refractory IBD,x7 hospitalised, x2 CDI recurrence, x2 IBD exacerbation, x1 small bowel obstruction, x1 CMV colitis. Deaths: none.	Selection/ eligibility reported: Yes. Consecutively recruited: No. Prospectively recruited: No. Loss to follow up explained: N/A. At least 90% followed up: N/A.

Supplementary Material 2 for *Gut*

			Antimotility: Loperamide optional for lower GI administration. Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: 24-48 hrs.			

Supplementary Material 2 for *Gut*

Fischer *et al, American Journal of Gastroenterology,* 2016	Case series. Number of patients: 328. Female: male: 241: 87. Age (mean/ standard deviation): 61.4 (+/-19.3) years. Comorbidities: 77 immunocompromised (x3 CVID, x3 selective IgA deficiency, x71 immunosupressants (20 for solid organ transplant, 29 for IBD, 6 for rheumatoid arthritis, 2 for SLE, 1 for pemphigoid, 1 for chronic obstructive airway disease, 1 for psoriasis)), x11 chemotherapy for malignancy, x63 IBD (25 UC, 33 Crohn's), x118 diverticulosis. CDI features: Recurrent disease in 87.2% and severe or severe-complicated in 12.8%. CDI diagnosis confirmation: Postive stool *C difficile* toxin or	Donors were 130 (40%) patient-directed donors, and 198 universal (60%). Donor working in healthcare: Not stated. Donor demographics: Not stated. Donor screening: Questionnaire – depended upon individual centre. Travel and antibiotic exclusion period: Depended upon individual centre. Screening blood tests: Depended upon individual centre. Screening stool test: Depended upon individual centre.	Amount of stool per transplant / administered to patients: Not specified. Diluent used to prepare: Not specified. Diluent used to store if frozen: Both fresh and frozen, but specific details not given. Preparation methods: Dependent upon individual centre. Time from preparation to transplant (fresh): Dependent upon individual centre. Time period for storage (frozen): Dependent upon individual centre. Route administered: Not specified ('predominantly colonoscopy'). Number of infusions: Dependent upon individual centre. Bowel purgative: Not specified. PPI: Not specified. Antimotility: Not specified. Prokinetics: Not specified. Time before CDI treatment was stopped before FMT: Dependent upon each centre.	Overall cure within stated follow up period: 1 month 81.4% (*n*=267/328). Cure with one infusion alone: Not specified. Total follow up period: Not specified.	Minor GI adverse events: Not specified. Minor non-GI adverse events: Not specified. Serious adverse events: Not specified. Deaths: Not specified.	Selection/ eligibility reported: Yes. Consecutively recruited: No. Prospectively recruited: No. Loss to follow up explained: N/A. At least 90% followed up: N/A.

Supplementary Material 2 for *Gut*

	PCR. Pre-FMT antibiotics: vancomycin.					

Supplementary Material 2 for *Gut*

Fischer *et al, Gut Microbes,* 2017	Case series. Number of patients: 57. Female: male: 34: 23. Age (median): Median 72 (range 25-99) years. Comorbidities: x7 toxic megacolon, x12 acute kidney injury (x3 needing dialysis), x10 with hypovolaemic/ septic shock, x7 mental status changes, x4 on mechanical ventilation. x10 patients had inflammatory bowel disease (x5 with Crohn's and x5 with ulcerative colitis) and x10 patients were on immunosuppressive medications. CDI features: Severe, recurrent and severe-complicated. CDI diagnosis confirmation: Positive stool *C.difficile* PCR. Pre-FMT antibiotics: Included vancomycin,	Donors were screened patient-selected donors for first 29 patients, whilst next 28 from OpenBiome stool bank. Donors working in healthcare: Not specified. Donor demographics: Not specified. Donor screening: Questionnaire – for patient-selected donors, this was as for Bakken *et al, Clin Gastoenterol Hepatol,* 2011; for OpenBiome, as per OpenBiome protocol. Travel and antibiotic exclusion period: For patient-selected donors, this was as for Bakken *et al, Clin Gastoenterol Hepatol,* 2011; for OpenBiome, as per OpenBiome protocol. Screening blood tests: For patient-selected donors, this was as for Bakken *et al, Clin Gastoenterol Hepatol,* 2011; for OpenBiome, as per OpenBiome protocol. Screening stool tests: Ffor patient-selected donors, this was as for Bakken *et al, Clin Gastoenterol Hepatol,* 2011;	Amount of stool per transplant / administered to patients: As per Fischer *et al, Alim Pharm Ther,* 2015 or OpenBiome. Diluent used to prepare: As per Fischer *et al, Alim Pharm Ther,* 2015 or OpenBiome. Diluent used to store if frozen: As per Fischer *et al, Alim Pharm Ther,* 2015 or OpenBiome . Preparation methods: As per Fischer *et al, Alim Pharm Ther,* 2015 or OpenBiome. Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): As per OpenBiome protocols. Route administered Upper GI: nil; lower GI: 57 via colonoscopy or sigmoidoscopy. Number of infusions: 32 patients: x1, 20 patients x2, 5 patients x3, 1 patient x4,1 patient x5. Pre-planned protocol for serial FMTs +/- vancomycin, as described in Fischer *et al, Alim Pharm Ther,* 2015. Bowel purgative: Not stated.	Overall cure within stated follow up period: 91% (*n*=52/57), i.e. 100% severe CDI (*n*=19/19), and 87% (*n*=33/38). Cure with one infusion alone: 52.6% (*n*= 30/57). Total follow up period: Up to 6 months.	Minor GI adverse events: Not stated. Minor non-GI adverse events: Not stated. Serious adverse events: Not stated. Deaths: x7 unrelated deaths, x4 CDI-related deaths.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: Yes. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	fidaxomicin, rectal vancomycin, intravenous metronidazole.	for OpenBiome, as per OpenBiome protocol.	PPI: Not stated. Antimotility: Not stated. Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: Not stated.			

Supplementary Material 2 for *Gut*

Fischer *et al, Alimentary Pharmacology and Therapeutics,* 2015	Case series. Number of patients: 29. Female: male: 17: 12. Age (mean/ standard deviation): Overall, mean 65.2 (+/-17.9) years (range 25-92 years); mean 60.8 (range 26-87) years in severe; 67.6 (range 60-78) years in severe-complicated. Comorbidities: x3 Crohn's, x2 UC, x1 hypogammaglobulinaemia, x1 ESKD, x1 ESLD, x1 renal transplant, x1 liver transplant, x4 on immunosuppressive meds. 12/19 of pts treated in ITU at the time with following complications: x5 patients with toxic megacolon (caecal diam >12cm or rectosigmoid> 6.5cm diameter); x7 AKI and hypovolaemic/ septic shock, x4 of which required vasopressors, x3 with change in mental status, x2 patients ventilated. x22 with	Donors were either patient selected-donor, or universal donors. If patient-directed, same donor used for subsequent FMTs if required. 44 FMTs in all - patient-selected for 16 FMTs, universal donor for 28 FMTs. Donors working in healthcare: Not described. Donor demographics: Not clear. Donor screening: Questionnaire: As per Bakken *et al, Clin Gastroenterol Hepatol,* 2011. Travel and antibiotic exclusion period: As per Bakken *et al, Clin Gastroenterol Hepatol,* 2011. Screening blood tests: As per Bakken *et al, Clin Gastroenterol Hepatol,* 2011. Screening stool tests: As per Bakken *et al, Clin Gastroenterol Hepatol,* 2011.	Amount of stool per transplant / administered to patients: 50-200g of stool. Diluent used to prepare: 300ml of saline. Diluent used to store if frozen: N/A – all fresh. Preparation methods: No additional details. Time from preparation to transplant (fresh): Six hours. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: flexible sigmoidoscopy or colonoscopy either proximal or distal to the splenic flexure at the discretion of the endoscopist. In practice – proximal to the splenic flexure in 18 FMTs, distal in 26. Number of infusions: As many as per protocol until end point. 16 x 1 FMT (7 severe, 9 complicated), 11 x 2nd FMT (3 severe, 8 compl), 2 x 3rd FMT (0 severe, 2 complicated). N.B. Oral vancomycin (125 mg every 6 hours) was resumed 24–48 hours after FMT for a minimum of 5 days if there were pseudomembranes present at colonoscopy. For patients who did not	Overall cure within stated follow up period: By 3 months, 62% (*n*=18/29) in remission. Cure with one infusion alone: 70% (*n*=7/10) in severe arm; 47% (*n*=9/19) in severe-complicated arm. Total follow up period: Up to 3 months.	Minor GI adverse events: Not stated. Minor non-GI adverse events: Not stated. Serious adverse events: Nil. Deaths: x2 deaths by 1 month; x1 death from sepsis within 24 hours of FMT); death following collectomy after 3x failed FMT in patient who was six weeks post-OLT. By 3 months – x2 further deaths from CDI recurrence, x1 death from cirhosis, x1 death from heart failure, x1 death from respiratory failure, x1 death from aspiration.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: Yes. Loss to follow up explained: Yes. At least 90% followed up: Yes.

	pseudomembranes at first FMT. CDI features: 9 patients with first episode of CDI; all others with previous episodes. CDI diagnosis confirmation: Diarrhoea (at least 3 loose stools/ day) and positive toxin. Pre-FMT antibiotics: Not stated.		improve by days 6–7, the vancomycin was stopped, and bowel prep was administered if no ileus was present. The next day (day 7–8), a repeat FMT, from the same donor as the first FMT if patient-directed, was performed by sigmoidoscopy or colonoscopy. If pseudomembranes were present, oral vancomycin was resumed for an additional 5 days. If no pseudomembranes were detected, antibiotics were not resumed following the repeat FMT. Bowel purgative: Split dose 4l Golytely if no ileus/ obstruction. PPI: Not described. Antimotility: Not described. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 12-24hr prior to FMT.			

Supplementary Material 2 for *Gut*

Garborg *et al, Scandanavian Journal of Infectious Diseases,* 2010	Case series. Number of patients: 40. Female: male: 21: 19. Age (mean): Mean age 75 (range 53-94) years. Comorbidities: x1 Wegener's, x1 AML. Repeated courses of antibiotics, not formally described. CDI features: Not described. CDI diagnosis confirmation: Diarrhoea and + *C difficile* toxin (testing for A and B). Pre-FMT antibiotics: All patients had had at least two courses of oral metronidazole (500mg three times daily) or vancomycin (125mg po four times daily).	Donors were close relatives/ household members. Donors working in healthcare: No. Donor demographics: Not stated. Donor screening: Questionnaire - "Symptoms of GI disease or history of chronic infectious disease". Travel and antibiotic exclusion period: Not stated. Screening bloods: Hepatitis A, B and C, HIV. Screening stools: MC&S, *Yersinia*. No routine paraiste screening ("low prevalence in Norway").	Amount of stool per transplant / administered to patients: 50-100g. Diluent used to prepare: 250ml sterile normal saline. Diluent used to store if frozen: All fresh. Preparation methods: Stool placed on gauze pad and strained; flushed with saline; drawn up into syringes ready for administration. Time from preparation to transplant (fresh): Same day. Time period for storage (frozen): N/A. Route administered: Upper GI: OGD with delivery in distal duodenum; 38; lower GI: Colonoscopy; 2. Number of infusions: One at baseline; follow up if 'did not respond' although not specifically defined. Bowel purgative: Not mentioned, even for colonoscopy. PPI: Not stated. Antimotility: Not stated. Prokinetics: Not stated.	Overall cure within stated follow up period: 835 (*n*=33/40). Cure with one infusion alone: 73% (*n*=29/ 40) (28 in duodenum, 1 in colon). Total follow up period: Up to 80 days.	Minor GI adverse events: Not stated. Minor non-GI adverse events: Not stated. Serious adverse events: Not stated. Deaths: x5 deaths within 3 weeks - 2 months post-FMT but none attributable to FMT. x2 deaths attributed to 'frailty', x1 advanced Wegener's, x1 AML/ antibiotics, one patients with advanced cardiovascular disease who had fulminant colitis, underwent colectomy, but died.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Time before CDI treatment was stopped before FMT: Evening prior to FMT.			

Supplementary Material 2 for *Gut*

Girotra *et al, Digestive Diseases and Sciences,* 2016	Case series. Number of patients: 29. Female: male: 6: 23. Age (mean/ standard deviation): 80.1 (+/-6.49) years (13 patients 70-79, 14 patients 80-89, 2 patients > 90 years). Comorbidities: x8 patients with diabetes mellitus. CDI features: No specific details - purely symptoms > 6 months, failed at least 3 antibiotic regimens. CDI diagnosis confirmation: At least three unformed stools in 24 hour and positive stool *C difficile* test by toxin (by ELISA) or toxin gene B (by PCR). All patients here defined RCDI by symptoms >6 months and at least x3 failed antibiotics. Pre-FMT antibiotics: Not indicated.	Donors were patient-selected family or friends. Donors working in healthcare: No. Donor demographics: Not stated. Donor screening: Questionnaire – peptic ulcer disease/GORD, IBS, IBD, polyps, malignancy, antibiotic use/ hospitalisation within past 3 months. Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within the past three months. Screening bloods: HIV, HTLV-I/-II, syphilis enzyme immunoassay, hepatitis A immunoglobulin M, hepatitis B surface antigen, hepatitis C antibody, and *Helicobacter pylori* antibody. Screening stools: MC&S/ ova, cysts and parasites x3, *Cryptosporidium, Microspora, C difficile* toxin.	Amount of stool per transplant / administered to patients: 450cc - 270cc via colonoscopy AND 180cc into jejunum via enteroscopy. Diluent used to prepare: Saline - whole stool sample (>30g) mixed with 50-70ml of sterile saline, made up to 5 x 90cc aliquots. Diluent used to store if frozen: Fresh. Preparation methods: Stool mixed with saline, homogenised in blender for <4 minutes, filtered x2 with coffee filter paper. Time from preparation to transplant (fresh): Within 6 hours. Time period for storage (frozen): N/A. Route administered: Enteroscopy into jejunum AND colonoscopy in all 29 patients. Number of infusions: 1 FMT per patient (combined upper and lower GI administration). Bowel purgative: Not described. PPI: 20mg omeprazole evening before/ morning of procedure. Antimotility: Not described.	Overall cure within stated follow up period: 100% (*n*=29/29). Cure with one infusion alone: 100% (*n*=29/29). Total follow-up period: Reported 25.37 +/- 12.8 months follow-up (range 8-50 months). In addition - researchers report 60% weight gain, 40% stable weight, 75% improved 'failure to thrive' (defined as decrease of weight >10% from baseline, with no improvement despite medical treatment of CDI and nutritional treatment).	Minor GI adverse events: Bloating 10% (*n*=3/29). Minor non-GI adverse events: Fever 7% (*n*=2/29) (transient for one day). Serious adverse events: None. Deaths: None.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: N/A. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Prokinetics: Not described. Time before CDI treatment was stopped before FMT: >12 hours.			

Supplementary Material 2 for *Gut*

Hagel *et al, Deutsches Arzteblatt International,* 2016	Case series. Number of patients: 133. Female: male: 86: 47. Age (median): Median 75 (IQR 59.5 - 81.5) years. Comorbidities: x3 chemotherapy, x19 immunosuppressants, x5 solid organ transplant, x1 allogeneic stem cell transplant, x43 GI comorbidities (no details). CDI features: Median of 3 recurrences (IQR 1-4); no specific details re recurrent vs refractory confirmation. Pre-FMT antibiotics: x4 metronidazole only, x13 vancomycin only, x2 fidaxomicin only, x61 metronidazole/ vancomycin, x8 vancomycin/ fidaxomicin, x34 metronidazole/ vancomycin/	Donors working in healthcare: not stated Donor demographics: Not stated. Donor screening: Questionnaire - not stated. Travel and antibiotic exclusion period: Not stated. Screening blood tests.: Rapid plasma reagin and fluorescent *Treponemal* antibody-absorbed. Screening stool tests: Not stated.	Amount of stool per transplant / administered to patients: Not stated. Diluent used to prepare: Not stated. Diluent used to store if frozen: Yes, in some cases - no details given. Preparation methods: Not stated. Time from preparation to transplant (fresh): Not stated. Time period for storage (frozen): Not stated. Route administered: Upper GI: 4 OGD, 40 enteroscopy, 19 nasoenteric tube; lower GI: 55 'endoscopic' (no further details); capsule: 13. x2 combination of jejunal and colonoscopic FMT. Number of infusions: 1 FMT. Bowel purgative: Yes - 117 (no details given). PPI: Yes - 31 (no details given). Antimotility: Yes - 31 (no details given). Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: Not stated.	Overall cure within stated follow up period: Primary cure on day 30 and 90 was achieved in 84.2% (*n*=101/120) and 78.3% (*n*=72/92). Cure with one infusion alone: No diarrhoea at 30 days in 84.2% (*n*=101/120); no diarrhoea at 90 days in 78.3% (*n*=72/92). Total follow up period: Median follow up 141 days (IQR 50-353 days).	Minor GI adverse events: x5 nausea, x3 abdominal pain, 2 belching, x2 vomiting, x2 'food intolerance', x1 IBS. Minor non-GI adverse events: x3 fever, x2 throat discomfort. Serious adverse events: x1 aspiration pneumonia, x1 haemorrhage (during endoscopy - no details), x1 loss of tooth, x1 polyneuropathy, x1 weight gain > 10kg in 12 months post-FMT. Deaths: x7 died during follow up, x2 within 90 days of FMT. In x6 cases, definitely not related to CDI (in one patient, recurrence of CDI one week after FMT contributed to her death (but	Selection/eligibility reported: Yes. Consecutively recruited: Not clear. Prospectively recruited: No. Loss to follow up explained: No. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	fidaxomicin, x11 unknown.				stroke described as primary cause of death).	

Supplementary Material 2 for *Gut*

Hamilton *et al, American Journal of Gastroenterology,* 2012	Case series. Number of patients: 43. Female: male: 31: 12. Age (mean/ standard deviation): Mean 59 (+/- 21) years. Comorbidities: x14 IBD patients. CDI features: Recurrent. CDI diagnosis confirmation: Toxin positive with at least two subsequent recurrences. Pre-FMT antibiotics: All had vancomycin, 17 patients had addition of vancomycin and 2 weeks of rifaximin (one of these 17 had 4 weeks of rifaximin); 3 patients took 2-4 weeks of nitazoxanide.	Donors were standard donors for 33 FMTs, and individual donors for 10 FMTs. Donors working in healthcare: Not stated. Donor demographics: Not stated. Donor screening: Questionnaire - before recruitment, the donors were required to submit available medical records and have a separate medical history interview away from the recipient patient. The history included assessment of infectious risk, including identification of known risk factors for HIV and hepatitis, current communicable diseases, and recent travel to areas of the world with a higher prevalence of diarrheal illnesses. Travel and antibiotic exclusion period: Excluded as donors if recent travel to areas where high prevelence of diarrheal illness (not specified), and/ or antibiotic use within the past six months.	Amount of stool per transplant / administered to patients: 50g. Diluent used to prepare: 250ml sterile, non-bacteriostatic normal saline. Diluent used to store if frozen: 10% glycerol. Preparation methods: Stool from individual donors was passed through stainless steel tea strainers; stool from universal donors was transported on ice to the lab, and processed within 2 hours. Material was weighed and homogenised in commercial blender under nitrogen gas. Slurry then passed through 2.0, 1.0, 0.5 and 0.25mm stainless steel lab sieves. The resulting material was then cetrifuged at 6000 x *g* for 15 minutes and resuspended to one-half the original volume in normal saline. Time from preparation to transplant (fresh): 1-2 hours. Time period for storage (frozen): 1-8 weeks. Route administered: Upper GI: nil; lower GI: colonoscopy (with majority into terminal ileum or caecum, with a small proportion into other colonic areas) in all 43; capsules: nil. Number of infusions: 1x FMT in 37	Overall cure within stated follow up period: 95% (*n*=41/43) within 2 months follow-up. Cure with one infusion alone: 86% (*n*=37/43). Total follow up period: 2 months following FMT.	Minor GI adverse events: ~1/3 of patients reported flatulance and excessive bowel movements within fortnight following procedure. Minor non-GI adverse events: None. Serious adverse events: None. Deaths: None.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: No. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

		Screening blood tests: HIV, hepatitis B/C, RPR, LFTs. Screening stool tests: *Clostridium difficile* toxin B PCR, MC&S, ova, cysts and parasites, *Giardia*, *Cryptosporidium, H pylori* antigen.	patients, 2x FMT in 6 patients. Bowel purgative: Yes - GoLYTELY or Moviprep. PPI: Not described. Antimotility: Not described. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 2 days.			

Supplementary Material 2 for *Gut*

Hefazi *et al, Mayo Clinic Proceedings,* 2017	Case series. Number of patients: 23. Female: male: 13: 10. Age (median): 66 (range 23-88) years. Comorbidities: x13 patients had haematological malignancy (x4 diffuse large B cell lymphoma, x2 Hodgkin's lymphoma, x1 chronic myeloid leukaemia, x1 follicular lymphoma, x1 stage IV cutaneous T cell lymphoma, x1 B cell acute lymphocytic leukaemia, x1 hairy cell leukaemia, x1 chronic lymphocytic leukaemia, x1 severe aplastic anaemia); x1 with active disease at time of FMT, x2 with recent chemotherapy use, x2 with neutropenia within 12 weeks prior to FMT. x10 patients with solid organ malignancy (x4 breast, x2 anal, x1 colon, x1 pancreatic, x1 tonsillar, x1 non-small	Donors: Fresh stool from family/ friends in 10 patients, frozen stool from standard donors in 13 patients. Donor working in healthcare: Not stated. Donor demographics: Not stated. Donor screening: As per Patel *et al, Mayo Clin Proc,* 2013. Travel and antibiotic exclusion period: As per Patel *et al, Mayo Clin Proc,* 2013. Screening blood tests: As per Patel *et al, Mayo Clin Proc,* 2013. Screening stools: As per Patel *et al, Mayo Clin Proc,* 2013.	Amount of stool per transplant / administered to patients: ~50g. Diluent used to prepare: 250ml normal saline. Diluent used to store if frozen: Not stated. Preparation methods: As per Patel *et al, Mayo Clin Proc,* 2013. Time from preparation to transplant (fresh): Not stated. Time period for storage (frozen): Not stated. Route administered: Upper GI: nil; lower GI: All 23 patients received FMT via colonoscopy into caecum. Number of infusions: 1 FMT. Bowel purgative: Not stated. PPI: Not stated. Antimotility: Not stated. Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: 24 hours.	Overall cure within stated follow up period: 92% (*n*=11/12) of haematological malignancy patients (other patient died), and 805 (*n*=8/10) solid malignancy patients. Cure with one infusion alone: 86% (*n*=19/22) by primary outcome criteria. Total follow up period: x1 CLL patient recurred at 22 months post-FMT in context of ibrutinib and coamoxiclav; successfully treated with 10 days of metronidazole. x1 tonsillar cancer patient had CDI recurrence at 14 months after exposure to cefalexin; successfully treated with 10 days of	Minor GI adverse events: x3 chronic diarrhoea for at least six months (despite negative *C difficile* laboratory tests), x8 transient diarrhoea, x3 abdominal cramps, x2 faecal urgency, x2 constipation, x1 nausea. Minor non-GI adverse events: None. Serious adverse events: None. Deaths: x1 death after cardiac arrest of Hodgkin's lymphoma patient at day 5 (multiple medical comorbidities thought likely cause, not FMT); x2 deaths at > 60 days related to the underlying malignancy progressing.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	cell lung. x5 with metastasis at time of FMT, x3 recent chemotherapy use, x1 with recent neutropenia. Other comorbidities include x1 COPD, x1 ESKD on haemodialysis, x1 graft versus host disease (on immunosuppression), x1 granulomatosis with polyangiitis (Wegener's) on immunosuppression, x1 hypogammaglobulinaemia on intravenous immunoglobulin, x1 inflammatory arthritis on corticosteroids. CDI features: All recurrent. CDI diagnosis confirmation: Not explicitly defined, but definitions of recurrent, severe and complicated CDI as per American College of Gastroenterology. Pre-FMT antibiotics: All given additional vancomycin until 24hrs			vancomycin then 10 days of fidaxomicin. N.B. In all - x10 more chemotherapy courses and x8 more antibiotic courses after FMT.		

Supplementary Material 2 for *Gut*

	prior to FMT. Median of 2.5 standard treatment courses per patient (defined as at least 10 days of metronidazole, vancomycin or fidaxomicin), x1 previous vancomycin taper, and x4 total treatment courses for CDI).					

Supplementary Material 2 for *Gut*

Hirsch *et al, BMC Infectious Diseases,* 2015	Case series. Number of patients: 19. Female: male: 13: 6. Age (mean): 61 (range 26-92) years. Comorbidities: x3 IBS, x2 diabetes mellitus, x1 diverticulitis, x1 lymphoma, x1 acute myeloid leukaemia, x1 renal cancer, x1 chronic renal failure. CDI features: Refractory and recurrent (2 or more episodes). CDI diagnosis confirmation: Not stated. Pre-FMT antibiotics: metronidazole, vancomycin +/or fidaxomicin.	Donors were 3 unrelated participants. Donors working in healthcare: Not stated. Donor demographics: Excluded if BMI>25, diabetes mellitus, psychiatric history, IBD, or IBS. Donor screening: Questionnaire - standard questionnaire, with details as above. Travel and antibiotic exclusion period: Excluded if travel outside the USA within 30 days prior to donation, and/ or use of antibiotics within the past 6 months. Screening blood tests: HIV, hepatitis A, B,C, *Treponema*/ syphilis, and HTLV-1. Screening stool tests: *Clostridium difficile* toxin B, *Salmonella, Shigella*, *Campylobacter*, *E. coli*, *Yersinia*, *Vibrio, Aeromonas, Plesiomonas.*	Amount of stool per transplant / administered to patients: 2.3g. Diluent used to prepare: 350ml in 0.9% normal saline. Diluent used to store if frozen: 15% glycerol. Preparation methods: Strict environmental contol <6 hours after defaecation. All sterile, wet weight of stool was homogenised in 350ml 0.9% normal saline and aliquoted; samples were then centrifudged at 200 x *g* for 10 mins. Supernatent was decanted and centrifuged at 4600 x *g* for 15 minutes. supernatant removed and pellet re-suspended in 0.9% normal saline with glycerol. The typical concentration was 0.5g/ml. The resulting FMT slurry was put in 5-10ml syringes and frozen at -80°C. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): 1-3 weeks at -80°C; prior to use, syringes were transferred to -20°C and used within six weeks. Route administered: Nil upper or lower GI; all capsules. Aliquots of 0.4 mL of FMT slurry were dispensed into Size 1 acid-resistant hypromellose capsules,	Overall cure within stated follow up period: 68% (*n*=13/19). Cure with one infusion alone: 68% (*n*=13/19) at 90 days. Total follow up period: Primary outcome assessed at 90 days, whilst secondary outcome assessed at 6 weeks after this.	Minor GI adverse events: x5 abdominal pain 5 (x4 self-resolved; x1 required opiates and was hospitalised). Minor non-GI adverse events: None. Serious adverse events: None. Deaths: x1 died from respiratory failure after failing FMT treatment.	Selection/ eligibility reported: Yes. Consecutively recruited: Not clear. Prospectively recruited: No. Loss to follow up explained: No. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			subsequently placed within Size 0 acid-resistant hypromellose capsules and then nested within Size 00 gelatin Caps. Capsules were administered immediately upon filling and capping. Number of infusions: One course was 8-12 capsules (one only took 6). Bowel purgative: Not described. PPI: Yes - evening and morning of procedure. Antimotility: Not described. Prokinetics: Yes - encouraged to drink 4 ounces of Kefir fermented milk product twice a day, and also given a list of prebiotics to consume for 3 days. Time before CDI treatment was stopped before FMT: On day prior to FMT.			

Supplementary Material 2 for *Gut*

Ianiro *et al, Clinical Microbiology and Infection,* 2017	Case series. Number of patients: 64. Female:male: 39: 25. Age (mean): Mean 74 years. Comorbidities: Not reported. CDI features: Recurrent CDI - all patients had 3 recurrences on average range (range 2-6). CDI diagnosis confirmation: Defined using ESCMID guidelines. Pre-FMT antibiotics: All patients had had prior metronidazole, vancomycin and/ or fidaxomicin.	Donors were unrelated for 36 FMTs, and related for 28 FMTs.. Donor working in healthcare: No. Donor demographics: Not specified. Donor screening: As per Cammarota *et al, Alim Pharm Ther,* 2015. Travel and antibiotic exclusion period: As per Cammarota *et al, Alim Pharm Ther,* 2015. Screening blood tests: As per Cammarota *et al, Alim Pharm Ther,* 2015. Screening stool tests: As per Cammarota *et al, Alim Pharm Ther,* 2015.	Amount of stool per transplant / administered to patients: not reported. Diluent used to prepare: 500ml of 0.9% saline. Diluent used to store if frozen: N/A – fresh. Preparation methods: After dilution, the solution was blended and supernatant strained and poured into sterile container. Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): Not specified. Route administered: Upper GI: nil: lower GI: all 64 given FMT via colonoscopy; capsules: nil. Number of infusions: 44 patients had x1 FMT, 20 patients had >1 FMT (undefined). Bowel purgative: 4l macrogol on last 1-2 days of antibiotcs treatment. PPI: Not specified. Antimotility: Not specified. Prokinetics: Not specified.	Overall cure within stated follow up period: 975 (*n*=62/64) at 8 weeks. Cure with one infusion alone: 69% (*n*=44/64). Total follow up period: 8 weeks.	Minor GI adverse events: Not specified. Minor non-GI adverse events: Not specified. Serious adverse events: Not specified. Deaths: Not specified.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Time before CDI treatment was stopped before FMT: FMT given on last 1 or two days of CDI treatment.			

Supplementary Material 2 for *Gut*

Kassam *et al, Archives of Internal Medicine,* 2012	Case series. Number of patients: 27. Female: male 13: 14. Age (mean): 69.4 (range 26-87) years. Comorbidities: Not specified. CDI features: Recurrent and refractory. CDI diagnosis confirmation: (1) Laboratory-confirmed *C difficile* toxin using EIA with no other cause for diarrhea; (2) refractory CDI (defined as ongoing diarrhea despite antimicrobial treatment) or recurrent CDI (defined as symptom resolution for at least 2 days after discontinuation of treatment with recurrence of diarrhea). Pre-FMT antibiotics: All had at least prior metronidazole; 19 had subsequent vancomycin monotherapy. 8 had	Donors were two healthy volunteers. Donors working in healthcare: Not specified. Donor demographics: Not specified. Donor screening: Questionnaire - not specified. Travel and antibiotic exclusion period: Excluded if used antibiotics within last 6 months. Screening blood tests: Hepatitis B surface antigen, hepatitis C antibody, *Helicobacter pylori* and syphilis serologic markers, HIV types -1 and -2, and HTLV types -I and -II. Screening stool tests: Stool was processed for enteric bacterial pathogens, *C difficile* toxin, and ova and parasites.	Amount of stool per transplant / administered to patients: 150g of stool. Diluent used to prepare: 300mls sterile water. Diluent used to store if frozen: N/A. Preparation methods: Not specified. Time from preparation to transplant (fresh): Not specified. Time period for storage (frozen): N/A – fresh. Route administered: Upper GI: nil; lower GI: 27 via retention enema. Number of infusions: 1 enema in 22 patients, 2 enemas in 5 patients. Bowel purgative: Not specified. PPI: Not specified. Antimotility: Not specified. Prokinetics: Not specified. Time before CDI treatment was stopped before FMT: At least 24 hours before.	Overall cure within stated follow up period: 81% (*n*=22/27). Cure with one infusion alone: 81% (*n*=22/27). Total follow up period: Mean follow-up of 427.3 days after transplant. .	Minor GI adverse events: Not specified. Minor non-GI adverse events: Not specified. Serious adverse events: Not specified. Deaths: Not specified.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	combination metronidazole and vancomycin therapy.					

Supplementary Material 2 for *Gut*

Kelly *et al, Journal of Clinical Gastroenterology,* 2012	Case series. Number of patients: 26. Female: male: 24:2. Age (mean): 59 years. Comorbidities: Not stated. CDI features: Recurrent. Mean duration of diagnosis of CDI prior to FMT of 12.6 (range 4 to 84) months. CDI diagnosis confirmation: Not stated. Pre-FMT antibiotics: All had previous treatment with metronidazole, and repeated tapering courses of vancomycin. 19 had failed at least one course of rifaximin. Some patients had prior *Saccharomyces boulardii* or *Lactobacillus* GG. Pre-FMT, all had 2 weeks of metronidazole or vancomycin, discontinued 2-3 days before FMT.	Donors were family members in 25 cases, and friend in 1 case. Donor working in healthcare: No. Donor demographics: Not specified. Donor screening: Questionnaire – asked regarding known exposure to HIV within 12 months, high-risk sexual behaviours, use of ilicit drugs, tattoo within 6 months, incarceration within 12 months, risk factors for Creutzfleldt-Jakob disease, GI co-morbidities, recent ingestion of allergen, systemic autoimmunity, chronic pain syndromes. Travel and antibiotic exclusion period: No antibiotics for preceeding 90 days. Screening blood tests: blood for hepatitis A, B and C, HIV-1&-2, *Trepenoma pallidum.* Screening stool tests: Stool for culture for bacteria, stain for ova and parasites, *C difficile* toxin A and B.	Amount of stool per transplant / administered to patients: "6:8 tablespoons of donor stool". Diluent used to prepare: 1 litre of sterile water passed through gauze. Aliquoted in 60ml syringes. Diluent used to store if frozen: N/A – fresh. Preparation methods: As above. Time from preparation to transplant (fresh): 6 hours prior to transplant. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: all 26 via colonoscopy; capsules: nil. Number of infusions: not explicitly stated but imples single infusion for all patients. Bowel purgative: PEG bowel prep night before transplant. PPI: Not stated. Antimotility: Not stated. Prokinetics: Not stated. Time before CDI treatment was stopped	Overall cure within stated follow up period: 92.3% (*n*=24/26). Cure with one infusion alone: 92.3% (*n*=24/26). Total follow up period: follow up of mean 10.7 months (ranged from 2-30 months).	Minor GI adverse events: Mild diarrhoea post-FMT in x3 patients. Minor non-GI adverse events: No. Serious adverse events: No. Deaths: No.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes

Supplementary Material 2 for *Gut*

			before FMT: 2-3 days.			

Supplementary Material 2 for *Gut*

Kelly et al, *American Journal of Gastroenterology,* 2014	Case series. Number of patients: 80. Female: male: 42: 38. Age (mean): N.B. 75 adults, and 5 children. Mean age of adults: 53 (range 20-88) years; mean age of paediatric patients: 10.9 (range 6.5–16) years. Comorbidities: x36 IBD, x19 solid organ transplant, x3 HIV/AIDS, x7 cancer, x4 rheumatoid arthritis, x1 adrenal insufficiency, x6 cirrhosis, x1 ESKD, x1 panhypopituatarism, x1 end-stage COPD, x1 ESKD with allograft failure, x1 Sjögrens. CDI features: Both refractory and recurrent patients included as well as severe/ complicated disease. CDI diagnosis: Not clearly specified. Pre-FMT antibiotics:	Donors working in healthcare: Not specified. Donor demographics: Not specified. Donor screening: Questionnaire: Varied by centre. Travel and antibiotic exclusion period: Varied by centre. Screening blood tests: Varied by centre. Screening stool tests: Varied by centre.	Amount of stool per transplant / administered to patients: Varied by centre. Diluent used to prepare: Varied by centre. Diluent used to store if frozen: Varied by centre. Preparation methods: Varied by centre. Time from preparation to transplant (fresh): Varied by centre. Time period for storage (frozen): Varied by centre. Route administered: Not specified. Number of infusions: 85% (*n*=68/80) had single FMT, 15% (*n*=12/80) had > 1 FMT. Bowel purgative: Varied by centre. PPI: Varied by centre. Antimotility: Varied by centre. Prokinetics: Varied by centre. Time before CDI treatment was stopped before FMT: Varied by centre.	Overall cure within stated follow up period: 89% (*n*=71/80) within a minimum of 12 weeks. Cure with one infusion alone: 78% (*n*=62/80). Total follow up period: 12 weeks post-FMT.	Minor GI adverse events: x3 self limiting diarrhoea, x3 bloating and abdominal discomfort, x1 Crohn's flare, x1 nausea, x1 minor mucosal tear at colonoscopy. Minor non-GI adverse events: x1 fever, x1 hip pain, x1 pertussis. Serious adverse events: x10 hospitalization (x1 for fever, encephalopathy and pancytopenia; x1 abdo pain post FMT, x3 IBD flares (x2 Crohn's, x1 UC), x1 stroke, x1 colectomy, x1 fall and sustained hip fracture, x1 influenza B and diarrhoea, x1 catheter infection. Deaths: x2 deaths (x1 pneumonia and x1 aspiration after	Selection/ eligibility reported: Yes. Consecutively recruited: No. Prospectively recruited: No. Loss to follow up explained: No. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	Vancomycin 67 (84%), fidaxomicin 23 (29%), rifaximin 13 (16%), metronidazole 55 (69%).				sedation for colonoscopic FMT).	

Supplementary Material 2 for *Gut*

Khoruts *et al, Clinical Gastroenterology & Hepatology,* 2016	Case series. Number of patients: 272. Female: male: 189: 83. Age (mean/ median/ standard deviation): Mean 57.2 (+/- 19.2) years; median 59.0 (range 16-100) years. Comorbidities: x10 dialysis, x22 established Crohn's, x21 established UC, x15 lymphocytic colitis, x5 diagnosed with Crohn's during colonoscopy for FMT, x1 diagnosed UC during colonoscopy for FMT, x14 newly-diagnosed lymphocytic colitis. x13 reclassified in terms of IBD. x8 solid organ recipients, x30 patients without IBD were taking biologics (anti-TNF, rituximab), immunomodulators (methotrexate, purine analogues), and/ or corticosteroids. CDI features: All patients had at least two	Donors working in healthcare: As per Hamilton *et al, Am J Gastroenterol,* 2012. Donor demographics: As per Hamilton *et al, Am J Gastroenterol,* 2012. Donor screening: Questionnaire - as per Hamilton *et al, Am J Gastroenterol,* 2012. Travel and antibiotic exclusion period: As per Hamilton *et al, Am J Gastroenterol,* 2012. Screening blood tests: As per Hamilton *et al, Am J Gastroenterol,* 2012. Screening stools: As per Hamilton *et al, Am J Gastroenterol,* 2012.	Amount of stool per transplant / administered to patients: As per Hamilton *et al, Am J Gastroenterol,* 2012. Diluent used to prepare: As per Hamilton *et al, Am J Gastroenterol,* 2012. Diluent used to store if frozen: As per Hamilton *et al, Am J Gastroenterol,* 2012. Preparation methods: As per Hamilton *et al, Am J Gastroenterol,* 2012. Time from preparation to transplant (fresh): As per Hamilton *et al, Am J Gastroenterol,* 2012. Time period for storage (frozen): As per Hamilton *et al, Am J Gastroenterol,* 2012. Route administered: Upper GI: nil; lower GI: colonoscopy (272); capsule: nil. Number of infusions: One routinely, more than one if required - specific criteria not defined. Bowel purgative: Yes - all had purgative on day prior to procedure (as per Hamilton *et al, Am J Gastroenterol,* 2012).	Overall cure within stated follow up period: 74% (*n*= 32/43) in IBD patients and 92.2% (*n*=211/229) in non-IBD patients. Cure with one infusion alone: 74% (*n*= 32/43) in IBD patients and 92.2% (*n*=211/229) in non IBD patients. Total follow up period: Up to 6 years.	Minor GI adverse events: Not specified. Minor non-GI adverse events: Not specified. Serious adverse events: 25.6% (*n*=11/43) of IBD patients diagnosed with FMT-related flare. x2 patients hospitalised with IBD flare within two months of FMT. Clearance of CDI by FMT generally associated with improved control of IBD over the long term. x6 patients struggled with IBD despite optimisation of immunosuppressive treatment, x3 of whom underwent colectomies. Deaths: Nil.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	spontaneous relapses of CDI following initial episode, defined as recurrence within three months of discontinuation of anti-CDI antibiotics treatment in conjunction with diarrheal symptoms. CDI diagnosis confirmation: Positive stool testing within two months of FMT - not clearly defined. Pre-FMT antibiotics: x206 patients had had prior metronidazole, x270 vancomycin, x69 fidaxomicin, x71 rifaximin, x104 probiotics.		PPI: Not described. Antimotility: Not described. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 2 days.			

Supplementary Material 2 for *Gut*

Lagier *et al, European Journal of Clinical Microbiology and Infectious Diseases,* 2015	Case series. Number of patients: 61. Female: male: 40:21. Age (mean): 84 (range 66-101) years. Comorbidities: Not Specified. CDI features: Some patients refractory/ recurrent; some during first CDI. CDI diagnosis confirmation:PCR that detects toxin and B genes, and toxin C gene deletion that characterises 027. Pre-FMT antibiotics: Patients divided into 'tardive transplant' (i.e. only after x3 antibiotic failures) or 'early transplant' (during first week of infection during first treatment, accompanied by antibiotics). Antibiotics were for non-severe disease: metronidazole	Donors were preferentially healthy family members, but also used healthy volunteer students and residents. Donor working in healthcare: Yes - some residents. Donor demographics: BMI<30, exclude active cancer, diarrhoea, current immunosuppressive drugs, antibiotics within past three months. Donor screening: Questionnaire: As above. Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within past three months. Screening blood tests: HIV, hepatitis A, B,C, E, active CMV, active EBV, *Treponema pallidum,* HTLV. Screening stool tests: MC&S, parasites, toxigenic *C difficile.'*	Amount of stool per transplant / administered to patients: >30g. Diluent used to prepare: Whole stool mixed with 400ml normal saline, homogenised for 10 minutes. Diluent used to store if frozen: N/A – fresh. Preparation methods: 10 minutes of homogenisation in blender, filtered, put into a syringe at room temperature. Time from preparation to transplant (fresh): <6 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: Via nasogastric tube in 61 patients; nil lower GI or capsules. Number of infusions: In early FMT arm - one FMT routine; but offered 2nd FMT if relapse. Bowel purgative: 4l Klean Prep/ two glasses of Fast Prep day before FMT. PPI: No - but used 200ml 1.4% bicarbonate 15 minutes before FMT. Antimotility: Not specified. Prokinetics: Not specified.	Overall cure within stated follow up period: Global death rate of 19% (*n*=3/16) in early transplant arm (day 20, day 37, day 166), 67% (*n*=2/3) died in arm of those treated by tardive transplant (day 28, day 54). None of these patients died with evidence of CDI. Cure with one infusion alone: 33% (*n*=1/3) treated by tardive FMT dead at day 31; 4.2% (*n*=1/16) treated by early FMT dead at day 31. Total follow up period: No details on absolute length of follow-up.	Minor GI adverse events: x24 diarrhoea (resolved day 1 after FMT), x1 nausea. Minor non-GI adverse events: Not specified. Serious adverse events: x1 acute heart failure - no details. Deaths: 3/16 in early transplant arm (vs 29/45 treated by abx only or tardive transplant). No sign of CDI at time of death (days 20, 37, 166).	Selection/ eligibility reported: Yes. Consecutively recruited: No - not stated. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	orally three times a day for 14 days, then vancomycin 125mg four times a day for 14 days, then fidaxomicin 200mg twice a day for 10 days; for severe disease (defined as AKI, paralytic ileus, or peritoneal fluid), used vancomycin and metronidazole for primary infection, then fidaxomicin if relapse/ failure.		Time before CDI treatment was stopped before FMT: Not specified.			

Supplementary Material 2 for *Gut*

Lee *et al, European Journal of Clinical Microbiology and Infectious Diseases,* 2014	Case series. Number of patients: 94 Female: male: 53: 41. Age (mean): Mean 71.8 (range 24-95) years. Comorbidities: x3 IBD, x3 post-renal transplant. CDI features: Some patients refractory (defined as ongoing diarrhea depsite treatment with at least 5 days of oral vancomycin, 125mg four times daily), or recurrent (symptom resolution for at least two days after the discontinuation of treatment with recurrence of diarrhoea. CDI diagnosis confirmation: Toxin positive by enzyme immunoassay or polymerase chain reaction. Pre-FMT antibiotics: Average of 2.1 previous anti-CDI antibiotic	Donors were volunteers. Donor working in healthcare: Not specified Donor demographics: Not specified. Donor screening: Questionnaire - describes use of questionnaire but no details given - "similar to the Full Length Donor History Questionnaire documents (US Food and Drug administration, DHQ version 1.3, May 2008" Travel and antibiotic exclusion period: Not specified. Screening blood testss: HIV-1/-2, HTLV-1 and -2. Hepatitis A IgG/M, hepatitis B surface antigen, hepatitis C antibody, *Treponema pallidum.* Screening stools: Ova, cysts and parasites, MC&S, *C difficile* toxin, norovirus, adenovirus, rotavirus.	Amount of stool per transplant / administered to patients: Not specified. Diluent used to prepare: 300ml water. Diluent used to store if frozen: N/A – fresh. Preparation methods: Homogenisation of stool in water using a disposable spatula. Time from preparation to transplant (fresh): Not specified. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: retention enema in all 94 patients; nil capsules. Number of infusions: No fixed number - as many as required to achieve remission. No clear definition of non-response. Bowel purgative: Not specified. PPI: Not specified. Antimotility: Not specified. Prokinetics: Not specified. Time before CDI treatment was stopped before FMT: Not specified.	Overall cure within stated follow up period: At 6 months – 87% (*n*=81/94) in remission after FMT. Cure with one infusion alone: 47.9% (*n*=45/94) with single FMT in remission at 6 months. Total follow up period: 24 months.	Minor GI adverse events: "10% experienced transient constipation and excess flatulence post-FMT". Minor non-GI adverse events: None described. Serious adverse events: None described. Deaths: 75% (*n*=6/8) patients not responding to FMT died (not clear when). All "over 70 years of age", with multiple underlying significant comorbidities and passed away due to critical illnesses; none had deaths attributable to FMT or directly due to CDI.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	courses (range 1-4), specifically: x74 metronidazole courses (79.3%), x71 vancomycin (75%), x14 vancomycin taper (15.2%), x3 probiotic monotreatment (0.03%), x16 concomitant metronidazole/ vancomycin (17.4%).					

Supplementary Material 2 for *Gut*

MacConnachie *et al, QJM*, 2009	Case series. Number of patients: 15. Female: male: 14: 1. Age (median): 81.5 (range 68-95) years. Comorbidities: no haematological or IBD. CDI features: Relapsing defined as recurrence of loose stool following successful antibiotic treatment in a patient with previous toxin positive CDI. CDI diagnosis confirmation: Not specified. Pre-FMT antibiotics: All had had previous metronidazole and vancomycin; x3 patients tapering vancomycin and intravenous Immunoglobulin.	Donors were healthy related volunteers. Working in healthcare: Yes – in three cases where relatives could not be identified. Donor demographics: Not specified. Donor screening: HIV-1/-2, HTLV- 1 and -2, hepatitis A IgG/M, hepatitis B surface antigen, hepatitis C antibody, *Treponema pallidum.* Questionnaire: Yes, but not specified. Travel and antibiotic exclusion period: Not specified. Screening stools: Ova, cysts and parasites, MC&S, *C difficile* toxin.	Amount of stool per transplant administered to patients: 30g. Diluent used to prepare: 0.9% normal saline. Diluent used to store if frozen: N/A – fresh. Preparation methods: Stool sample prepared in less than 6 hours; add 50-70ml of normal saline, homogenise with handheld stool blender,gradually advance speed, continue for 2-4 mins until smooth, filter suspension in coffee filter paper. Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): Not applicable. Route administered: Upper GI: All 15 patients received FMT via nasogastric tube; lower GI and capsules: nil. Number of infusions: 1 FMT per patient routinely, repeat if required. Bowel purgative: Not given. PPI: Omeprazole 20mg eve before and on morning. Antimotility: Not given.	Overall cure within stated follow up period: 84% (*n*=15/18) “resolution”. Cure with one infusion alone: 884% (*n*=15/18) “resolution”. Total follow-up period: 90 days.	Minor GI adverse events: x1 diarrhoea. Minor non-GI adverse events: Nil. Serious adverse events: Nil. Deaths: x2 (not felt related to FMT).	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Prokinetics: Not given. Time before CDI treatment was stopped before FMT: Stopped on the evening before FMT.			

Supplementary Material 2 for *Gut*

Mattila *et al, Gastroenterology,* 2012	Case series. Number of patients: 70. Female: male: 42: 28. Age (mean): Mean 73 (range 22-90) years. Comorbidities: No IBD, one adenocarcinoma of colon diagnosed during colonoscopy for FMT. CDI features: Recurrent, mean of 3.5 previous episodes of CDI pre-FMT (range 1-12). CDI diagnosis confirmation: Positive culture and toxin. Pre-FMT antibiotics: Mixture of metronidazole, vancomycin, rifaximin - no patient-level data.	Donors: 61 donors were close relatives/ other household members; in 9 cases, healthy volunteers. Donors working in healthcare: Not specified. Donor demographics: Not specified. Donor screening: Questionnaire - "No antibiotics and no intestinal symptoms within 6 months". Travel and antibiotic exclusion period: Excluded as donor if any antibiotic use within past six months; no details of travel restrictions. Screening blood tests: Hepatitis B surface antigen, Hepatitis C antibody, HIV-1/-2 , *Treponema pallidum* plasma reagin test; total blood count, C-reactive protein, creatinine, liver enzymes. Screening stool tests: *C difficile* culture/ tox A/ B; MC&S, ova cysts and parasites.	Amount of stool per transplant / administered to patients: 20-30ml stool. Diluent used to prepare: 100-200ml water; 100ml of suspension administered to caecum. Diluent used to store if frozen: N/A – all fresh. Preparation methods: Not specified. Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: colonoscopy (70); capsules: nil. Number of infusions: 1 FMT. Bowel purgative: 4l PEG (Colonsteril). PPI: Not specified. Antimotility: Not specified. Prokinetics: Not specified. Time before CDI treatment was stopped before FMT: Average of 36 hours.	Overall cure within stated follow up period: 94% (*n*=66/70) (100% (*n*=34/34) of those with non-027, 89% (*n*=32/36) with 027) within 12 weeks. Cure with one infusion alone: 94% (*n*=66/70) (100% (*n*=34/34) of those with non-027, 89% (*n*=32/36) with 027) within 12 weeks. Total follow up period: One year.	Minor GI adverse events: Not specified. Minor non-GI adverse events: Not specified. Serious adverse events: Not specified. Deaths: x4 patients infected with 027 did not respond to FMT and died within 3 months. 10 other patients died of 'unrelated illnesses' during one year of follow-up.	Selection/ eligibility reported: Yes. Consecutively recruited: Not clear. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

Meighani *et al, European Journal of Gastroenterology and Hepatology,* 2016	Case series. Number of patients: 201. Female: male: 125: 76. Age (mean/ standard deviation): Mean age 66.6 (+/-18.3) years. Comorbidities: x37 cancer, x30 immunosuppressed, x26 CKD. Immunosuppressed defined as chemotherapy within 1 year of FMT, HIV with CD4 < 200, or prednisolone use greater than or equal to 20mg for more than 1 month.) CDI features: 61 with refractory, 140 with recurrent. CDI diagnosis confirmation: Positive toxin or polymerase chain reaction. Pre-FMT antibiotics: Not specified.	Donors working in healthcare: not specified. Donor demographics: not specified. Donor screening: Questionnaire - not specified. Travel and antibiotic exclusion period: Not specified. Screening blood tests: Not specified. Screening stool tests: Not specified.	Amount of stool per transplant / administered to patients: Not specified. Diluent used to prepare: Not specified. Diluent used to store if frozen: Not specified. Preparation methods: Not specified. Time from preparation to transplant (fresh): Not specified. Time period for storage (frozen): Not specified. Route administered: Upper GI: nasogastric tube x 76, PEG x5; lower GI: x45 enema, x75 colon; capsules: nil. Number of infusions: Some people received multiple FMT procedures - repeat FMTs within 90 days of previous FMT were still maintained as a 'single infection unit'. Bowel purgative: Not specified. PPI: Not specified. Antimotility: Not specified. Prokinetics: Not specified.	Overall cure within stated follow up period: 88% (*n*=176/201) over 90 days. Cure with one infusion alone: 73.1% (*n*=147/201). Total follow-up period: Each patient for 90 days.	Minor GI adverse events: Not specified. Minor non-GI adverse events: Not specified. Serious adverse events: Not described. Deaths: 18 deaths in cohort but no clear timeframe, and not clear if any related to FMT. Described as mortality rate of 6.25% in response group, 28% in failure rate.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Time before CDI treatment was stopped before FMT: 24 hour - not specifically stated as anti-CDI treatment.			

Supplementary Material 2 for *Gut*

Meighani *et al, Digestive Diseases and Sciences,* 2017	Case series. Number of patients: 201. Female: male: 124: 77. Age (mean/ standard deviation): Mean 68.79 (+/-16.78) years for x181 non-IBD patients, mean 46.9 (+/-19.97) for the x20 IBD patients. Comorbidities: 13/20 IBD patients were immunosuppressed (no further details); no further specific details about immunosuppression). CDI features: Recurrent CDI in 13/20 of IBD patients, primary refractory in 7/20. 1.90 (+/- 1.02) CDI infections in past three months for IBD patients, 1.79 (+/1.17) CDI infections in past three months for non-IBD patients. CDI diagnosis confirmation: GDH first, then toxin A and B; PCR	Donors were typically family members, but small number of unrelated universal donors. Amongst IBD cohort - 6 patients had family members as donor, universal donor in other 14. Donor working in healthcare: Not defined. Donor demographics: Not defined. Donor screening: Questionnaire - not defined. Travel and antibiotic exclusion period: Not defined. Screening blood tests: Not defined. Screening stool tests: Not defined.	Amount of stool per transplant / administered to patients: Not defined. Diluent used to prepare: Not defined. Diluent used to store if frozen: Not defined. Preparation methods: Not defined. Time from preparation to transplant (fresh): Not defined. Time period for storage (frozen): Not defined. Route administered: Upper GI: 5 nasogastric (IBD patients only; not described re non-IBD patients) lower GI: 13 colonoscopy (IBD patients only; not described in non-IBD patients); 2 retention enema (IBD patients only; not described re non-IBD patients) (15). Number of infusions: Any relapse beyond 90 days was defined as 'new infection'. However, not made clear if patients given more than one FMT. Bowel purgative: Not described. PPI: Not described. Antimotility: Not described. Prokinetics: Not described.	Overall cure within stated follow up period: As per primary outcome - difficult to give more specific information than already given. Cure with one infusion alone: 87.3% (*n*=158/181) in non-IBD, 75% (15/20) in IBD; but 17.15 (*n*=31/181) non-IBD relapse within 90 days/ 13.9% (*n*=25/180) beyond 90 days, and 25% (*n*=5/20) IBD relapse within 90 days/ 20% (*n*=4/20) beyond 90 days. 3/5 failures in IBD arm had newly-diagnosed IBD, other had severe active disease. Total follow up period: At least 90 days.	Minor GI adverse events: None. Minor non-GI adverse events: None. Serious adverse events: None. Deaths: None.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	used if discordance. Pre-FMT antibiotics: Not defined for non-IBD; for IBD, 15 vancomycin alone, 5 vancomycin and oral metronidazole.		Time before CDI treatment was stopped before FMT: No specific deails.			

Supplementary Material 2 for *Gut*

Patel *et al, Mayo Clinic Proceedings,* 2013	Case series. Number of patients: 31. Female: male: 17: 14. Age (mean/ standard deviation): Mean 61.26 (+/- 19.34) years. Comorbidities: x5 diverticulosis, x5 IBS, x3 UC, x1 Crohn's, x1 gastroparesis, x1 coloanal fistula, x3 prev sigmoid surgery for diverticulitis, x2 subtotal colectomy with ileosigmoid anastomosis, x1 left hemicolectomy with colostomy, x3 long term corticosteroids, x2 hypogammaglobulinaemia, x1 OLT, x1 renal transplant, x1 long term methotrexate. CDI features: Recurrent - mean +/- SD number of confirmed relapses before FMT of 4 +/- 1.4 (range 2-7) episodes. CDI diagnosis confirmation: At least 3x unformed stools/ day, at	Donors were healthy family/ contacts of recipients - 14 spouses, 9 children, 5 siblings, 3 parents, 1 niece, 1 friend. Working in healthcare: Not stated. Donor demographics: No stated age/ BMI limits. Donor screening: Questionnaire - exclude if: chronic GI disease, active peptic ulcer disease, GORD requiring daily PPI, IBS, IBD, history of colon polyps/ cancer, antibiotics or hospitalisation in past three months. Travel and antibiotic exclusion period: No stated travel restrictions; excluded as donor if antibiotic use within past 3 months. Screening blood tests: hepatitis A IgM, HBsAg, HBc IgG/M, hepatitis C antibody, HIV-1/-2 antibody, HTLV-1/-2 antibody, RPR/ syphilis EIA. Screening stool tests: MC&S, ova, cysts and parasites, *Cryptosporidium* antigen,	Amount of stool per transplant / administered to patients: Whole stool - median transplanted weight of 115g (range 18-397g). Diluent used to prepare: Normal saline - "added in 100ml increments until mixture suitable for instillation through working channel of colonoscope". Median volume of FMT 360 (range 180-900) ml. Diluent used to store if frozen: N/A – fresh. Preparation methods: Blender/ pitcher. Time from preparation to transplant (fresh): Six hours; kept at room temperature until processing. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: colonoscopy (31); capsule: nil. Number of infusions: One initially. Bowel purgative: Yes - PEG day before FMT. PPI: Not described. Antimotility: 4mg loperamide either pre- or immediately after colonoscopy.	Overall cure within stated follow up period: At 3 months – 91.3% (*n*=21/23) said diarrhoea no longer present; at 1 year, 100% (*n*=6/6) reported maintained improvement or resolution. Cure with one infusion alone: Of 29 with diarrhoea – 24.1% (*n*=7/29) reported improvement and 75.9% (*n*=22/29) resolution of diarrhoea by median time of three days. Total follow up period: One year.	Minor GI adverse events: Not described. Minor non-GI adverse events: Not described. Serious adverse events: Microperforation - caused by biopsy of an area of presumed ischaemic small bowel injury during the FMT procedure; managed conservatively. Deaths: x1 death at three months - directly related to recently diagnosed metastatic pancreatic cancer, not related to FMT .	Selection/ eligibility reported: Yes. Consecutively recruited: Yes, implied that were. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes - at least as far as primary outcome.

Supplementary Material 2 for *Gut*

	least 2 x toxin positive episodes previously to participate. Pre-FMT antibiotics: All 31 previous methotrexate, all 31 previous vancomycin, 6 previous fidaxomicin, 10 previous rifaximin, 23 prior probiotic.	*Microsporidia* smear, *C difficile* toxin (PCR or EIA).	Prokinetics: Not described. Time before CDI treatment was stopped before FMT: Antibiotics continued until 4 hours before prep (i.e. stopped day prior to FMT).			

Supplementary Material 2 for *Gut*

Pathak *et al, Clinical & Experimental Gastroenterology,* 2013	Case series. Number of patients: 12. Female: male: 8: 4. Age (mean): Mean 71.9 (range 37 – 90) years. Comorbidities: x1 UC, 1 renal transplant, x1 left colon adenocarcinoma and diverticulitis; x1 ruptured appendix; x2 ventilator-dependent. CDI features: Recurrent; full details not given. Two of the patients had had recurrent CDI treated with FMT 'many years ago'. CDI diagnosis confirmation: Not specifically defined. Pre-FMT antibiotics: All vancomycin, 8 patients fidaxomicin, 4 patients methotrexate.	Donors were preferrably family/ first degree relatives; family used in all cases here. Working in healthcare: Not specifically addressed. Donor demographics: Not given. Donor screening: Questionnaire - exposure to HIV, hepatitis, STDs; high risk sexual behaviour; drug use, tattoos/ piercings, imprisonment, other high risk behaviour; known current communicable disease; GI morbidities including IBD or GI malignancy; antibiotic use within 90 days. Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within last 90 days. Screening blood tests: HIV-1/-2, hepatitis A/B/C, STDs. Screening stool tests: MC&S, ova, cysts and parasites, *C difficile* toxin A and B.	Amount of stool per transplant / administered to patients: About 6-8 tablespoons. Diluent used to prepare: 1l of tap water. Diluent used to store if frozen: N/A - all fresh. Preparation methods: No specific details. Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: nasoduodenal tube (1; as a second FMT); lower GI: colonoscopy (12). Number of infusions: 1 FMT initially. Bowel purgative: PEG the night before FMT. PPI: Not described. Antimotility: 2 tablets diphenoxylate/ atropine post-FMT. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 24 hours.	Overall cure within stated follow-up period: 91.7% (*n*=11/12). Cure with one infusion alone: 91.7% (*n*=11/12). Total follow up period: 2-26 months.	Minor GI adverse events: Not stated. Minor non-GI adverse events: Not stated. Serious adverse events: Not stated. Deaths: x1 death. Patient with perforated appendix developed rCDI; didn't respond to six months of anti-CDI treatment, went to ITU. Donor was husband - no screening, and no response to colonoscopic FMT. For 2nd FMT, used healthy volunteer donor FMT via nasoduodenal tube - responded. Urinary tract infection at nursing home few months later – antibiotic treatment precipitated further CDI. Further sepsis, returned to ITU -	Selection/eligibility reported: Yes. Consecutively recruited: Yes, implied that were. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

					declined treatment, then died, four months after initial FMT.	

Supplementary Material 2 for *Gut*

Rohlke *et al, Journal of Clinical Gastroenterology,* 2010	Case series. Number of patients: 19. Female: male: 17: 2. Age (mean): Mean age 49 years. Comorbidities: Not described. CDI features: Recurrent CDI. CDI diagnosis confirmation: Positive *C difficile* toxin and consistently recurring symptoms over a span of six months. Pre-FMT antibiotics: Not given in detail - all at least three courses of conventional anti-CDI antibiotics, including pulsed and tapered vancomycin.	Donors were 4 family members, 14 partners, and 1 housemate. Donors working in healthcare: Excluded. Donor demographics: Donor screening: Questionnaire – included current or recent diarrhoeal illness, sexual behaviour. Travel and antibiotic exclusion period: Excluded if 'recent antibiotic use'; not further defined. Screening blood tests.: HIV, hepatitis A, B and C, and *Trepenoma* serology. Screening stool tests: *C difficile*, bacterial culture, ova, cysts and parasites, *Giardia, Cryptosporidium.*	Amount of stool per transplant / administered to patients: 350mls. Diluent used to prepare: Normal saline. Diluent used to store if frozen: N/A - fresh. Preparation methods: Fresh preparation, with manual shaking of stool and saline in large suction canister, followed by filtering. Time from preparation to transplant (fresh): Not stated. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: all given via colonoscopy. Number of infusions: One routinely, with one patient having a second FMT. Bowel purgative: PEG. PPI: Not described. Antimotility: Loperamide post-FMT. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 1-3 days.	Overall cure within stated follow up period: 100% (*n*=20/20). Cure with one infusion alone: 95% (*n*=19/20). Total follow-up period: 6 months to 5 years.	Minor GI adverse events: Nil reported. Minor non-GI adverse events: Nil reported. Serious adverse events: Nil reported. Deaths: Nil reported.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes – variable follow-up. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

Rubin *et al, Anaerobe,* 2013	Case series. Number of patients: 75. Female: male: 49: 26. Age (median): Median 63 (range 6-94) years. Comorbidities: x10 diabetes mellitus, x8 malignancy, x7 corticosteroids in prior three months. CDI features: Not stated. CDI diagnosis confirmation:Not described. Pre-FMT antibiotics: Oral metronidazole or vancomycin alone or in combination for initial FMT in all cases; not clear exact breakdown/ use for recurrences.	Donors were healthy people from the same household as the patient. Donors working in healthcare: Not stated. Donor demographics: Not described. Donor screening: Questionnaire – as per Aas *et al, Clin Infect Dis,* 2003. Travel and antibiotic exclusion period: As per Aas *et al, Clin Infect Dis,* 2003. Screening blood tests: As per Aas *et al, Clin Infect Dis,* 2003. Screening stool tests: As per Aas *et al, Clin Infect Dis,* 2003.	Amount of stool per transplant/ administered to patients: 30g of stool. Diluent used to prepare: Saline - As per Aas *et al, Clin Infect Dis,* 2003. 25ml of stool/ saline mixture per FMT. Diluent used to store if frozen: N/A - fresh. Preparation methods: As per Aas *et al, Clin Infect Dis,* 2003. Time from preparation to transplant (fresh): As per Aas *et al, Clin Infect Dis,* 2003. Time period for storage (frozen): N/A – fresh. Route administered: Upper GI: 64 nasogastric, 4 PEG, 7 OGD (75 administrations to 74 patients); lower GI: nil; capsule: nil. Number of infusions: One routinely. Bowel purgative: Not described. PPI: Evening prior to/ morning of procedure - no further details. Antimotility: Not described. Prokinetics: Not described.	Overall cure within stated follow up period: 78.7% (*n*=59/75). Cure with one infusion alone: 78.7% (*n*=59/75). Total follow up period: Up to 60 days.	Minor GI adverse events: Nil. Minor non-GI adverse events: Nil. Serious adverse events: Nil. Deaths: No - up to 60 days.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Time before CDI treatment was stopped before FMT: Stopped on the day prior to procedure.			

Supplementary Material 2 for *Gut*

Satokari *et al, Alimentary Pharmacology and Therapeutics,* 2015	Case series. Number of patients: 49. Female: male: 34: 15. Age (mean): Fresh: 52 (range 22-81) years; frozen: 61 (range 20-88) years. Comorbidities: Not described in significant details. CDI features: Recurrent - mean 4.6 (range 2-12) relapses in fresh; mean 4.9 (range 1-6) relapses in frozen. CDI diagnosis confirmation:"Positive culture and toxin". Pre-FMT antibiotics: Describes using vancomycin with all, but no specific details.	Donors were: 15 fresh FMTs with individual donors, 11 fresh FMTs with universal donors; and 23 frozen FMTs with universal donor. Donor working in healthcare: Not stated. Donor demographics: No clear age or BMI limits. Donor screening: Questionnaire - "No antibiotics in past six months and no intestinal symptoms". Travel and antibiotic exclusion period: Excluded as donors if had used antibiotics in past six months. Screening bloods: Total blood count, CRP, creatinine, LFTs, hepatitis B and C, HIV-1/-1, *Treponema*. Screening stools: *C difficile* culture and toxin A/B test, MC&S, ova, cysts and parasites.	Amount of stool per transplant / administered to patients: Fresh - approximately 30g of stool. Diluent used to prepare: Fresh - approximately 150ml of tap water. Diluent used to store if frozen: Frozen - 30g of stool added to 150ml N/saline and then glycerol Preparation methods: As described. Time from preparation to transplant (fresh): Fresh - less than 6 hours between delivery and administration; less than 15 minutes between making FMT and delivery. Time period for storage (frozen): Up to 16 weeks; thawed over 4-5 hours at room temp or in 37^{o}C water bath. Route administered: Upper GI: nil; lower GI: colonoscopy (49); capsules: nil. Number of infusions: One FMT routinely. Bowel purgative: 4l Colonsteril PEG/ 2l MoviPrep. PPI: Not described. Antimotility: Not described.	Overall cure within stated follow up period: Fresh: 96% (*n*=25/26); frozen: 96% (*n*=22/23). Total follow up period: 12 weeks.	Minor GI adverse events: N/A. Minor non-GI adverse events: Mild transient fever in x2 patients with frozen FMT. Serious adverse events: N/A. Deaths: x1 fresh faeces patient died within one year of FMT - not related; x2 frozen patients had relapse within one year, both treated with further antibioitcs – x1 died of recurrent CDI, x1 died of arterial thrombosis.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Prokinetics: not described. Time before CDI treatment was stopped before FMT: Stopped at an average of 36 hours prior to administration.			

Supplementary Material 2 for *Gut*

Yoon *et al, Journal of Clinical Gastroenterology,* 2010	Case series. Number of patients: 12. Female: male: 9: 3. Age (mean)*: Mean 66 (range 30 - 86) years. Comorbidities: 9 with diverticulosis (with 2 of these having diverticulitis as index infection). CDI features: 1 patient with first CDI, 2 with 2nd, 5 with 3rd, 1 with 4th, 1 with 5th, 1 with 6th, 1 with 8th. CDI diagnosis confirmation: Toxin testing for either toxin A or B, or assessment of both via EIA. Pre-FMT antibiotics: 12 had oral metronidazole, 3 had intravenous metronidazole, 12 had oral vancomycin, 4 x rifaximin, no mention of fidaxomicin.	Donors were spouses/ partners in 8 patients; for other 4 patients, donors were one son, two daughters, and one granddaughter. Donors working in healthcare: No. Donor demographics: No details. Donor screening: Questionnaire - no details. Travel and antibiotic exclusion period: No details given Screening bloods: Hepatitis B and C, HIV. Screening stools: *C difficile* toxin, enteric pathogens, ova, cysts and parasites - at treating clinician's discretion.	Amount of stool per transplant / administered to patients: Stool (unclear how much) mixed with 1l normal saline; approx 250-450cc of FMT administered in total. Diluent used to prepare: Normal saline. Diluent used to store if frozen: N/A. Preparation methods: Manually shaken then filtered through gauze. Time from preparation to transplant (fresh): No details. Time period for storage (frozen): N/A. Route administered: Upper GI: (N/A) Lower GI: 10-20cc of FMT administered every 5-10cm of withdrawal distance in all 12 patients. Number of infusions: Single. Bowel purgative: All colonoscopic, but no specific details given. PPI: Not described. Antimotility: Not described. Prokinetics: Not described.	Overall cure within stated follow up period: 100% (*n*=12/12). Total follow up period: 3 weeks to 8 years - no details on relation to individual patients.	Minor GI adverse events: Nil described. Minor non-GI adverse events: Nil described. Serious adverse events: Nil described. Deaths: Nil described.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: No. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Time CDI treatment was stopped before FMT: 3 days.			

Supplementary Material 2 for *Gut*

Youngster *et al, JAMA,* 2014	Prospective case series. Number of patients: 20. Female: male: 9: 11. Age (median): Median 64.5 (range 11-89) years. Comorbidities: Specific comorbidities not described. CDI features: Included patients with both recurrent or refractory CDI. CDI diagnosis confirmation:Toxin and ELISA, PCR if toxin negative but ELISA is positive or indeterminate. Pre-FMT antibiotics: Failed vancomycin taper and/ or fidaxomicin.	Donors were unrelated adult volunteers. Donor working in healthcare: Not stated. Donor demographics: Age range 18-50 years, BMI 18.5 - 25. Donor screening: Questionnaire - American Association of Blood Banks donor questionnaire. Travel and antibiotic exclusion period: Excluded as potential donors if used antibiotics within preceeding 6 months. Screening blood tests: Antibodies to hepatitis A, B, and C; HIV; and *Treponema pallidum* within 2 weeks of donations. Screening stool tests: " Enteric pathogens".	Amount of stool per transplant / administered to patients: 30 capsules (single treatment) - total 48g of stool. Diluent used to prepare: saline in 1/10th volume of stool. Diluent used to store if frozen: 10% glycerol. Preparation methods: Faecal matter solution was pipetted into size 0 capsules (650 µL), which were closed and then secondarily sealed in size 00 capsules. Capsules were stored frozen at −80°C until use. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): Mean 113 days (30-252 days). Route administered: All courses were 30 oral capsules. Number of treatments: 1 course (given as 15 capsules on 2 consecutive days). If failed, retreated at a mean of 7 days. Bowel purgative: Not described. PPI: Not described. Antimotility: Not described.	Overall cure within stated follow up period: 90% (*n*=18/20). Cure with one infusion alone: 70% (*n*=14/20). Total follow up period: 8 weeks.	Minor GI adverse events: Transient abdominal cramping and bloating in 6 patients (30%) that resolved in 72 hours. Minor non-GI adverse events: Not described. Serious adverse events: x1 hospitalised with a documented relapse of severe CDI after taking 15 capsules, but had successful treatment after receiving the remaining 15 capsules. No other severe adverse events (grade 2 or above). Deaths: none.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: Yes. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

			Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 48 hours prior to FMT.			

Supplementary Material 2 for *Gut*

Youngster *et al, BMC Medicine,* 2016	Case series. Number of patients: 180. Female: male: Not stated. Age (median): Median 64 (range 7–95) years. Comorbidities: Not described. CDI features: Three or more mild-to-moderate episodes of CDI or two episodes requiring hospitalisation. CDI diagnosis confirmation: Not specifically described. Pre-FMT antibiotics: Not described.	Donors were healthy volunteers. Donors working in healthcare: Not mentioned. Donor demographics: 18-50 years of age, on no medications, with a 'normal body mass index'. Donor screening: Questionnaire - initial screening using the American Association of Blood Banks donor questionaire for exposure to infectious agents. Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within 6 months. Screening bloods: Blood was screened for antibodies to hepatitis A, B, and C; HIV; and *Treponema pallidum* within 2 weeks of donations. Screening stool test: Donor faeces were screened for enteric bacterial pathogens including rotavirus, *Listeria monocytogenes, Vibrio cholerae, Escherichia coli* O157, ova and parasites (including general microscopy, acid-fast staining, and/or antigen testing	Amount of stool per transplant / administered to patients: 30 capsules derived from a mean of 48g of faeces. Diluent used to prepare: Normal saline. Diluent used to store if frozen: 10% glycerol. Preparation methods: Homogenised using a commercial blender then passed through sieves in ambient air. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): Study of capsulised FMT. Faecal slurry was double-encapsulated in hypromellose capsules (Capsugel, Cambridge, MA) and stored at –80 °C for up to 6 months pending use. Route administered: All received 30 capsules as a 'dose'. Number of infusions: 1 course of capsules in 147 patients, 2 courses in 26 patients and 3 course in 4 patients. Bowel purgative: not mentioned. PPI: not mentioned. Antimotility: not mentioned.	Overall cure within stated follow up period: 91% (*n*=164/180) Cure with one infusion alone: 82% (*n*=147/180) Total follow up period: 8 weeks for primary response.	Minor GI adverse events: x5 vomiting, x112 diarrhoea, x45 nausea/ bloating, x40 abdominal pain. Minor non-GI adverse events: x3 fever, x54 fatigue, malaise, and headache, x12 other complaints. Serious adverse events: Related serious (x1 fever, x2 new UC, x6 hospitalisations for CDI/ diarrhoea). Unrelated serious adverse events: x26 hospitalisations, x14 deaths. Deaths: x14 (unrelated).	Selection/eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

		for *Giardia, Cryptosporidium, Isospora, and Microsporidia*), *C. difficile*, and *Helicobacter pylori* antigen.	Prokinetics: not mentioned. Time before CDI treatment was stopped before FMT: 24–48 hours prior.			

Supplementary Material 2 for *Gut*

Zainah *et al, Digestive Diseases and Sciences,* 2014	Case series. Number of patients: 14. Female: male: 9:5. Age (mean +/-range)*: 73.4 (+/-11.9) years. Comorbidities: x4 patients with cancer, x1 OLT patient. CDI features: 8 patients had had prev CDI episodes (2-5 episodes prior). CDI diagnosis: Diarrhoea (at least 3 unformed stool/d for 2 consecutive days) + positive *C difficile* EIA and/or PCR. All patients here severe by definition - defined here as age >60 years, albumin <2.5mg/dl, temp at least 38.3ºC, WBC > 15 within 48 hour of CDI diagnosis; or at least one of the following: pseudomembranes, treatment in intensive care.	Donors: 12 patients received FMT from related donor (7 spouse, 5 children); the other two used unrelated donors. Donors working in healthcare: Not stated. Donor demographics: Not stated. Donor screening: Questionnaire - not described. Travel and antibiotic exclusion period: No details. Screening blood tests: HIV-1/-2, hepatitis A IgM, hepatitis B serology, hepatitis C antibody, syphilis (RPR and FTA-ABS). Screening stools: *C difficile* toxin by PCR, stool ova, cysts and parasites.	Amount of stool per transplant / administered to patients: 30-50g. Diluent used to prepare: Warm tap water. Diluent used to store if frozen: N/A. Preparation methods: Homogenised mixture, then filtered through gauze; 120-180ml of suspension if through nasogastric tube, 300-500ml if through colonoscopy. Time from preparation to transplant (fresh): "Same day". Time period for storage (frozen): N/A. Route administered: Upper GI: Nasogastric administration in all but one patient (13 patients); lower GI: colonoscopic administration in one patient (1 patient). Number of infusions: One routinely; repeated if no response at 48-72hr. Bowel purgative: No details. PPI: Yes, pre nasogastric administration - no details given. Antimotility: Not described.	Overall cure within stated follow up period: 79% (*n*=11/14) by seven days. Cure with one infusion alone: 71% (*n*=10/14). Total follow up period: Up to 100 days .	Minor GI adverse events: Not described. Minor non-GI adverse events: Not described. Serious adverse events: Not described. Deaths: x1 within 7 days of FMT - but died of their malignancy.	Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.

Supplementary Material 2 for *Gut*

	Pre-FMT antibiotics: 14 patients prior vancomycin, 12 prior metronidazole too.		Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 24 hours.			

Supplementary Material 2 for *Gut*

C.2. Reviewed randomised studies of FMT for recurrent or refractory CDI

Paper	Study and patient characteristics	Donor characteristics	FMT characteristics	Outcomes	Adverse events
Camacho-Ortiz *et al, PLoS ONE,* 2017	Intervention: FMT (pooled from three donors). Number of patients: 9. Female: male: 3: 4 (data only presented for 7 patients). Age: Mean of 39.7 (+/- 24.8) years. Comparator: Vancomycin (250mg every 6 hours for 10-14 days). Number of patients: 10. Female: Male: 3: 6 (data only presented for 9 patients). Age (mean/median): Mean of 46.7 (+/- 15.8) years. Comorbidities: In FMT arm – x1 abdominal abscess, x1 Child B cirrhotic, x1 pulmonary TB; in vancomycin arm – x2 haemodialysis patients, x1 meningeal TB, x1 'abscessed squamous cell carcinoma'. CDI features: All first episode of CDI, occurring at least 48hrs after admission. CDI diagnosis confirmation: >3 bowel movements during the previous 24 hours, Bristol scale > 5, positive *C. difficile* EIA or PCR. Pre-FMT antibiotics: no antibiotics within FMT arm; patients in vancomycin arm received 250mg	Donors working in healthcare: Not stated. Donor demographics: >18 years, non-pregnant, BMI 20-25kg/m^2 Donor screening: On questionnaire, rejected potential donors who in the past three months had had use of PPI, use of antibiotics, use of immunosuppressives, hospitalisation and/ or diarrhoea. Also excluded if high risk sexual behaviour, first degree relative with diabetes mellitus, abdominal surgery, and any GI disease/ cancer. Travel and antibiotic exclusion period: Excluded if antibiotics within the past 3 months. Screening blood tests: Normal full blood count and liver enzymes essential for inclusion. Also screened for HAV, HBV, HCV, HIV, CMV, EBV, *Trypanosoma, Brucella, Treponema pallidum*. Screening stool tests: Included parasites, enteropathogenic bacteria, rotavirus.	Amount of stool per transplant: 45ml of pooled donor stool (from three donors), at ~0.19g/ml. Diluent used to prepare: 0.9% saline. Diluent used to store if frozen: 15% v/v glycerol. Preparation methods: Stool from donors pooled, mixed, resuspended in saline, filtered to remove particles > 330μm . Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): Not stated. Route administered: Upper GI: 14 by OGD; 1 by nasojejunal tube. Lower GI: colonic (1; patient with anatomical abnormality due to head and neck neoplasia). Capsule: nil. Number of infusions: routinely 1; patients not resolving after first FMT received 2nd FMT (as did patients not improving with vancomycin). Bowel purgative: Not stated.	Treatment arm: FMT Overall cure rate: 71.4% (*n*=5/7) (after 2 x FMT) Cure with one infusion alone: 57.1% (*n*=4/7). Treatment arm: Vancomycin Overall cure rate: 88.9% (*n*=8/9) (not clear if failed patient received FMT subsequently, as is described in protocol).	Minor GI adverse events: Nil stated. Minor non-GI adverse events: Nil stated. Serious adverse events: Nil stated. Deaths: Nil.

	every 6hrs for 10-14 days. Total follow up period: up to one year. Cochrane Collaboration risk of bias assessment: uncertain risk of bias.		PPI: Not stated. Antimotility: Not stated. Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: Nil given.		

Cammarota *et al, Alimentary Pharmacology and Therapeutics,* 2015	Intervention: FMT. Number of patients: 20. Female: Male: 12: 8. Age (mean/median): Mean 71 (range 29-89) years. Comparator: Vancomycin (125mg four times daily for 10 days, follow by a pulse regimen (125-500mg/day every 2-3 days, for at least three weeks). Number of patients: 19. Female: Male: 11: 8. Age (mean/median): Mean 75 (range 49-93) years. Comorbidities: No significant difference of Charlson comorbidity index between groups. CDI features: All recurrent. 7/20 in FMT arm with pseudomembranous colitis. CDI diagnosis confirmation: Diarrhoea and CDT positive within 10 weeks of previous antibiotic treatment. Pre-FMT antibiotics: All had had vancomycin or metronidazole. 19/20 of FMT arm and 16/20 of vancomycin arm had had previous vancomycin taper. Total follow up period: 10 weeks.	Donors working in healthcare: no. Donor demographics: Less than 50 years of age, no antibiotics within past 6 months. Donor screening: Questionnaire - no antibiotics for last 6/12. Excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, high risk lifestyle in last three months. Travel and antibiotic exclusion period: 3 month travel exclusion period, 6 month antibiotic exclusion period. Screening blood tests: Hepatitis A, B, and C, HIV, EBV, syphilis, *Stongyloides, Entomoeba histolytica,* FBC, LFTs, creatinine, CRP. Screening stool tests: *C. difficile* cult and toxin, enteric bacteria, ova, cysts and parasites, VRE, MRSA, Gram negative multi-drug resistant bacteria.	Amount of stool per transplant / administered to patients: Not specified. Diluent used to prepare: Normal saline 500mls. Diluent used to store if frozen: N/A – fresh. Preparation methods: Blended and strained. Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: colonic (20); capsule: nil. Number of infusions: 14 had 1 infusion, 4 had 2 infusions, 1 had 3 infusions and 1 had 4 infusions. Initial protocol was that if non-response to first FMT, then second FMT after one week; however, after first two patients, changed to all patients with pseudomembranous colitis receiving repeat FMT every 3 days until resolution of CDI. Bowel purgative: Macrogol. PPI: No.	Treatment arm: FMT Overall cure rate: 90% (*n*=18/20). Cure with one infusion alone: 65% (*n*=13/20); none of these were patients with pseudomembranous colitis. The 7 patients not cured with first FMT all had pseudomembranous colitis; of these, 5/7 cured with protocol of recurrent FMTs. Treatment arm: Vancomycin: Overall cure rate: Cure with one infusion alone: 26% (*n*=5/19).	Minor GI adverse events: x19 diarrhoea, x12 bloating (all resolved at 12 hours). Minor non-GI adverse events: None. Serious adverse events: None. Deaths: x2 from *C difficile*-related complications.

	Cochrane Collaboration risk of bias assessment: uncertain risk of bias.		Antimotility: No. Prokinetics: No. Time before CDI treatment was stopped before FMT: Between five and two days prior to FMT.		

Allegretti *et al, Gastroenterology (abstract),* 2016	Intervention: Low dose FMT capsules (30 pills once). Number of patients: 10. Female: male: Not stated. Age (mean/median): Not stated. Comparator: High dose FMT. capsules (30 pills daily on two consecutive days). Number of patients: 9. Female: male: Not stated. Age (mean/median): Not stated. Comorbidities: Not stated. CDI features:Not stated. CDI diagnosis confirmation: Not stated. Pre-FMT antibiotics: Not stated. Total follow up period: 8 weeks. Cochrane Collaboration risk of bias assessment: uncertain risk of bias.	Donors were unrelated donors from universal stool bank (OpenBiome). Donors working in healthcare: No. Donor demographics: mean age 26, mean BMI 22.2. Donor screening: Questionnaire - as per OpenBiome protocol. Travel and antibiotic exclusion period: As per OpenBiome protocol. Screening bloods: As per OpenBiome protocol. Screening stools: As per OpenBiome protocol.	Amount of stool per transplant / administered to patients: 30 pills a day for one day. Diluent used to prepare: Not stated. Diluent used to store if frozen: Stored at -80^{o}C prior to use. Preparation methods: Capsules physically stable for 30 days at 25^{o}C using an emulsion-based production protocol. Time from preparation to transplant (fresh): Not stated. Time period for storage (frozen): Not stated. Route administered: All capsule – as described above. Number of infusions: 30 tablets (over one day). Bowel purgative: Not stated. PPI: Not stated. Antimotility: Not stated. Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: Not stated.	Treatment arm: Low dose FMT capsules (30 pills once). Overall cure rate: 70% (*n*=7/10). Treatment arm: High dose FMT capsules (30 pills daily on two consecutive days). Overall cure rate: 77.8% (*n*=7/9).	Minor GI adverse events: None. Minor non-GI adverse events: None. Serious adverse events: None. Deaths: None.

Hota *et al, Clinical Infectious Diseases,* 2016	Intervention: FMT. Number of patients: 16. Female: male: 11: 5. Age (mean/ standard deviation): Mean 75.7 +/- 14.5 years. Comparator: 6 week vancomycin taper. Number of patients: 12. Female: male: 8: 4. Age (mean/ standard deviation): Mean 69.6 +/- 14.2 years. Comorbidities: Not stated, but similar Charlson comorbidity index score between groups. CDI features: All recurrent. CDI diagnosis confirmation: Symptoms and toxin or PCR detection. Pre-FMT antibiotics: At least 1 course of vancomycin for a minimum of 10 days. The majority of patients in both arms had had prior vancomycin tapers. Total follow up period: 120 days. Cochrane Collaboration risk of bias assessment: uncertain risk of bias.	Donors working in healthcare: Not stated. Donor demographics: ≥18yrs. Donor screening: Questionnaire - self-screening questionnaire of behaviours associated with risk for blood-borne pathogens. Travel and antibiotic exclusion period: Antibiotic use for at least two days in the preceding three months. Screening blood tests: Extensive screening comparable with previous studies. Screening stool tests: Extensive screening comparable with previous studies.	Amount of stool per transplant / administered to patients: 50g. Diluent used to prepare: 500mls normal saline. Diluent used to store if frozen: N/A – fresh. Preparation methods: Stomacher laboratory blender. Time from preparation to transplant (fresh): 48 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: 16; capsule: nil. Number of infusions: All had 1 infusion. Bowel purgative: None. PPI: None. Antimotility: None. Prokinetics: None. Time before CDI treatment was stopped before FMT: Day prior to FMT.	Treatment arm: FMT: Overall cure rate: 43.8% (*n*=7/16). Cure with one infusion alone: 43.8% (*n*=7/16). Treatment arm: 6 week vancomycin taper. Overall cure rate: 58.3% (*n*=7/12).	Minor GI adverse events: abdominal pain, tenderness and bloating, equal in both groups. Minor non-GI adverse events: Nil. Serious adverse events: x1 developed anasarca from liver disease, x1 had perforated bowel from diverticulitis at 35 days post-FMT. Deaths: None.

Jiang *et al, Alimentary Pharmacology and Therapeutics,* 2017	Intervention: Fresh FMT. Number of patients: 25. Female: male: 21:4. Age (mean): Mean 75 (range 19-97) years. Comparator: Lyophilised FMT. Number of patients: 23. Female: Male: 13: 10. Age (mean): Mean 63 (range 20-87) years. Comparator: Frozen FMT. Number of patients: 24 Female: Male: 18: 6. Age (mean): Mean 62.5 (range 33-88) years. CDI features: All recurrent. CDI diagnosis confirmation:Not explicitly stated, but includes CDI toxin. Pre-FMT antibiotics: Not stated. Total follow up period: 2 months. Cochrane Collaboration risk of bias assessment: high risk of bias.	Donors working in healthcare: Not stated. Donor demographics: "Normal BMI". Donor screening: Questionnaire - as per van Nood *et al, NEJM,* 2013. Travel and antibiotic exclusion period: As per van Nood *et al, NEJM,* 2013. Screening blood tests: As per van Nood *et al, NEJM,* 2013. Screening stool tests: As per van Nood *et al, NEJM,* 2013.	Amount of stool per transplant / administered to patients: 50g. Diluent used to prepare: Normal saline. Diluent used to store if frozen: Implied use of glycerol for frozen product but not clearly stated. Preparation methods: mix stool with normal saline (1:10), aerobic conditions, use Stomacher to homogenise. Time from preparation to transplant (fresh): Within 2 hours of preparation. Time period for storage (frozen): Not specified. Route administered: All colonoscopic. Number of infusions: 1 Bowel purgative: PEG on night before FMT. PPI: No. Antimotility: 4mg loperamide 3 hours before. Prokinetics: No.	Treatment arm: Fresh: Overall cure rate: 100% (*n*=25/25). Cure with one infusion alone: 100% (*n*=25/25). Treatment arm: Frozen: Overall cure rate: 83% (*n*=20/24). Cure with one infusion alone: 83% (*n*=20/24). Treatment arm: Lyophilised: Overall cure rate: 78% (*n*=20/23). Cure with one infusion alone: 78% (*n*=20/23).	Minor GI adverse events: no differences in the three groups. Mild transient abdominal pain and diarrhoea in 86% of patients. x6 experienced fatigue and x4 had a headache. x2 gained weight. Minor non-GI adverse events: None stated. Serious adverse events: None. Deaths: None.

			Time before CDI treatment was stopped before FMT: Not specified.		

Kao *et al, JAMA,* 2017	Comparitor: Oral FMT capsules. Number of patients: 57. Female: male: 43: 14. Age (median/standard deviation): 58.7 (+/-18.5) years. Comparitor: Colonoscopic FMT. Number of patients: 59. Female: male: 36: 13. Age (median/standard deviation): 57.4 (+/-19.1) years. CDI features: All recurrent. CDI diagnosis: Recurrence of diarrhea (>3 unformed bowel movements every 24 hours) within 8 weeks of completing a prior course of treatment, with either a positive *C difficile* toxin by glutamate dehydrogenase and *C difficile* toxins A/B (*C diff* QuikChek Complete; Techlab) or by detection of glutamate dehydrogenase and *C difficile* cytotoxin B gene (Cepheid), plus resolution of diarrhea for the current episode. Pre-FMT antibiotics: Oral vancomycin (125mg twice daily) up to 24hrs before FMT. Total follow-up period: 12 weeks.	Donors were unrelated volunteers. Working in healthcare: Not stated. Donor demographics: Not stated. Donor screening: Questionnaire: As per Kelly *et al, Gastroenterology,* 2015. Travel and antibiotic exclusion period: As per Kelly *et al, Gastroenterology,* 2015. Screening blood tests: As per Kelly *et al, Gastroenterology,* 2015. Screening stool tests: As per Kelly *et al, Gastroenterology,* 2015.	Amount of stool per transplant / administered to patients: 80-100g. Diluent used to prepare: Normal saline. Diluent used to store if frozen: 100% glycerol. Preparation methods: Mix stool with 200ml of normal saline, and filtered using a Stomacher to homogenise 180ml of faecal slurry. Time from preparation to transplant (fresh): up to 2 months frozen, collected fresh within 12 hours. Time period for storage (frozen): up to 2 months. Route administered: lower GI: 59 (colonoscopy); capsule: 57. Number of infusions: x1 of colonoscopy, or x40 capsules as one-off. Bowel purgative: PEG on the night before. PPI: No. Antimotility: Not stated. Prokinetics: Not stated.	Treatment arm: Oral FMT capsules: 96.2% (*n*=51/53) absence of CDI at 12 weeks. Cure with one treatment alone: 96.2% (*n*=51/53). Treatment arm: FMT via colonoscopy: 96.2% (*n*=50/52). Cure with one infusion alone: 96.2% (*n*=50/52).	Minor GI adverse events: Capsule group: x3 nausea, x2 vomiting, x1 abdominal pain. Colonoscopy group: x1 nausea, x1 vomiting, x1 fever, x5 abdominal pain. Minor non-GI adverse events: .1 developed confusion in the colonoscopy group between time of screening and delivery of FMT. This was not communicated to team, and despite an uneventful FMT she died three days later from heart failure. Serious adverse events: None. Deaths: x1 in each group from cardiopulmonary disease (see above for colonoscopy). The other patient developed *Staphylococcus epidermis* bacteraemia 10 weeks after capsule

			Time before CDI treatment was stopped before FMT: 24 hours.		treatment and died from sepsis.

Kelly *et al, Annals of Internal Medicine,* 2016	Intervention: Donor FMT. Number of patients: 22. Female: male: 18: 4. Age (mean/ standard deviation): Mean age 48 (+/-16) years. Comparator: Autologous FMT. Number of patients: 24. Female: male: 19: 5. Age (mean/ standard deviation): Mean age 55 (+/-14) years. Comorbidities: Similar median Charlson comorbidity scores between groups. CDI features: Recurrent. CDI diagnosis confirmation: ≥3 unformed stools over 24 hours for 2 consecutive days, and either a positive stool test result for *C difficile* or pseudomembranes on colonoscopy. Pre-FMT antibiotics: All patients had had prolonged prior courses of vancomycin. Total follow up period: 8 week outcome follow up, 6 month safety follow-up. Cochrane Collaboration risk of bias assessment: low risk of bias.	Donors working in healthcare: Not stated. Donor demographics: Not stated. Donor screening: Questionnaire - potential donors also completed a modified AABB full-length donor history questionnaire, and those with risk factors for infectious agents were excluded. Travel and antibiotic exclusion period: Excluded as donor if antibiotics within preceeding 90 days. Screening bloods: Testing for HIV-1 and HIV-2 was performed within 2 weeks before donation for FMT. Other serologic testing was performed within 1 month before FMT and included testing for hepatitis A, B, and C viruses; also, testing for *Treponema pallidum*. Screening stool tests: polymerase chain reaction (PCR) testing for detection of *C difficile* toxin; culture for enteric pathogens (*Escherichia coli, Salmonella, Shigella, Yersinia, Campylobacter, Listeria monocytogenes, Vibrio parahaemolyticus,* and *V cholerae*); testing for fecal *Giardia* and *Cryptosporidium* antigens; acid-fast stain for detection of *Cyclospora* and	Amount of stool per transplant / administered to patients: Mean stool dose of 64 g (standard deviation of 25 g; range, 20 to 100g). Diluent used to prepare: 100g of stool in 500mls of normal saline. Diluent used to store if frozen: N/A. Preparation methods: Not reported. Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: all patients in both groups (colonoscopy); capsule: nil. Number of infusions: 1 infusion only. Bowel purgative: polyethylene glycol (PEG). PPI: No. Antimotility: Not described. Prokinetics: No. Time before CDI treatment was stopped before FMT: continued	Treatment arm: Donor FMT: Overall cure rate: 90.9% (*n*=20/22). Cure with one infusion alone: 90.9% (*n*=20/22). Treatment arm: Autologous FMT Overall cure rate: 62.5% (*n*=15/24). Cure with one infusion alone: 62.5% (*n*=15/24).	Minor GI adverse events: Low rates of abdominal pain, bloating, nausea, vomiting, diarrhea, flatulence, anorexia, and constipation; these did not differ significantly between groups. Minor non-GI adverse events: None described. Serious adverse events: None described. Deaths: None.

		Isospora; ova and parasite testing; and enzyme immunoassay for detection of Rotavirus.	therapy until 2 to 3 days before the procedure.		

Lee *et al*, *JAMA*, 2016	Intervention: Frozen FMT. Number of patients: 108. Female: male: 72: 36. Age (mean/ standard deviation): Mean age 73.0 (+/- 16.4) years. Comparator: Fresh FMT. Number of patients: 111. Female: Male: 74: 37. Age (mean/ standard deviation): Mean age 72.5 (+/- 16.2) years. Comorbidities: Not described. CDI features: All recurrent disease. CDI diagnosis confirmation: Toxin and PCR. Pre-FMT antibiotics: All had had prior metronidazole, vancomycin, or both in combination. Almost all patients had had prior vancomycin taper. Total follow up period: 13 weeks. Cochrane Collaboration risk of bias assessment: low risk of bias.	Donors were unrelated volunteers. Donors working in healthcare: Not specifically described. Donor demographics: Not defined. Donor screening: questionnaire – comparable to blood donor screening questionnaire. Travel and antibiotic exclusion period: Excluded as donor if travel (within the last 6 months) to areas of the world where diarrheal illnesses are endemic or risk of traveler's diarrhea is high; also excluded if antibiotics within the preceeding 3 months. Screening blood tests: HIV-1 and -2, hepatitis A IgM, HBsAg, anti-HBc (both IgG and IgM), and anti-HBs, hepatitis C antibody, RPR and FTA-ABS. Screening stool tests: *Clostridium difficile* toxin B by PCR; if unavailable, then evaluation for toxins A and B by EIA; routine bacterial culture for enteric pathogens; faecal *Giardia* antigen; faecal *Cryptosporidium* antigen; Acid-fast stain for *Cyclospora,*	Amount of stool per transplant / administered to patients: 100g of stool. Diluent used to prepare: 300mls of water. Diluent used to store if frozen: no solvents used for storage. Preparation methods: 100g of stool homogensied and mixed in 300mls of water. Time from preparation to transplant (fresh): If fresh, administered within 24hrs. Time period for storage (frozen): If frozen, kept for 30 days at -20°C. Route administered: Upper GI: nil; lower GI: enema FMT for all patients in both groups; capsule: nil. Number of infusions in frozen arm: 57 patients had 1 infusion; 24 patients had 2 infusions; rest had >2 infusions; in fresh arm: 56 patients had 1 infusion; 22 patients had 2 infusion; rest had >2 infusions. Bowel purgative: Not described. PPI: Nil.	Treatment arm: Frozen: Overall cure rate: 90.7% (*n*=98/109). Cure with one infusion alone: 52.8% (*n*=57/108). Treatment arm: Fresh: Overall cure rate: 85.6% (*n*=95/111). Cure with one infusion alone: 50.5% (*n*=56/111).	Minor GI adverse events: Transient diarrhoea (70%), abdominal cramps (10%), nausea (5%) in 24 hours post-FMT; constipation (20%) and flatulence (25%) in follow-up period. No difference between the two groups. Minor non-GI adverse events: None described. Serious adverse events: x12 patients required hospitalization because of ilnesses unrelated to FMT. Deaths: x6 deaths in frozen and x13 deaths in fresh arm (all unrelated to FMT).

		Isospora and, if antigen testing unavailable, *Cryptosporidium;* ova, cysts and parasites.	Antimotility: Not described. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: Discontinued 24 - 48 hours prior to FMT.		

van Nood *et al, New England Journal of Medicine,* 2013	Intervention: FMT + bowel lavage. Number of patients: 16. Female: male: 8: 8. Age (mean/ standard deviation): 73 (+/- 13) years. Comparator: Vancomycin (500mg orally four times daily for 14 days). Number of patients: 13. Female: male: 7: 6. Age (mean/ standard deviation): 66 (+/-14) years. Comparator: Vancomycin (500mg orally four times daily for 14 days) + bowel lavage. Number of patients: 13. Female: Male: 3: 10. Age (mean/ standard deviation): 69 (+/-16) years. Comorbidities: No significant difference in median Charlson comorbidity index between groups. CDI features: All recurrent. CDI diagnosis confirmation: Toxin and PCR. Pre-FMT antibiotics: At least one course of adequate antibiotic therapy (≥10 days of vancomycin at a dose of ≥125mg four times a day or ≥10 days of metronidazole	Donors were healthy volunteers. Donors working in healthcare: No. Donor demographics: <60 years of age. Donor screening: questionnaire: questionnaire addressed risk factors for potentially transmissible diseases. Travel and antibiotic exclusion period: Excluded as donor if travel to tropical area within past 3 months, or antibiotic use within the past two months. Screening blood tests: Blood was screened for HIV; human T-cell lymphotropic virus types 1 and 2; hepatitis A,B, and C; cytomegalovirus; Epstein-Barr virus; *Treponema pallidum; Strongyloides stercoralis;* and *Entamoeba histolytica.* Screening stool tests: Donor feces were screened for parasites, including *Blastocystis hominis* and *Dientamoeba fragilis*; *C*	Amount of stool per transplant / administered to patients: A mean (+/-standard deviation) of 141+/-71g of faeces was infused. Diluent used to prepare: Faeces were diluted with 500mls of sterile saline, 0.9%. Diluent used to store if frozen: N/A. Preparation methods: The solution was stirred, and the supernatant strained and poured in a sterile bottle. Time from preparation to transplant (fresh): Mean time from defecation to infusion was 3.1+/-1.9 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: 16 (via nasoduodenal tube); lower GI: nil; capsule: nil. Number of infusions: 16 patients had 1 infusion; 3 who did not respond in this group had 2nd infusion. Bowel purgative: 4 litres of macrogol solution (Klean-Prep) on the last day of antibiotic treatment. PPI: Not stated.	Treatment arm: FMT + bowel lavage Overall cure rate: 94% (*n*=15/16). Cure with one infusion alone: 81% (*n*=13/16). Treatment arm: Vancomycin: Overall cure rate: 315 (*n*=4/13) patients at 10 weeks. Treatment arm: Vancomycin + bowel lavage: Overall cure rate: 23% (*n*=3/13) patients at 10 weeks.	Minor GI adverse events: 94% immediate diarrhoea, 31% abdominal pain with cramping, 19% belching - resolved within 3 hours. During follow-up, x3 patients had constipation (19%). Minor non-GI adverse events: Nil. Serious adverse events: Nil described. Deaths: None.

	at a dose of 500mg three times per day). Total follow up period: After first infusion at 10 weeks; follow-up was extended to 10 weeks after the second infusion. Cochrane Collaboration risk of bias assessment: low risk of bias.	*difficile*, and enteropathogenic bacteria.	Antimotility: Not stated. Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: 24 hours.		

Youngster *et al, Clinical infectious diseases,* 2014	Intervention: Colonoscopic FMT. Number of patients: 10. Female: male: 6:4. Age (mean/ standard deviation): Mean 50.4 (+/- 28.8) years. Intervention: Nasogastric FMT. Number of patients: 10. Female: male: 5: 5. Age (mean/ standard deviatoin): Mean 58.6(+/-19.6) years. Comorbidities: Not defined. CDI features: Relapsing or recurring (having at least 3 episodes of mild-to-moderate *CDI or* at least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity. CDI diagnosis confirmation: Toxin; initial GDH enzyme-linked immunosorbent assay, followed by PCR only if the GDH test is positive or indeterminate. Pre-FMT antibiotics: Treatment failures of a 6- to 8-week taper with vancomycin (95% of patients) with or without an alternative antibiotic, including fidaxomicin (70% of participants). Total follow up period: 8 weeks follow-up for primary response.	Donors were healthy volunteer non-pregnant adults. Donors working in healthcare: No. Donor demographics: 18-50 years of age, on no medications, with a normal body mass index. Donor screening: questionnaire - initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents. Travel and antibiotic exclusion period: Excluded if antibiotic use within 6 months. Screening blood tests: Blood was screened for antibodies to hepatitis A, B, and C; HIV; and *Treponema pallidum* within 2 weeks of donations. Screening stool tests: Donor faeces were screened for enteric bacterial pathogens including rotavirus, *Listeria monocytogenes, Vibrio*	Amount of stool per transplant / administered to patients: 90mls of thawed FMT (41g). Diluent used to prepare: Normal saline. Diluent used to store if frozen: 10% glycerol. Preparation methods: Homogenised using a commercial blender then passed through sieves. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): Inocula were stored frozen for up to 156 days, range, 29-156 days. Route administered: Upper GI (nasogastric) 10; lower GI (colonoscopy): 10; capsule: nil. Number of infusions: Colonoscopy: 8 patients - 1 infusion, 2 patients – 2 infusions; NG: 7 patients - 1 infusion; 3 patients – 2 infusions. Bowel purgative: For colonic route - 4 liters of PEG solution. PPI: 20mg of omeprazole orally for 48 hours prior to FMT.	Treatment arm: Overall Overall cure rate: 90% (*n*=18/20). Cure with one infusion alone: 70% (*n*=14/20). Treatment arm: Colonoscopy: Overall cure rate: 100% (*n*=10/10). Cure with one infusion alone: 80% (*n*=8/10). Treatment arm: Nasogastric: Overall cure rate: 80% (*n*=8/10). Cure with one infusion alone: 60% (*n*=6/10).	Minor GI adverse events: Mild abdominal discomfort and bloating in x4 patients (20%). X1 child treated colonoscopically had a transient fever of 38.8°C on day 2 that resolved spontaneously. Minor non-GI adverse events: Nil described. Serious adverse events: x1 new diagnosis of malignancy, x1 hospitalisation for Fournier gangrene (unrelated to FMT). Deaths: x2 deaths (unrelated to FMT).

	Cochrane Collaboration risk of bias assessment: uncertain risk of bias.	*cholerae, Escherichia coli* O157, ova and parasites (including general microscopy, acid-fast staining, and/or antigen testing for *Giardia, Cryptosporidium, Isospora,* and *Microsporidia*), *C difficile,* and *Helicobacter pylori* antigen.	Antimotility: single dose of oral loperamide prior to procedure. Prokinetics: Nil. Time before CDI treatment was stopped before FMT: Patients were required to discontinue all antibiotics at least 48 hours prior to the procedure.		

C.3. Reviewed randomised studies of FMT for non-CDI indications

Paper	Study and patient characteristics	Donor characteristics	FMT characteristics	Outcomes	Adverse events
Moayyedi *et al, Gastroenterology,* 2015	Intervention: FMT. Number of patients: 38. Female: male 20: 18. Age (mean +/-range)*: 42.2+/-15.0 years. Comparator: Water enema. Number of patients: 37. Female: male: 11: 26. Age (mean +/-range)*: 35.8 +/-12.1 years. Primary outcome: Remission at week 7, defined as full Mayo score < 3 and complete healing of mucosa at flexible sigmoidoscopy (endoscopic Mayo score: 0). Secondary outcome: Clinical response (at least 3 point reduction in Mayo score), change in Mayo, IBD Questionnaire scores, EQ-5D scores. Inclusion criteria: >18 years with UC - Mayo at least 4 with endoscopic subscore at least 1 (included patients with severe disease). Exclusions - antibiotics/ probiotics in past 30 days, concomitant *C difficile*/ other enteric pathogens, disease severity requiring hospitalisation, pregnancy, unable	Donors were unrelated volunteers - six donors used. Plus - one patient in active treatment arm had spouse as donor (treatment failure). Working in healthcare: Not specifically stated. Donor demographics: 18-60 years. Donor screening: Questionnaire – yes. Travel and antibiotic exclusion period: Retesting of stool whenever donor travelled outside North America. Excluded as donor if antibiotics within past 3 months. Screening repeated regardless every 6 months. Screening blood tests: HIV, hepatitis A IgM, HBsAg, hepatitis C antibody, syphilis, HTLV-1/-2. Screening stool tests: MC&S, ova, cysts and parasites, *C difficile* toxin, VRE, MRSA.	Amount of stool per transplant / administered to patients: 8.3g of stool per enema Diluent used to prepare: 50g of stool mixed with 300ml of commercial bottled drinking water, then 50ml of mixture administered as enema. Diluent used to store if frozen: No glycerol. FMT administered either fresh, or stored at -20 degrees. 21 received frozen, 15 received fresh, 1 mixture of fresh and frozen. Preparation methods: Not anaerobic. Single donor per FMT. Time from preparation to transplant (fresh): Processing within 5hr of collection. Time period for storage (frozen): Not stated. Route administered and frequency: Upper GI: nil; lower GI: enema - weekly for 6 weeks. Aimed to retain for at least 20 mins (38); capsule: nil. Bowel purgative: No PEG. PPI: Not described. Antimotility: Not described.	FMT arm: Remission rates: 24% (*n*=9/38). Clincial response rates: 40% (*n*=15/38) had reduction in full Mayo score of at least 3 points. Quality of Life Assessment: Yes - IBDQ and EQ-5D not significantly different between groups. Water enema arm: Remission rates: 5% (*n*=2/37) (*p*=0.03) Clincial response rates: 24% (*n*=9/37) had reduction in full Mayo score of at least 3 points (*p*=0.16).	FMT arm: Minor GI adverse events: Two patients developed patchy inflam in the colon and also rectal abscess formation - resolved with antibiotics. Minor non-GI adverse events: None. Serious adverse events: x2 patients had diagnosis changed to Crohn's colitis, one was *C difficile* toxin positive at end of therapy. Deaths: None. Water enema arm: Minor GI adverse events: x1 patient developed patchy inflammation in the colon and also rectal abscess formation - resolved with antibiotics. Minor non-GI adverse events: None. Serious adverse events: x1 patient changed diagnosis from UC to Crohn's colitis; x1

	to give informed consent. Concomitant medications: Stable dose thiopurines, mesalamine, corticosteroids, and anti-TNF allowed as long as stable dose for at least 12 weeks (4 weeks for steroids). Total follow-up period: Up to 12 months. Cochrane Collaboration risk of bias assessment: low risk of bias.		Prokinetics: Not described.		admitted with hospital with active severe colitis and required colectomy. Deaths: None.

Rossen *et al, Gastroenterology,* 2015	Intervention: Donor faeces. Number of patients: 23. Female: male: 12: 11. Age (median, (range)): 40 (33-56) years. Comparator: Autologous faeces. Number of patients: 25. Female: male: 14:11. Age (median, (range)): 41 (30 – 48) years. Primary outcome: Clinical remission (defined as a SCCAI score ≤2) in combination with 1-point improvement on the combined Mayo endoscopic score of the sigmoid and rectum, as compared with baseline sigmoidoscopy, 12 weeks after the first treatment. Secondary outcome: Endpoints at 6 and 12 weeks were clinical response (defined as a reduction of 1.5 points on the Simple Clinical Colitis Activity Index (SCCAI), a validated disease activity index tool in ulcerative colitis), clinical remission (defined as a SCCAI of ≤2), endoscopic response, change in median (Inflammatory Bowel Disease Questionnaire [IBDQ]) score from baseline to shortly after treatment (week 6), and adverse events. Inclusion criteria: enteric infection, use of biologics within 8 weeks or	Donors were healthy partners, relatives, or volunteers. Working in healthcare: Not stated Donor demographics: >18 yrs Donor screening: Questionnaire - Dutch Red Cross Questionnaire addressing risk factors for potential transmissible diseases used for screening of blood donors in The Netherlands. Travel and antibiotic exclusion period: Excluded as donor if antibiotics within 8 weeks. Screening blood tests: CMV (IgG + IgM), EBV (IgG + IgM), hepatitis A (total antibody), hepatitis B (HBsAg), hepatitis C (hepatitis C virus antibody), HIV (1+2 antibodies/antigen), HTLV (I + II antibodies), *Entamoeba* (antibodies against *Entamoeba histolytica*), *Strongyloides* (*Strongyloides* ELISA). Screening stools: Multiplex PCR containing probes against enteral viruses (*rotavirus, norovirus, enterovirus parechovirus, sapovirus, adenovirus 40/41/52, astrovirus*), FT + TFT II: PCR op *Giardia, SSYC, Clostridium* toxin	Amount of stool per transplant / administered to patients: 120g Diluent used to prepare: Normal saline Diluent used to store if frozen: not stated Preparation methods: Not anaerobic Time from preparation to transplant (fresh): not stated Time period for storage (frozen): not stated Route administered and frequency: Upper GI: Nasoduodenal route. 2 infusions three weeks apart. Nil lower GI or capsule Bowel purgative: Macrogol before both infusions PPI: Not described Antimotility: Not described Prokinetics: Not described	Donor faeces arm: Remission rates: 30% (*n*=7/23) Clincial response rates: 47.8% (*n*=11/23) at 12 weeks. Quality of Life Assessment: IBDQ only calculated based on responders vs nonresponders. Autologous faeces arm: Remission rates: 20% (*n*=5/25), (*p*=0.51). Clincial response rates: 52% (*n*=13/25) at 12 weeks.	Minor GI adverse events: 78.3% (*n*=18/23) of donor stool and 64% (*n*=16/25) of autologous stool experienced side effects post FMT: transient borborygmus, diarrhoea, vomiting, fever. Minor non-GI adverse events: None. Serious adverse events: x4 overall (small bowel perforation – secondary to Crohn's), CMV infection, abdominal pain, cervical carcinoma. Deaths: Nil.

	methotrexate within 4 weeks Concomitant medications: stable doses of thiopurines, mesalamine, or corticosteroids 10 mg/day for the 8 weeks before inclusion. Total follow-up period: 12 weeks. Cochrane Collaboration risk of bias assessment: low risk of bias.				

Paramsothy *et al, Lancet,* 2017	Intervention: FMT. Number of patients: 41. Female: male 19: 22. Age (median, (range)): 35.6 (27.8-48.9) years. Comparator: Placebo-isotonic saline with added colourant odourant and glycerol cryoprotectant (concentration 10%). Number of patients: 40. Female: male: 15: 25. Age (median, (range)): 35.4 (27.7-45.6) years. Primary outcome: Composite of steroid-free clinical remission and endoscopic remission or response at week 8, defined as a total Mayo score of 2 or less, with all Mayo subscores of 1 or less, and at least a 1 point reduction from baseline in the endoscopy subscore. Secondary outcome: Secondary outcomes were: steroid-free clinical remission (defined as combined Mayo subscores of 1 or less for rectal bleeding plus stool frequency); steroid-free clinical response (defined as either a decrease of 3 points or more on the Mayo score, a 50% or greater reduction from baseline in combined rectal bleeding plus stool frequency Mayo subscores, or both); steroid-free endoscopic	Donors were between 3-7 unrelated donors. Working in healthcare: No. Donor demographics: Not described. Donor screening: Questionnaire asked regarding: · Known HIV, hepatitis B or hepatitis C infection · Known exposure to HIV or viral hepatitis within the previous 12 months · High risk sexual behavior (e.g. sexual contact with anyone with HIV/AIDS or viral hepatitis, men who have sex with men, sex for drugs or money) · Use of illicit drugs · Tattoo or body piercing within the preceding 6 months · Incarceration or history of incarceration · Known current communicable disease (e.g. upper respiratory tract infection) · Risk factors for variant Creutzfeldt-Jakob disease · Travel within last 2 weeks to areas of the world where diarrhoeal illnesses are endemic or risk of traveler's diarrhea is high · History of or current inflammatory bowel disease (IBD) · History of or current irritable	Amount of stool per transplant / administered to patients: 37.5g of blended stool to isotonic saline; volume of each infusion was 150ml. Diluent used to prepare: isotonic saline with 10% glycerol cryoprecipitant. Diluent used to store if frozen: -80°C with glycerol cryoprotectant (concentration 10%). Preparation methods: Donors had to provide faeces within 4 hours of a bowel movement, which was inspected visually for suitability (formed stool, no blood or mucous). Donor stool homogenised for a given batch on each day in a biosafety cabinet in isotonic saline then filtered. Placebo infusions comprised isotonic saline; brown food colourant, odourant, and glycerol cryoprotectant (concentration 10%) was added to all study infusions (investigational and placebo). The volume of each infusion was 150 mL. Infusions were stored at −80°C until dispensation to patients at fortnightly study visits for home freezer storage at −20°C before daily administration. Time from preparation to transplant (fresh): Not described.	Donor FMT arm: Remission rates: 275 (*n*=11/41). Clincial response rates: 54% (*n*=22/41). Quality of Life Assessment: Not described. Placebo arm: Remission rates: 8% (*n*=3/40) (*p*=0.021). Clincial response rates: 23% (*n*=9/40) (*p*=0.04). Quality of Life Assessment: Not described.	FMT arm: Minor GI adverse events: abdominal pain x12 (29%), colitis x10 (24%), flatulance x10 (24%), bloating x8 (20%), nausea x2 (5%), elevated ALT x2 (5%), vomiting x2 (5%), enterocolitis x1 (2%), diarrhoea x1 (2%), reflux x1 (2%), haemorrhoids x1 (2%), elective surgical procedure x1 (2%). Minor non-GI adverse events: None. Serious adverse events: x2 (5%) - x1 clinical deterioration and colectomy, x1 needed intravenous intravenous steroids. Deaths: Nil. Placebo arm: Minor GI adverse events: abdominal pain x11 (28%), colitis x9 (23%), flatulance x8 (20%), bloating x11 (28%), nausea x5 (13%), vomiting x1 (3%), enterocolitis x3 (8%), anal fissure x1 (3%), faecal incontinence x1

	response (defined as a Mayo endoscopy subscore of 1 or less, with a reduction of at least 1 point from baseline); steroid-free endoscopic remission (defined as a Mayo endoscopy subscore of 0); quality of life (assessed with the IBDQ); and safety (assessed by adverse events). Inclusion criteria: 1. 18-75 years; 2. UC for >3 months; 3. UC of any extent except isolated proctitis <5cm; 4. currently active mild-moderate UC as mesured by a Mayo score of 4-10, endoscopy score must be greater or equal to 1 and a physician global assessment score of less than or equal to 2; 5. Written consent. Concomitant medications: Drugs permitted as long as the dose was stable preceding enrolment: oral 5-aminosalicylates (stable dose for 4 weeks); thiopurines and methotrexate (on medication for ≥90 days and dose stable for 4 weeks); and oral prednisolone (dose ≤20mg daily and stable for 2 weeks). During the study, patients remained on the same dose of 5-aminosalicylate, thiopurine, and methotrexate. For oral prednisolone, patients received a mandatory taper of up to 2·5 mg per week so that patients would be steroid-free by week 8.	bowel syndrome (IBS), chronic constipation, chronic diarrhea or other intrinsic gastrointestinal illness / condition · History of or current gastrointestinal malignancy or known polyposis or strong family history of colorectal cancer · History of major gastrointestinal surgery (e.g. gastric bypass, partial colectomy)h Antimicrobials (antibiotics, antivirals, antifungals), probiotics or proton pump inhibitors (PPIs) within the preceding 3 months · Major immunosuppressive medications (e.g. calcineurin inhibitors, biological agents, exogenous glucocorticoids) · Systemic anti-neoplastic agents · Household members with active GI infection Systemic autoimmunity (e.g. multiple sclerosis, connective tissue disease) · Atopic disease (e.g. moderate - severe asthma, eosinophilic disorders of the gastrointestinal tract) · Metabolic syndrome, obesity (BMI >30) or moderate to severe under-nutrition / malnutrition · Chronic pain syndromes (e.g. chronic fatigue syndrome, fibromyalgia) or neurologic / neurodevelopmental disorders · History of malignant illness or ongoing oncologic therapy	Time period for storage (frozen): Not described. Route administered and frequency: Upper GI: 0; lower GI: 5 enemas per week following colonosopic delivery -5 days on, two days off for 8 weeks (40 enemas per patient); capsule: 0. Bowel purgative: Yes, but no details PPI: Not described Antimotility: Not described Prokinetics: Not described		(3%), elevated ALT x2 (5%). Minor non-GI adverse events: None. Serious adverse events: x1 (3%) - admitted to hospital (no details why). Deaths: Nil.

	Cochrane Collaboration risk of bias assessment: low risk of bias.	Travel and antibiotic exclusion period: Excluded if travel within last 2 weeks to areas where diarrheal illnesses are endemic or risk of travelers diarrhea is high. Screening blood tests: Complete blood count, electrolytes, urea and creatinine, LFTS, ESR, CRP, HIV-1 and -2, hepatitis A IgM, hepatitis B SAg, hepatitis B core antibody (IgM and IgG) and surface antibody, hepatitis c antibody, rapid plasma reagin and/or fluorescent treponemal antibody-absorbed, HTLV-1 and HTLV-2. Screening stools: *C difficile* PCR, faecal MC&S with routine bacterial culture for enteric pathiogens, *Giardia* antigen, *Cryptosporidium* antigen, faecal ova/cysts/parasites including *Blastocystitis hominis* and *Dientamoeba fragilis,* and Norovirus.			

Costello *et al, Journal of Crohn's and Colitis (abstract),* 2017	Intervention: Donor FMT. Number of patients: 38. Female: male: Not stated. Age (mean/median): Not stated. Comparator: Control - autologous FMT in saline. Number of patients: 35. Female: male: Not stated. Age (mean/median): Not stated. Primary outcome: Steroid-free remission of UC, as defined by total Mayo of 2 or less with an endoscopic Mayo score of 1 or less at week 8. Secondary outcome: Clinical response (at least 3 point reduction in Mayo score), clinical remission (i.e. SCCAI of 2 or less), endoscopic remission (Mayo 1 or less), and safety. Inclusion criteria: UC - Mayo 3-10 with endoscopic subscore at least 2. Concomitant medications: Stable dose of immunomodulator, 5-ASA, biological, tapering prednisolone. Cochrane Collaboration risk of bias assessment: uncertain risk of bias.	Donors were healthy volunteers. Working in healthcare: Not clear. Donor demographics: Not described. Donor screening: Questionnaire – yes but no details described. Travel and antibiotic exclusion period: Not described. Screening blood tests: Yes but not described . Screening stool tests: Yes but not described.	Amount of stool per transplant / administered to patients: 50g of stool for first FMT, 25g of stool in subsequent enemas. Diluent used to prepare: 65% saline. Diluent used to store if frozen: Yes - frozen with 10% glycerol. Preparation methods: Anaerobic prep, donor stool pooled from 3-4 donors. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): Not stated. Route administered and frequency: Upper GI: nil; lower GI: FMT via colonoscopy on day 0, followed by 2 enemas on day 7 (38); capsule: nil Bowel purgative: PEG before colonoscopy but not enema PPI: Not described Antimotility: Not described Prokinetics: Not described	Donor FMT arm: Remission rates: 32% (*n*=12/38) in steroid-free remission at week 8. Clincial response rates: 55% (*n*=21/38). Quality of Life Assessment: Not described. Autologous FMT arm: Remission rates: 9%. (*n*=3/35) in steroid-free remission at week 8 (*p*<0.01). Clincial response rates: 20% (*n*=7/35) (*p*<0.01). Quality of Life Assessment: Not described.	Donor FMT arm: Minor GI adverse events: Nil. Minor non-GI adverse events: Nil. Serious adverse events: Worsening colitis in x2 patients Deaths: Nil. Control - autologous FMT in saline arm. Minor GI adverse events: Nil. Minor non-GI adverse events: None. Serious adverse events: Worsening colitis in x2 placebo patients. x1 patient requiring colectomy, x1 pneumonia. Deaths: Nil.

Johnsen et al, *Lancet Gastroenterology and Hepatology,* 2017	Intervention: Donor FMT. Number of patients: 55. Female: male: 36: 19. Age (median, (range)): 44 (33-54) years. Comparator: Control - autologous FMT . Number of patients: 28. Female: male: 19: 9. Age (median (range)): 45 (34-57) years. Primary outcome: Symptom relief of more than 75 points assessed by IBS-SSS at 3 months after FMT. Inclusion criteria: 18-75 yrs of age, IBS with diarrhoea or mixed IBS according to Rome III criteria. Exclusion criteria: participants with severe cardiac disease, pulmonary disease, or kidney failure, non-IBS type abdominal pain, immunodeficiency or on immunomodulating agents. Cochrane Collaboration risk of bias assessment: low risk of bias	Donors were two volunteers screened at start and at 7 months post donation. Working in healthcare: Not stated. Donor demographics: Not described. Donor screening: Questionnaire - new tattoos or piercings in the past 3 months; high-risk sexual behaviour; former imprisonment; or history of any of the following conditions: chronic diarrhoea, constipation, inflammatory bowel disease, IBS, colorectal polyps or cancer, immunosuppression, obesity, metabolic syndrome, atopic skin disease, or chronic fatigue. Travel and antibiotic exclusion period: Excluded if antibiotics within past three months. Screening blood tests: Glycated haemoglobin; and serology for HIV, *Treponema pallidum*, and hepatitis A, B, and C. Screening stool tests: *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Yersinia* spp, and toxin-producing *C difficile*; faecal tests for *Helicobacter pylori* antigen,	Amount of stool per transplant / administered to patients: 50 to 80g of stool in 50mls. Diluent used to prepare: 200ml isotonic saline and 50mls of 85% glycerol. Diluent used to store if frozen: glycerol, only for autologous transplants. Preparation methods: Aerobic, stool from both donors was mixed together. Time from preparation to transplant (fresh): 7 hours. Time period for storage (frozen): 2-4 weeks. Route administered and frequency: upper GI: none; lower GI: single infusion of FMT via colonscopy; nil capsule. Bowel purgative: Picoprep. PPI: Not described. Antimotility: Loperamide 8mg 2 hours before. Prokinetics: Not described.	Donor FMT arm: Remission rates: 66% (*n*=36/55) . Quality of Life Assessment: Not described. Autologous FMT arm: Remission rates: 43% (*n*=12/28) (*p*=0.49). Quality of Life Assessment: Not described.	FMT arm: Minor GI adverse events: Self limiting intermittent abdominal pain x1, self limiting nausea and vertigo x1. Minor non-GI adverse events: Nil. Serious adverse events: Nil. Deaths: Nil. Placebo arm: Minor GI adverse events: Self limiting intermittent abdominal pain x2. Minor non-GI adverse events: Nil. Serious adverse events: Nil. Deaths: Nil.

		viruses (norovirus, rotavirus, Sapovirus, adenovirus), and faecal calprotectin.			

Bajaj *et al, Hepatology,* 2017	Intervention: Donor FMT. Number of patients: 10. Female: male: 0: 10. Age (mean+/-standard deviation): 64.5 +/- 5.1 years. Aetiology (HCV / alcohol / HCV+alcohol / NAFLD / others): 2/4/2/2/0. Comparator: Standard of care (lactulose/ rifaximin). Number of patients: 10. Female: male: 0: 10. Age (mean+/-standard deviation): 62.9 +/- 9.8 years. Aetiology (HCV / alcohol / HCV+alcohol / NAFLD / others): 1/5/2/1/1. Primary outcome: Proportion of participants with FMT-related serious adverse events (SAEs) at day 150, a composite endpoint of death, hospitalisations, emergency room visits or transmissible infections, as defined by the FDA. Secondary outcomes: Changes in cognitive function at day 20, cirrhosis severity (MELD score, albumin), changes in liver function and white blood cell (WBC) count, development of all adverse events (AEs), and changes in microbiota composition and function in the FMT arm compared to standard of care arm.	Single donor only - identified based on highest relative abundances of *Lachnospiraceae* and *Ruminococcaceae* (16S rRNA gene sequencing analysis) among a universal stool donor bank (OpenBiome). Working in healthcare: Not stated. Donor demographics: Not described Donor screening: Based on OpenBiome screening. 178-point clinical assessment for infectious and microbiome-mediated diseases and 30 stool pathogen and serological tests before and after the stool is collected. Screening blood tests: HIV-1/-2 status, hepatitis A/B/C, *Treponema pallidum*, LFT, Complete Blood Count (CBC) (Includes differentials and platelets), HTLV-I/II antibody, with Reflex to Confirmatory Assay. Screening stool tests: *Clostridium difficile* Toxin B and PCR, *Cyclospora* and *Isospora* Examination, ova, cysts and parasites with *Giardia* Antigen EIA, *Salmonella/ Shigella/ Campylobacter* Culture, Shiga Toxin EIA with Reflex to *E. coli* O157 Culture and *Vibrio* Culture, *Cryptosporidium* Antigen EIA, *Helicobacter pylori* Antigen EIA,	Amount of stool per transplant / administered to patients: 37.5g of stool. Diluent used to prepare: 90mls glycerol saline buffer in total. Diluent used to store if frozen: glycerol. Preparation methods: Aerobic. Time from preparation to transplant (fresh): N/A - frozen. Time period for storage (frozen): not stated. Route administered and frequency: Upper GI: non; lower GI: Single infusion of FMT via enema. Bowel purgative: Picoprep. PPI: Not described. Antimotility: Loperamide 8mg 2 hrs before. Prokinetics: None. Others: Lactulose and rifaximin were continued for all patients throughout the trial. A 5-day broad-spectrum coverage regimen was used (metronidazole 500 mg orally three times daily, ciprofloxacin 500 mg orally twice-daily, and amoxicillin	FMT arm: Patients with SAEs at day 150: 20% (*n* =2/10) (*p*=0.02). Total SAEs at day 150: 20% (*n* =2/10) (*p*=0.01). Patients with altered mental status by day 150: 0% (*n* =0/10) (*p*=0.03). Total HE episodes at day 150: 0% (*n* =0/10) (*p*=0.03). Stroop OffTime+OnTime change (day 0 and day 20); positive indicates improvement: 29.1 +/- 27.9 (*p*=0.04) (N.B. Stroop OffTime+OnTime is a validated tool for objectively assessing for hepatic encephalopathy using a smartphone app). PHES score change (day 0 and day 20); negative indicates improvement -3.1+/-2.1 (*p*=0.01). MELD score change (day 0 and day 35): 0.1+/-2.0 (*p*=0.78). Standard of care arm: Patients with SAEs at day 150: 80% (*n* =8/10).	FMT arm: Serious adverse events: x1 hospitalisation for acute kidney injury, and 1 was due to chest pain (all within 5 months post FMT). Deaths: Nil. Standard of care arm: Serious adverse events: x11 in total. x9 events linked to liver-related complications, of which x4 needed hospitalisation. x1 patient developed pneumonia and x1 developed gastroenteritis. Deaths: Nil.

	Inclusion criteria: >/:18 yrs outpatients with cirrhosis and recurrent hepatic encephalopathy (HE) defined as at last two documented overt HE episodes requiring therapy. Exclusion criteria: MELD score >17, on oral or intravenous antimicrobial agents besides nonabsorbable rifaximin, allergies to pretreatment antibiotics, immunosuppressive medications, positive C. difficile test, pregnancy, active infection, those with active alcohol abuse, and unable to provide informed consent Cochrane Collaboration risk of bias assessment: low risk of bias	Stool Norovirus EIA, Stool Rotavirus Antigen Detection, Adenovirus Antigen Detection, Gastroenteritis EIA, Vancomycin-resistant Enterococcus Culture, *Microsporidia* Exam.	500 mg orally three times daily). All antibiotics were discontinued at least 12 hours before FMT. This regime was not used in patients randomised to standard of care arm.	Total SAEs at day 150: 11. Patients with altered mental status day 150: 50% (*n* =5/10). Total HE eps day 150: 6 Stroop OffTime+OnTime change (day 0 and day 20): -43.5 +/- 95.7. PHES score change (day 0 and day 20): 0.0 +/- 3.1. MELD score change (day 0 and day 35): 0.2 +/- 2.7. N.B. no significant difference in serum albumin, AST, ALT, WBC or haemoglobin counts between the two groups.	

Tian *et al*, *PLoS ONE*, 2017	Intervention: Donor FMT (one for six days in a row). Number of patients: 30. Female: male 19: 11. Age (mean+/-SD): 53.1 +/- 10.2 years. Comparator: Standard of care (education, behavioural strategies, oral laxaives; expressively told to avoid antibiotics). Macrogol permitted if no bowel movement for three days, and enema permitted if even this failed. Number of patients: 30. Female: male 21: 9. Age (mean+/-SD)*: 55.4 +/- 12.1 years. Primary outcome: At least three complete spontaneous bowel movements (CSBMs) per week during the 12 week follow-up. Secondary outcomes: 1) Proportion of patients with average increase of at least 1 CSBM per week; 2) Number of CSBMs per week; 3) Colonic transit time (assessed via abdominal x-ray/ radiopaque markers); 4) subjective stool consistency; 5) Wexner constipation scale. Inclusion criteria: ≥18 yrs outpatients with cirrhosis and recurrent hepatic encephalopathy (HE) defined as at last two	One universal donor used throughout (24 year old healthy university student). Working in healthcare: No. Donor demographics: As above. Donor screening: Similar to FDA blood screening. Screening blood tests: Full blood count, chemistry and iron profile, hepatitis A, B and C, HIV-1 and-2, CMV, EBV, HSV, VZV, and *Treponema pallidum.* Screening stool tests: *Yersinia spp, Salmonella spp, Shigella spp, Campylobacter jejuni, C difficile* toxin, helminths, ova, parasites, and *Helicobacter pylori.*	Amount of stool per transplant / administered to patients: 100g of stool. Diluent used to prepare: Either 500mls normal saline, or normal saline amended with glycerol to final concentration of 10%. Diluent used to store if frozen: Glycerol. Preparation methods: Not stated. Time from preparation to transplant (fresh): 2 hours. Time period for storage (frozen): 1-4 weeks. Route administered and frequency: Upper GI: all via nasojejunal tube (originally placed endoscopically); lower GI: nil. Bowel purgative: Not described. PPI: Not described. Antimotility: Not described. Prokinetics: None.	Donor FMT arm Meeting primary outcome: 37% (*n*=11/30) (*p*=0.04). Meeting second outcomes: At least one more CSBM per week: 53% (*n*=16/30) (*p*=0.009). Number of CSBMs per week: 3.2+/-1.4. Stool consistency score: 3.9+/-1.3. Colonic transit time (hours): 58.5+/-9.8. Wexner constipation score: 8.6+/-1.5. Quality of Life Assessment: Not described. Autologous FMT arm: Meeting primary outcome: 13% (*n*=4/30) Meeting second outcomes: At least one more CSBM per week: 20% (*n*=6/30). Number of CSBMs per week: 2.1+/-1.2. Stool consistency score: 2.4+/-1.1.	FMT arm: 50 in total (1 x sedation contraindications, x22 endoscopy-related respiratory difficulty, x12 nausea, x5 abdominal pain, x4 diarrhoea, x4 flatulence, x2 transient fever). Placebo arm: x4 in total (x0 sedation contraindications, x0 endoscopy-related respiratory difficulty, x0 nausea, x3 abdominal pain, x0 diarrhoea, x1 flatulence, x0 transient fever).

	documented overt HE episodes requiring therapy. Exclusion criteria: At least 18 years, BMI of 18-25 kg/m^2, and slow transit constipation defined as colonic transit time of >48hr, and symptoms unresponsive to dietary modification, enemas or biofeedback in the previous six months. Cochrane Collaboration risk of bias assessment: low risk of bias.			Colonic transit time (hours): 73.6+/-8.7. Wexner constipation score: 12.7+/-2.5. Quality of Life Assessment: Not described.	

Vrieze et al, *Gastroenterology*, 2012	Intervention: Donor FMT Number of patients: 9. Female: male 0: 9. Age (mean+/-SD): 47 +/- 4 years. Comparator: Autologous FMT. Number of patients: 9. Female: male 0: 9. Age (mean+/-SD): 53 +/- 3 years. Primary outcome: Effect of lean donor gut microbiota infusion on insulin sensitivity after 6 weeks. Secondary outcomes: Change in specific small- and large-gut microbiota as well as produced fecal short chain fatty acids Inclusion criteria: Male Caucasian obese subjects with characteristics of the metabolic syndrome, specifically with a body mass index > 30 kg/m^2, or waist circumference > 102 cm, and a fasting plasma glucose level > 5.6 mmol/L. Exclusion criteria: History of cholecystectomy were excluded, as well as subjects who used any medication, probiotics, and/or antibiotics in the past 3 months. Cochrane Collaboration risk of bias assessment: low risk of bias.	Lean healthy Caucasian males (body mass index < 23 kg/m^2. Working in healthcare: Not stated. Donor demographics: As above. Donor screening: Questionnaires regarding diet and bowel habits, travel history, comorbidity including (family history of) diabetes mellitus, and lack of medication use. Screening blood tests: Human immunodeficiency virus; human T-lymphotropic virus; hepatitis A, B, and C; cytomegalovirus; Epstein–Barr virus; *Strongyloides*; and amoebiasis. Screening stool tests: Presence of parasites (eg, *Blastocystis hominis* or *Dientamoeba fragilis*), *Clostridium difficile*, or other pathogenic bacteria (*Shigella, Campylobacter, Yersinia, Salmonella*)	Amount of stool per transplant / administered to patients: Not stated. Diluent used to prepare: 500mls of normal saline. Diluent used to store if frozen: N/A. Preparation methods: Faeces was covered with sterile saline (500 ml 0.9% NaCl) to reduce exposure to oxygen, transferred to a blender, and mixed for 10 minutes. The homogenized solution then was filtered twice through a clean metal sieve. Time from preparation to transplant (fresh): Same day. Time period for storage (frozen): N/A. Route administered and frequency: Upper GI: all via nasoduodenal tube (originally placed endoscopically); lower GI: nil. Bowel purgative: PEG solution. PPI: Not described. Antimotility: Not described. Prokinetics: None.	Donor FMT arm: Median rate of glucose disappearance, Rd: from 26.2 to 45.3 μmol/kg/min; p<0.05). Autologous FMT arm: Median rate of glucose disappearance, Rd: from 18.9 to 19.5 μmol/kg/min). Quality of Life Assessment: Not described. Secondary outcomes: No change in the total numbers of fecal bacteria (allogenic, from 10.8 +/- 0.2 to 11.0 +/- 0.4 vs autologous, from 11.6 +/- 0.6 to 11.3 +/- 0.4 $\log_{10}$ bacteria/g faeces, non significant [NS]). Fecal short-chain fatty acids decreased after allogenic gut microbiota infusion (median acetate from 49.5 to 37.6; p <0.05; butyrate, from 14.1 to 8.9; p < 0.05; and propionate, from 18.2 to 16.3 mmol/kg feces; NS).	No adverse events

Kootte et al, *Cell Metabolism*, 2017	Intervention: Donor FMT Number of patients: 26. Female: male 0: 26. Age (mean): 54 years. Comparator: Autologous FMT. Number of patients: 12. Female: male 0: 12. Age (mean): 54 years. Primary outcome: Change in intestinal microbiota composition upon FMT in relation to insulin sensitivity. Secondary outcomes: Post-prandial lipid, glucose excursions and plasma metabolites Inclusion criteria: All adult (age 21-69 years) Caucasian males, who had obesity (body mass index (BMI) > 30 kg/m^2), fulfilled the National Cholesterol Education Program (NCEP)-criteria for metabolic syndrome, were treatment-naive and who where otherwise healthy. Exclusion criteria: History of recent weight loss, cardiovascular event, cholecystectomy and the use of any medication known to influence gut microbial composition in the last three months (including proton pump inhibitors, antibiotics and pre-/pro-/synbiotics) or treatments targeting metabolic diseases.	Lean healthy Caucasian males (body mass index < 25 kg/m^2. Working in healthcare: Not stated. Donor demographics: As above. Donor screening: Questionnaires regarding diet and bowel habits, travel history, comorbidity including (family history of) diabetes mellitus, and lack of medication use. Screening blood tests: Human immunodeficiency virus; human T-lymphotropic virus; hepatitis A, B, and C; cytomegalovirus; Epstein–Barr virus; *Strongyloides*; lues and amoebiasis Screening stool tests: Pathogenic parasites (e.g., *Blastocystis hominis, dientamoeba fragilis, giardia lamblia*), bacteria (*Shigella, Campylobacter, Yersinia, Salmonella,* enteropathogenic *E. coli* and *Clostridium difficile*) or viruses (noro-, rota-, astro-, adeno (40/41/52)-, entero-, parecho- and sapovirus).	Amount of stool per transplant / administered to patients: Not stated. Diluent used to prepare: 500mls ofnormal saline. Diluent used to store if frozen: N/A. Preparation methods: Faeces was covered with sterile saline (500 ml 0.9% NaCl) to reduce exposure to oxygen, transferred to a blender, and mixed for 10 minutes. The homogenized solution then was filtered twice through a clean metal sieve. Time from preparation to transplant (fresh): Same day. Time period for storage (frozen): N/A. Route administered and frequency: Upper GI: Single infusion all via nasoduodenal tube (originally placed endoscopically). A subgroup of patients receiving donor FMT had a second infusion; lower GI: nil. Bowel purgative: PEG solution. PPI: Not described. Antimotility: Not described. Prokinetics: None.	Donor FMT arm: improved peripheral insulin sensitivity at week 6 (from 25.8 to 28.8 μmol/kg/min, , $p < 0.05$. This change was no longer significant at week 18 (including those that had a second infusion). Autologous FMT arm: FMT had no effect at week 6 (from 22.5 to 20.8 μmol/kg/min, NS) Quality of Life Assessment: Not described. Secondary outcomes: No significant changes in fecal butyrate levels (butyrate from 13 to 20 mmol/g faeces, $p = 0.096$). Fecal acetate levels, however, were significantly increased from 62 to 85] mmol/g feces ($p < 0.05$) after allogenic FMT, whereas fecal proprionate was borderline signifi- cantly altered (from 23 to 28 mmol/g faeces, $p = 0.062$).	No adverse events

	Cochrane Collaboration risk of bias assessment: low risk of bias.				

Appendix D. Excluded clinical studies

D.1. *Clostridium difficile* infection:

D.1.1. Studies excluded at Sift 2 by working group:

Paper:	Grounds for exclusion:
Allegretti JR, Allegretti AS, Phelps E, *et al.* Asymptomatic *Clostridium difficile* carriage rate post-fecal microbiota transplant is low: a prospective clinical and stool assessment. *Clin Microbiol Infect* 2017; doi: 10.1016/j.cmi.2017.10.022	Prospective case series of FMT for CDI, but insufficient patient data to fully populate data table (study primarily designed to evaluate *C. difficile* carriage post-FMT).
Aroniadis OC, Brandt LJ, Greenberg A, *et al.* Long-term follow-up study of fecal microbiota transplantation for severe and/or complicated *Clostridium difficile* infection: a multicenter experience. *J Clin Gastroenterol* 2016;50(5):398-402.	Case series of FMT for CDI, but insufficient patient data to fully populate data table.
Cammarota G, Ianiro G, Masucci L, *et al.* OC.12.9 Fecal microbiota transplantation for recurrent *C. difficile* infection: a 2-year experience from a European referral centre. *Dig Liver Dis* 2016;48 S2:e118.	Case series of FMT for CDI, but abstract only.
Dutta SK, Girortra M, Garg S, *et al.* Efficacy of combined jejunal and colonic fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Clin Gastroenterol Hepatol* 2014;12(9):1572-1576.	Prospective case series of FMT for CDI, but heterogenous primary endpoint (combination of clinical symptoms and *C difficile* toxin, but assessed between 1-3 months after FMT).
Ganc AJ, Ganc RL, Reimao SM, *et al.* Fecal microbiota transplant by push enteroscopy to treat diarrhea caused by *Clostridium difficile.* *Einstein* 2015;13(2):338-339.	Case series of FMT for CDI, but insufficient patient data to fully populate data table.
Ganc A, Ganc R, Frisoli Jr A, *et al.* Fecal transplantation – an original per-oral endoscopic technique with a pediatric colonoscope. *J Gastroenterol Hepatol* 2013;28 S3:115	Case series of FMT for CDI, but abstract only.
Jorup-Ronstrom C, Hakanson A, Sandell S, *et al.* Fecal transplant against relapsing *Clostridium difficile*-associated diarrhea in 32 patients. *Scand J Gastroenterol* 2012;47(5):548-552.	Case series of 'FMT' for CDI, but bacteriotherapy rather than true FMT.
Kao D, Roach B, Beck P, *et al.* A dual center, randomized trial comparing colonoscopy and oral capsule delivered fecal microbiota transplantation in the treatment of recurrent *Clostridium difficile* infection: preliminary results. *Am J Gastroenterol* 2015;110:S553.	Abstract of RCT of capsulised vs colonoscopic FMT for CDI, but same trial/ data set reported in more developed stage at later date[48], so this abstract excluded.
Mah XJ, Paramsothy R, Lo-Cao E, *et al.* Faecal microbiota transplant (FMT) for recurrent and life	Case series of FMT for CDI, but abstract only.

threatening *Clostridium difficile* infection. *J Gastroenterol Hepatol* 2016;31:167-168.	
Mandali A, Ward A, Tauxe W, *et al.* Fecal transplant is as effective and safe in immunocompromised as non-immunocompromised patients for *Clostridium difficile*. *Int J Colorectal Dis* 2016;31(5):1059-1060.	Case series of FMT for CDI, but insufficient patient data to fully populate data table.
Oprita R, Bratu M, Oprita B, *et al.* Fecal transplantation – the new, inexpensive, safe, and rapidly effective approach in the treatment of gastrointestinal tract disease. *J Med Life* 2016;9(2):160-162.	Prospective case series of FMT for CDI or UC, but insufficient patient data to fully populate data table.
Ott SJ, Waetzig GH, Rehman A, *et al.* Efficacy of sterile fecal filtrate transfer for treating patients with *Clostridium difficile* infection. *Gastroenterology* 2017;152(4):799-811.	Case series of 'FMT' for CDI, but only five patients. Furthermore, sterile faecal filtrate rather than true FMT.
Orenstein R, Dubberke E, Hardi R, *et al.* Safety and durability of RBX2660 (microbiota suspension) for recurrent *Clostridium difficile* infection: results of the PUNCH CD study. *Clin Infect Dis* 2016;62(5):596-602.	Prospective case series of FMT for CDI, but using 'microbiota suspension' derived from stool rather than conventional FMT.
Ray A, Jones C, Shannon B, *et al.* Does the donor matter? Results from PUNCH CD 2: a randomized controlled trial of a microbiota-based drug for recurrent *Clostridium difficile* infection. *Am J Gastro* 2016;111:S65-S66.	Abstract of RCT of treatment for CDI, but 'microbiota suspension' rather than true FMT.
Ray A, Smith R, Breaux J. Fecal microbiota transplantation for *Clostridium difficile* infection: the Ochsner experience. *Ochsner Journal* 2014;14(4):538-544.	Case series of FMT for CDI, but heterogenous primary end point.
Rupali P, Mittal C, Deol A, *et al.* Fecal microbiota transplantation for *Clostridium difficile* infection in immunocompromised hosts: one easy strategy, one giant success. *Transplantation* 2014;98:687-688.	Case series of FMT for CDI, but abstract only.
Russell GH, Kaplan JL, Youngster I, *et al.* Fecal transplant for recurrent *Clostridium difficile* infection in children with and without inflammatory bowel disease. *J Pediatric Gastroenterol Nut* 2014;58(5):588-592.	Case series of FMT for CDI, but all children, and presented as separate cases rather than as group of 10 recipients.
Tauxe WM, Haydek JP, Rebolledo PA, *et al.* Fecal microbiota transplant for *Clostridium difficile* infection in older adults. *Ther Adv Gastroenterol* 2016;9(3):273-281.	Case series of FMT for CDI, but heterogenous primary end point.
True E, Tsoraides S, Wang H, *et al.* Predictors of failure with fecal microbiota therapy for recurrent *Clostridium difficile* colitis. *Dis Colon Rectum* 2014;57(5):e99-e100.	Case series of FMT for CDI, but abstract only.
Tvede M, Tinggaard M, Helms M. Rectal bacteriotherapy for recurrent *Clostridium difficile*-associated diarrhoea: results from a case series of 55	Case series of 'FMT' for CDI, but bacteriotherapy rather than true FMT.

patients in Denmark 2000-2012. *Clin Micro Infect* 2015;21(1):48-53.	

D.1.2. Abstracts not fulfilling selection criteria:

Borody TJ, Wettstein A, Nowak A, Finlayson S, Leis S. Fecal microbiota transplantation (FMT) eradicates clostridium difficile infection (CDI) in inflammatory bowel disease (IBD). United Eur Gastroenterol J. 2013;1)(PG-A57):A57.

D.N. S, Seril DN, Shen B. Clostridium difficile infection in patients with ileal pouches. Am J Gastroenterol. B. Shen, Department of Gastroenterology/Hepatology-A31, Digestive Disease Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States. E-mail: shenb@ccf.org: Nature Publishing Group (Houndmills, Basingstoke, Hampshire RG21 6XS, United Kingdom); 2014;109(7):941–7.

Ganc AJ, Ganc RL. Fecal microbiota transplantation, by means of push enteroscopy. A novel endoscopic technique, for the treatment of chronic diarrhea associated with clostridium difficile-a pilot study. Gastrointest Endosc. 2014;1)(PG-AB380-AB381):AB380-AB381.

Garg S, Fricke WF, Girotra M, Dutta A, Von Rosenvinge EC, Dutta S. Recurrent clostridium difficile infection: A longitudinal study of alterations in fecal microbiome in patients-donor pairs before and after fecal microbiota therapy. Gastroenterology. 2013;1)(PG-S184-S185):S184–5.

Garg S, Fricke WF, Girotra M, Von Rosenvinge EC, Dutta A, Dutta SK. Emerging role of fecal microbiota therapy in the treatment of recurrent clostridium difficile infection in children. Gastroenterology. 2013;1)(PG-S45):S45.

Garg S, Song Y, Han MAT, Girotra M, Fricke WF, Dutta S. Post-infectious irritable bowel syndrome in patients undergoing fecal microbiota transplantation for recurrent clostridium difficile colitis. Gastroenterology. 2014;1)(PG-S83-S84):S83–4.

Girotra M, Bartlett J, Koerner K, Dutta S. Combined jejunal and colonic fecal bacteriotherapy in patients with recurrent clostridium difficile infection (RCDI). Am J Gastroenterol. 2011;106(PG-S162-S163):S162–3.

Girotra M, Dutta A, Koerner K, Bodner B, Dutta SK. Recurrent clostridium difficile infection (RCDI) in geriatric patients: A long-term follow up of simultaneous jejunal and colonic administration of fecal bacteriotherapy (FT). Gastroenterology. 2012;1)(PG-S130):S130.

Goyal A, Chu A, Calabro K, Firek B, Bush B, Morowitz M. Safety and efficacy of fecal microbiota transplant in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2016;63(PG-S212):S212.

Goyal A, Kufen A, Jackson Z, Morowitz M. A study of fecal microbiota transplantation in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22:S74.

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D.1.4. Case reports

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D.1.10. Not relevant, miscellaneous

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Appendix E. Peer review

Healthcare Infection Society

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

Closing date: 5pm on 18 January 2018

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Section	Comments	Working group response
A	This is an important consultation of an important treatment for recurrent or refractory CDI. The recommendations are sensible and will help produce a universal service to patients across the UK.	Thank you for your comment.
B	Hudson et al doi: 10.1128/CMR.00049-16Clin. Microbiol. Rev. January 2017 vol. 30 no. 1 191-2311 January 2017 review suggests that faecal microbiotca transplant in the United States is used not only in refractory or recurrent Clostridium Difficile (CDI) but also in initial CDI and Ulcerative colitis	We cannot find mention of FMT use as treatment for initial CDI in this review. Updated searches have identified a small RCT evaluating the use of FMT as treatment for first CDI (Camacho-Ortiz *et al,* 2017), and this is now evaluated by the working group within the guideline (**Section 8.1.1.3**). All published RCTs evaluating the use of the FMT as treatment for ulcerative colitis have been reviewed by the working group within the guideline (**Section 8.6.2**).
C	There is a lack of GP representation on the working group (5.6) and this is reflected in the consultation with a lack of a suggested referral pathway for community based patients	We agree that the implications of this guideline for primary care were not well-described, and we have strengthened this within the guideline. In particular, we have more strongly highlighted the responsibility of microbiology staff in clinical laboratories to liaise proactively with primary care teams regarding the possibility of FMT when recurrent positive stool samples are received from the community on a particular patient (**Section 8.7.1**).
D	There has also been a reported case of the development of obesity following FMT from an overweight donor but this has not been substantiated in other studies. The BMI restriction on donors (8.3.2) may restrict donors.	The recruitment of suitable donors is relatively restrictive by necessity since FMT is an unlicensed and poorly-studied medicinal product. There is a growing literature base demonstrating an association between a high or low BMI and perturbation of the structure and/or function of the gut microbiota and subclinical chronic inflammation. The implications of this for the safety and efficacy of FMT are not well-defined. The suggested BMI range does not make it prohibitively difficult to find suitable donors. As such, the working group believes that their existing recommendation is reasonable.

Section	Comments	Working group response
E	It would be useful to have a standard UK pre and post questionnaire for patients to standardise recording (8.1.2.3)	We agree that the introduction of standardised questionnaires would have clear potential advantages for clinical care and/ or research. We now discuss this further in **Section 10**, 'further research'.
F	It may useful to consider measuring the micriobiol strains of donors to monitor the impact of combinations of specific microbial strains to understand the undefined nature of faecal preparations	We agree of the importance of this, and this is now discussed in more detail in **Section 10**, 'further research'.
G	The lack of universal definitions of cures (8.1.2.4) is likely to hamper future studies	We agree with this comment. **Section 10**, 'further research' has been amended accordingly. Furthermore, we expect that the attention generated by this guideline will highlight this inadequacy.
H	With the introduction of the clinical term SNOMECT across primary care in 2018 and secondary care in 2020 it is important to record faecal microbiota transplant so that long term sequaelae can be measured and patients can be potentially contacted in the future.	We agree that there should be specific procedure codes for FMT (according to route of administration), so that this can be accurately recorded in the patient's medical record. This would also lay the foundation for a future HRG code and tariff for the procedure which is not currently funded by CCGs. Members of the working group are in discussion with NHS England about this.

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Healthcare Infection Society

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

Closing date: 5pm on January 2018

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Section	Comments	Working group response
8.1.1.1	I dont think you should limit FMT for first recurrence to those with specific risk factors. If clinicians wish to use FMT rather than fidaxomicin for the first recurrence on cost effectiveness grounds then that is reasonable. Suggest that you recommend FMT may be offered for the first or second or subsequent recurrences.	As FMT is currently an unlicensed medicinal product with poorly-studied long term sequelae, the working group considered that it should generally be reserved for patients who have had more than three episodes of infection. There are no studies directly comparing its effectiveness with some of the newer agents such as fidaxomicin or bezlotoxumab, hence this recommendation is made on the basis of safety. However, the working group felt that it may be reasonable in certain patient groups (with ongoing risk factors for further

Section	Comments	Working group response
		recurrence) to offer FMT after the second episode. Cost effectiveness analysis was outside the remit of the working group.
8.1.1.3 (ii)	I disagree that patients should have previously been treated with extended/pulsed vancomicin or fidaxomicin before being offered FMT. You dont present any evidence to show that these antibiotic treatment is superior to FMT. Where FMT is the preferred treatment for the first recurrence it is quite likely that the patient will not have had a prolonged or tapered course, and this should not be a barrier to giving FMT which as you say is highly efficacious.	As above, there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota *et al,* 2017). The safety profile of these medications is well-established from large randomised controlled trials, whilst randomised studies involving FMT have tended to be smaller, and have more variable patient follow-up. As such, on the balance of safety, the working group agreed that antimicrobial/antitioxin therapy associated with reduced CDI recurrence should be considered prior to FMT. Reflecting the uncertainties in this area within the reviewed literature, the relevant recommendation is 'conditional' rather than 'strong'.
8.1.1.3 (iii)	You dont cite any evidence that fidaxomicin or bezlotoxumab have better cure rates than FMT. My practice has been not to use fidaxomicin in life threatening C. difficile due to lack of evidence of efficacy in this setting, though I may be out of date with this.	Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, *n*=12/92) than when treated with vancomycin (26.6%, *n*=29/209) (Louie *et al,* 2011); this finding was replicated in another randomised controlled trial, with 8.3% (n=4/48) and 32.6% (n=14/43) experiencing a recurrence respectively (Cornely *et al,* 2012). In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared to standard of care antibiotics alone (10.9% (*n*=6/55) vs 20% (*n*=13/65) respectively) (Wilcox *et al,* 2017). The working group noted that there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota *et al,* 2017). The working group agreed that in the absence of this evidence, on

Section	Comments	Working group response
		the balance of safety and potential risks, consideration should be given to using antimicrobial/ antitoxin therapy associated with reduced CDI recurrence prior to considering the use of FMT.
8.5.1.1 (iii)	Is there adequate published material or experience to ensure the safety of loperamide? It is usually avoided in C. difficile disease due To increased risk of complications.	We agree that loperamide should not be used expressly for the treatment of CDI diarrhoea. However, a number of studies (references within the guideline) have used a single dose of loperamide after lower GI FMT to retention, and no potential safety issues associated with this use have been identified.

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Healthcare Infection Society

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

Closing date: 5pm on January 2018

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Section	Comments	Working group response
8.3.4.	Laboratory Screening of donors "Whilst vancomycin-resistant *Enterococci* (VRE) carriage is relatively common in the community, they are of low pathogenicity, and screening for them was not felt to be justified." VRE can cause life threatening infections that are difficult to treat. Any patient who is VRE positive requires isolation in a sideroom with ensuite facilities. I would suggest that donors should be screened for VRE before accepting stool for donation. If there is a shortage of donor patients	Whilst vancomycin-resistant *Enterococci* (VRE) carriage is relatively common in the community (probably related to food consumption) (Endtz *et al,* 1997), community strains of VRE are genetically distinct from (and generally of much lower pathogenicity than) those found nosocomially (Willems *et al,* 2005); as such, the working group felt that routine screening was not justified. However, the working group acknowledged that the potential infection risk from VRE (and MRSA) would vary regionally dependent upon local prevalence and pathogenicity, and as such recommended that a risk assessment was performed to assess whether screening for these organisms should be considered.

Section	Comments	Working group response
	should be offered VRE positive donations only with informed consent.	

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Healthcare Infection Society

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

Organisation	**On behalf of European Study Group for C*. difficile* (ESGCD), and the National Donor Feces Bank at Leiden University Medical Center (drs. E. Terveer, drs. E. Boeije-Koppenol, prof. Hein Verspaget, dr. Y van Beurden, drs. R Ooijevaar, dr. Josbert Keller) and Department of Infectious Diseases, University of Koln (dr. Maria Vehreschild).**
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Section	Comments	Working group response
general	The literature was searched until April 2017, but please use the recently published document of E.M Terveer et al. entitled "How to: Establish and run a stool bank" and published in Clin Microbiol Infect. 2017 Dec;23(12):924-930. This document has considerable overlap with the proposed guideline, but also shows some important unresolved issues.	This reference has been added. Literature searches have been updated, to January 2018.
Lay summary, line 3	Capsules may also be prepared by use of non-freeze dried microbiota. Also, the possibility of using frozen products in general may be mentioned in this sentence.	We agree that these changes are important, and these amendments have been accordingly.
8.1.1.1	The authors are correct that CDI due to Type 07 responds less to FMT compared with CDI due to other PCR ribotypes. We register all infections by PCR ribotype to obtain more insights in successes and failures associated with strain characteristics and think that this is relevant for future recommendations, such as repeated FMT treatments for specific PCR ribotypes.	We presume that this refers to ribotype 027, and agree that this is important, and further reference has been made to this in **Section 10**, further research.
recommendation	"FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong)." Please elucidate how this risk assessment can be performed.	The working party noted that these risk factors are well-described in previous studies, and do not require further elucidation within the manuscript.

Section	Comments	Working group response
8.1.1.2	Refractory CDI is also considered as an indication for FMT. Can the authors please provide a recommendation on the number of FMTs that should be used? Are patients on Intensive Care Units with refractory CDI also eligible? in 8.2.1 IC admission can be considered as a contraindication, but there are sufficient publications supporting to apply it for patients with severe CDI at ICU.	In **Section 8.2.1**, the working group reviewed the literature on contraindications to receiving FMT, and noted that certain studies have made 'admission to Intensive Care' such a contraindication. However, the working group have not themselves at any point stated that this is a contraindication to receiving FMT. As stated in **Section 8.1.1.2**, there are a relatively small number of cases reported in the reviewed literature of refractory CDI. As such, the working group are unable to give recommendations that patients with refractory CDI receiving FMT should be managed in any particular way differently to those with recurrent CDI.
8.1.1.3	Antibiotic treatment of rCDI. Though the literature search was until April 2017, please mention the recent trials of tapered doses of vancomycin and fidaxomicin (PMID 29273269, PMID: 28591789; PMID 29255732).	We agree that these trials are all relevant, and have updated the guideline accordingly.
	Recommendation II is less clear. How have the authors interpreted the literature that a tapered dosage of vancomycin before FMT increases the success rate of FMT? Are these studies also available for fidaxomicin?	There are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota *et al,* 2017). The safety profile of these medications is well-established from large randomised controlled trials, whilst randomised studies involving FMT have tended to be smaller, and have more variable patient follow-up. Furthermore, FMT remains (in the UK) an unlicensed medicine. As such, on the balance of safety, the working group agreed that antimicrobial/ antitioxin therapy associated with reduced CDI recurrence should be considered prior to FMT. Reflecting the uncertainties in this area within the reviewed literature, the relevant recommendation is 'conditional' rather than 'strong'.

Section	Comments	Working group response
	Recommendation iii is difficult to understand; do the authors recommend to treat severe and complicated CDI not with vancomycin, but with fidaxomicin or vanco+bezlo? If a recurrence occurs, then followed by a FMT?	The wording of this recommendation has been amended, along with expansion of the explanatory text of **Section 8.1.1.4.**
	A recommendation for FMT treatment in severe (refractory), complicated CDI is missing (e.g. multiple sequential FMTs); should this also be accompanied with anti-CDI antibiotics? See review v. Beurden, Ther Advances in Gast, 2017 and Fischer, Ali Pharm Ther 2015	As stated in **Section 8.1.1.2**, there are a relatively small number of cases reported in the reviewed literature of refractory CDI. As such, the working group are unable to give recommendations that patients with refractory CDI receiving FMT should be managed in any particular way differently to those with recurrent CDI.
8.1.2.1	We suggest to differentiate between "non-responding" and "late failure". The latter can be defined as a relapse of CDI after an initial response to FMT. For instance, use of antibiotics in the first month after FMT may provoke a new episode of CDI. This new episode doesn't need a FMT and can be treated with conventional anti-CDI treatment, preferably microbiota sparing such as fidaxomicin.	We agree that this distinction is useful, and have amended the guideline accordingly.
8.1.2.2	Should a psychological questionnaire routinely be taken from recipients (before and after FMT) and from donors (regularly)? A ten-week follow-up is too short to recognize long term side-effects of FMT.	The working group did not consider that this was a priority.
8.1.2.3	We consider swallowing disorders a contraindication for upper GI delivery; death of a patient due to aspiration pneumonia with upper GI delivery has been described (PMID: 29026601); this patient had a swallowing disorder following oropharyngeal radiation after surgical removal of a maxillary carcinoma.	We note that this patient received a very large volume (500ml) of nasoduodenal FMT. This guideline recommends a much lower maximum volume with the specific aim of minimising this problem. Nevertheless, we agree that this is an important consideration, and have amended **Section 8.1.2.3** and **Section 8.5.2.2** accordingly.
8.2.1	What is the advice of the committee for coeliac patients with recurrent CDI?	The working group did not have any specific advice regarding patients with coeliac disease.
8.2.2	FMT in immunocompromised patients: we think that the presence of neutropenia ($<0.5 \times 10^9$/L) can be considered as a contraindiction for FMT, especially if hematological patients are treated with	The working group have recommended that FMT is offered 'with caution' to immunosuppressed patients, reflecting the careful individualised assessment required for each patient.

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	selective gut decontamination to prevent translocation and infections with aerobe Gram-negatives. Second, should donors and immunocompromised recipients be matched for the EBV and CMV status to prevent a herpesvirus infection?	We agree with the comment regarding matching donors and immunosuppressed recipients for EBV and CMV status, and have updated **Section 8.2.2** and **Section 8.3.4** accordingly.
8.2.3	The effect of FMT on the IBD status for IBD patients with rCDI is under discussion. Is it possible that FMT will result in cure of CDI but an exacerbation of IBD. Should we differentiate UC from CD? Ref 71 suggests that IBD can worsen. The recommendation "strong" is debatable. Is the IBD group not a better candidate for vancomycin tapering, fidaxomicin (tapering) or bezlotoxumab before FMT is given?	We agree that there is evidence that FMT to treat CDI in patients with IBD may be associated with a flare of IBD activity (Qazi *et al,* 2017); we have updated the recommendation accordingly.
8.3.2	Age and BMI of the donor. We agree with the BMI of the donor but have some difficulties with the age, We consider an age above 50 as a contraindication, based on the risks to develop colon carcinoma and metabolic (diabetes) diseases. Additionally, older people seems to have a less stable gut microbiota.	We note from a recent paper that *Bacteroides: Firmicutes* ratio and microbial diversity were similar in donors > 60 years compared to younger donors, and donations from older donors had similar efficacy and no higher rate of adverse outcomes (Anand *et al,* 2017). As such, the working group agreed to uphold their prior recommendation.
8.3.3.	Donor screening history. Donors should also undergo a long term follow-up to recognize microbiota related diseases, including colon malignancies, autoimmune diseases, metabolic diseases and psychiatric illnesses.	We agree with the principle of this statement, and allude to this in **Section 8.7.7.**
	Please consider to add to the recommendation/evidence: Potential donors should be extensively screened by a questionnaire and a personal interview concerning risk factors for transmissible diseases and factors influencing the intestinal microbiota	We agree with this suggestion, and have amended **Section 8.3.3** accordingly.
8.3.4	Screening of the donor. Table 4. The Dutch guideline advises screening donors for multi-drug resistant bacteria (MDR), including VRE, MRSA, CPE and ESBL-producing Gram-negatives, and quinolone/aminoglycoside resistant Enterobacteriaceae. Most of the patients with rCDI have much comorbidity and are frequently hospitalized or encounter nosocomially acquired infections, such as	The working group reviewed their recommendation regarding screening for multi-drug resistant bacteria, and **Section 8.3.4** has been updated accordingly. We agree with the principle of a 'window period'/ quarantine prior to repeat donor screening in centres using frozen FMT;

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	UTI. Infections with MDR are more difficult to treat, mostly with intravenously administered antibiotics. If these patients become colonized with MDR they should be nursed with specific infection control precautions. We also apply a "window period"; donors stools samples are stored in quarantine for 2 months and only become available after a negative second screening. We additionally screen for: *Yersinia enterocolitica, Yersinia pseudotuberculosis, Plesiomonas shigelloides*, shiga toxin producing *E. coli* (not only 0157 E.coli), Astrovirus, Sapovirus, Adenovirus, Enterovirus, Parechovirus, Hepatitis E, *Entamoeba histolytica*, *Microsporidium* species, *Blastocystis hominis, Dientamoeba fragilis*, and Strongyloides (if a travel history to Middle and South America, Africa, or Asia is present). We advise to include carriership of *E. histolytica* and Strongyloides to the mandatory screening, because of the serious infections that occur in immunocompromised patients. We have detected unexpectedly a donor carrying *E. histolyica* (Terveer, CMI, 2017).	**Section 8.3.5** has been updated accordingly, and a new flow chart to illustrate the process (**Figure 1**) added. The working group agreed that recommendations should be made to test for Shiga toxin-producing *Escherichia coli,* hepatitis E IgM, *Entamoeba histolytica* serology and *Strongyloides stercoralis* IgG (**Table 3**). However, the working group consensus was that screening with the other tests suggested is not justified.
8.4.1	Recommendation i. Please elucidate how donors should deliver their stools. We favour the use of specific device systems to prevent contamination with environmental microorganisms. Recommendation ii. Processing within 6 hours is proven effective, consider changing 'conditional' to 'strong' recommendation Recommendation iii. A meta-analysis concludes that lless than 50 gram of feces is related to a 4-fold increase in recurrence rates. The recommendation status should be changed to 'strong'.	i. We think that the text as it stands gives sufficient information about best practice in this area. ii. We agree with this suggestion, and have amended **Section 8.4.1** accordingly. iii. We agree with this suggestion, and have amended **Section 8.4.1** accordingly.

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8.4.2	An important advantage of frozen FMT is the possibility to use a "window period" of, for example, two months. When donors are screened after this window period, the results determine if the stored FMTs can be used.	We have cross-referenced **Section 8.4.2** to **Section 8.3.5**, where the concept of a window period/ quarantine is discussed in more detail.
8.4.3	We think that there is not enough evidence to state that feces suspensions can only be used up to six months from preparation. There is no sufficient data that show a decreased efficacy with feces suspensions stored over 6 months. Additionally, multiple stool banks set the expiration date at 1 year after storage.	A trend towards decrease in the viability of certain gut bacterial groups was noted when faecal aliquots were frozen in 10% glycerol for six months (Costello *et al, Alimentary Pharm & Ther*, 2015), and as such, the working group agreed that six months was the acceptable limit for freezing of an FMT in glycerol. This rationale is now within the text.
	Good practice point: Thawing overnight in a 4C refrigerator is also a good and much used alternative.	None of the working group had sufficient experience with this means of thawing FMT, and as such were unable to make this good practice point.
8.5.1.1.	It is not clear, why the administration of a bowel lavage in upper GI administration, of PPI, of loperamide and of metroclopramide are recommended. There is no evidence to support their use, and all of them are drugs with known side effects. The only reason why they are used is that the first RCT used them. However, the RCT did not assess their importance, and there are many case series showing that FMT has a high success rate even without their use.	All of these interventions have a clear biological or practical rationale for their use. Significant side effects in association with a single dose of these medications are generally rare, and their use has not been associated with adverse outcomes in FMT studies. Our recommendations for their use are only conditional. As such, the working group uphold their recommendations.
8.5.2.1.	Not all capsules necessarily contain lyophylized microbiota, frozen preparations have also been shown to be effective.	We agree with this comment, and have updated the guideline accordingly.
8.5.2.2	Are there studies indicating that 50 ml for upper gastrointestinal have comparable efficacy as 250 ml? If not, this should be more pronounced mentioned, also in the research session. We use at least 50 gram suspended in 200 ml and a slow infusion of 10cc/min.	As described in the text, the working group considered that mass of stool was a more important consideration than volume of diluent. They also noted that as low as 25ml of FMT has been demonstrated to be effective as upper GI FMT (Aas *et al, Clin Infect Dis,* 2003). However, the working group revised their decision, and now recommend 100ml as the threshold volume for upper GI FMT administration.

Section	Comments	Working group response
8.5.2.4.	The recommendation not to use capsules seems rather strong. It is unlikely that concerning transmission of infection, the risk would differ in any way from other ways of administration. Also, no safety concerns based on endoscopic complications can possibly arise. We would therefore not pronounce a recommendation against use.	We agree with this statement. Of note, whilst the Kao *et al,* 2017 study (RCT of capsulised vs colonoscopic FMT) was not published at the time of initial searches, it has been identified by updated searches and has now been reviewed by the working group. As such, the guideline has been updated accordingly.
8.6	Consider to add that specific donor microbiota may have better outcomes (e.g. donor B in Moayyedi, gastroenterology, 2015) FMT for other conditions than rCDI. Why have the authors not included the role of FMT to eradicate MDR from the intestinal tract?	Reference to Donor B in this paper has been added to **Section 8.6.2.2.** In keeping with NICE methodology, for the consideration of FMT as treatment for non-CDI conditions, only RCTs could be considered. The working group are aware of case studies and case series using FMT to attempt gut decolonisation of multidrug resistant microorganisms. Members of the working party have themselves contributed to the literature in this field. But no RCTs currently exist.
8.6.3.	Consider adding: characterisation of specific CU patient population that would potentially benefit from FMT. "However, recommendations for clinical use for this indication cannot be made until there is clearer evidence of the most appropriate **CU patient characteristics**, methodology for its preparation, route of delivery, and intensity of administration of FMT"	We agree with this comment, and have updated the guideline accordingly.
8.7.2 and 8.7.4	FMT is considered as a medicinal product under supervision of MHRA and licensing should follow the GMP guidelines. The activities should be performed in a dedicated containment level 2 laboratory with personal protective equipment and a quality assessment system. Does this indicate that FMTs should be prepared under GMP conditions at the Pharmacy Department and not within the Medical Microbiology? Or is this statement too strong?	No. MHRA guidance does not specify where the manufacture should take place. This could be pharmacy, the microbiology laboratory, or another place.
8.7.6	Please consider to add that aliquots of donor FMT materials (and original feces samples) used for patients treatment should be stored,	We agree, and we have updated **Sections 6.3** and **8.7.6** accordingly.

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	enabling to use these samples when adverse effects after FMT developed. This should also been included in 6.3 (auditing).	
Table 4	PCRs are more sensitive than conventional microscopy and antigen tests for parasites. Second, can the authors please specify the parasites? There is some debate on the significance of Blastocystes spp. and Dientamoeba spp. Why is only E. coli 157 excluded and not other STEC pathogens?	**Table 4** has been updated to specify Shiga toxin-producing *Escherichia coli* screening by PCR. The working group did not consider that specific screening for *Blastocystis spp* or *Dientamoeba spp* was justified.
Propose to add: Eligibility of patients for FMT	At the NDFB, all requests by the treating physician are evaluated by at least two clinical members of our feces bank board to determine the eligibility of the patient. It is required that patients have a laboratory documented episode of recurrent CDI following at least one course of adequate CDI antibiotic therapy. Recurrent CDI is defined as the re-appearance of diarrhoea (≥ 3 unformed stools per 24 hours for two consecutive days; or ≥ 8 unformed stools per 48 hours) within eight weeks after cessation of antibiotic therapy in combination with a positive diagnostic test for *C. difficile*. We strongly recommend a two-stage testing algorithm, as recently advised by the *C. difficile* working group/ESCMID (ESGCD). Using this algorithm, we reject approximately 20% of all requests for FMT. We would like to add our experience that of 79 candidate patients for FMT, only 75% were considered as suitable candidates for FMT treatment; most rejected requests were patients with underlying IBD who concomitantly carried *C. difficile.*	Thank you for this comment. Definitions of recurrent CDI are outside of the remit of this working group. Testing is discussed in **Section 8.1.1.,** where we refer to current ESCMID guidance.
Need for antimicrobial stewardship after FMT (also for 8.5.1.3)	After FMT, we advise that an infectious disease specialist or medical microbiologists should be involved for antibiotic treatment (or prophylaxis) of the patient during the first month after FMT, since 50% of our registered failures were patients who received antibiotics within one month after FMT. Interestingly, all patients responded to conventional anti-CDI treatment and did not need a second FMT. It can be considered to use microbiota sparing fidaxomicin after FMT.	We agree with this comment, and have updated **Section 8.5.1.3** accordingly.

Closing date: Please forward this electronically by 5pm on January 2018 at the very latest to consultations@his.org.uk

Healthcare Infection Society

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

Closing date: 5pm on January 2018

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Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, section 1 Introduction and line number). If your comment relates to the guideline as a whole then please put 'general'. Add extra rows if required.

Section	Comments	Working group response
8.1.1.1. Recurrent *Clostridium difficile* infection	***"FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong)."*** We agree however for full clarity we would recommend re-wording to: ***"FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI (strong)."***	We agree with this statement, and have updated the guideline accordingly.
8.1.1.2. Refractory Clostridium difficile infection:	***"FMT should be considered in cases of refractory CDI (conditional)."*** We agree.	Thank you for this comment.
8.1.1.3. Antimicrobial therapy prior to considering FMT for patients with CDI:	***i. FMT for recurrent CDI should only be considered after failure of antimicrobial anti-C. difficile therapy which has been administered for a minimum of 10 days (conditional).*** ***ii. Recipients of FMT as treatment for recurrent CDI should have previously been treated with extended/ pulsed vancomycin and/or fidaxomicin (conditional).*** ***iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT (conditional).*** We suggest rewording point *iii*, that recommends fidaxomicin or bezlotoxumab should be offered to patients with severe or	Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, *n*=12/92) than when treated with vancomycin (26.6%, *n*=29/209) (Louie *et al,* 2011); this finding was replicated in another randomised controlled trial, with 8.3% (n=4/48) and 32.6% (*n*=14/43) experiencing a recurrence respectively (Cornely *et al,* 2012). In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared to standard of care antibiotics alone (10.9% (*n*=6/55) vs 20% (*n*=13/65) respectively) (Wilcox *et al,* 2017). The working group noted that there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study

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	complicated CDI before FMT. There is little evidence on the role of bezlotoxumab and fidaxomicin in severe or severe-complicated CDI. Although the evidence base is similarly lacking for FMT in severe or severe-complicated disease, there is a growing body of evidence from trials, multiple case series and reports indicating the potential for FMT in this population. **Bezlotuxumab:** The performance of bezlotuxumab has not been evaluated in a severe or severe-complicated population. Results from MODIFY I and II suggest a modest 10% improvement in rates of sustained cure with bezlotoxumab. Importantly, only 15.6% were severe CDI. Based on the modest gains in efficacy and the few severe/severe-complicated patients in the MODIFY trials, we feel that further evidence is required before proposing bezlotuxumab be offered ahead of FMT in this patient population. In comparison, across similar patient populations FMT has demonstrated in several randomized controlled trials reduced risk of recurrence. Based on the available evidence we therefore feel that the statement that bezlotuximab is "associated with reduced risk of recurrence" compared to FMT is not supported by the evidence. **Fidaxomicin:** Similarly, there is a dearth of evidence on the role of fidaxomicin in the severe CDI population. We agree that it has demonstrated superior efficacy compared to vancomycin in the general CDI population. In an RCT comparing extended-pulsed fidaxomicin versus vancomycin for CDI, Guery et al (2017) observed increased recurrence in severe CDI compared to non-severe CDI with an odds ratio 0.57 (95% CI 0·36–0·91) p=0.019. We therefore recommend that fidaxomixin should be offered to patients with severe CDI. However, there is no evidence to suggest that the	comparing a vancomycin taper to FMT (Hota *et al,* 2017). The working group agreed that in the absence of this evidence, on the balance of safety and potential risks, consideration should be given to using antimicrobial/ antitoxin therapy associated with reduced CDI recurrence prior to considering the use of FMT.

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	performance of fidaxomicin would be better than FMT. We acknowledge that access to fidaxomicin is likely to be more timely in settings where FMT is not readily available. **The role of FMT in severe CDI:** In their recent review, Van Beurden et al (2017) reviewed the literature on FMT in severe CDI and found 23 reports (12 case reports; 11 case series) about FMT as treatment for severe or complicated CDI. The patients described (n=200) all had severe or complicated CDI, did not respond to conventional CDI antibiotic treatment and received FMT as last resort treatment. In all studies, patients were treated with (sequential) FMT, whether or not followed by additional antibiotic treatment for CDI. FMT, with or without additional antibiotic CDI treatment, appears to be a promising curative treatment option in patients with severe and complicated CDI who do not respond sufficiently to conventional antibiotic treatment. FMT has been proposed by Fischer et al (2015) as an option utilizing an endoscopic response-guided approach, which may be particularly useful in non-surgical candidates. In an open-label cohort study (n = 17), FMT was delivered by colonoscopy. If pseudomembranes were identified, patients reinitiated oral vancomycin 24 hour after FMT and continued for 5 days. A repeat FMT by colonoscopy was given on day 7. If pseudomembranes persisted, vancomycin was restarted the following day for a 5 days course and a third FMT was offered on day 13. If pseudomembranes were absent during any colonoscopy, no further therapy was initiated. The results were promising with a combined clinical cure rate of 88%. In conclusion, we agree that there is a lack of evidence available to make a strong recommendation on the role of FMT in severe CDI. However, there is insufficient evidence to suggest that fidaxomicin	

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	or bezlotuximab would be superior to FMT in this population. On the contrary, the growing pool of experience in using FMT in severe and severe-complicated CDI patients demonstrates that it appears to be generally safe and effective (quality of evidence: 3). We would therefore suggest re-wording point iii to: ***iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin or bezlotuxumab), or offering FMT (conditional).*** Fischer M, Sipe BW, Rogers NA, et al. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated Clostridium difficile infection: description of a protocol with high success rate. Aliment Pharmacol Ther. 2015;42(4):470-476. doi:10.1111/apt.13290. Van Beurden YH, Nieuwdorp M, van de Berg PJEJ, Mulder CJJ, Goorhuis A. Current challenges in the treatment of severe Clostridium difficile infection: early treatment potential of fecal microbiota transplantation. Therapeutic Advances in Gastroenterology. 2017;10(4):373-381. doi:10.1177/1756283X17690480.	
8.1.2.1. Management of FMT failure:	***Further FMT should be offered after initial FMT failure (strong).*** We agree.	Thank you for this comment.
8.1.2.2. General approach to follow-up post-FMT:	***All FMT recipients should routinely receive follow-up. Given the relative novelty of FMT and the potential for unexpected sequelae, clinicians should follow-up FMT recipients for long enough to fully***	Thank you for this comment. In light of other comments from the working group and stakeholders, this follow-up period has been adjusted to 'at least eight weeks in total'.

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	establish efficacy/ adverse events, and at least ten weeks in total (strong). We agree.	
8.1.2.3. Management of the FMT recipient:	***i. Immediate management after endoscopic administration of FMT should be as per endoscopy unit protocol (strong).*** ***ii. Patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare (strong).*** ***iii. After enteral tube administration, patients may have the tube removed and oral water given from 30 minutes post-administration (strong).*** We agree.	Thank you for this comment.
8.1.2.4. Definition of cure post-FMT for CDI:	***A decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis (strong).*** We agree.	Thank you for this comment.
8.1.2.5. Definition of treatment failure post-FMT for CDI:	***Treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for C. difficile toxin after FMT is not recommended, but is appropriate to consider in the case of persistent CDI symptoms/suspected relapse (strong).*** When testing is to be performed, we would recommend clinicians follow the 2016 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for CDI testing, which state that no single commercial test can be used as a stand-alone test for diagnosing CDI, and recommend a 2-step approach (highly sensitive with reflex to highly specific test). These guidelines recommend performing an initial test with a high negative predicative value;	We agree on the use of ESCMID guidelines in CDI testing, and refer to these clearly in **Section 8.1.1.1**. However, **Section 8.1.2.5** specifically refers to diagnosing failure post-FMT for CDI rather than initial diagnosis of CDI, and no good uniform definition exists for this. We think that the guidance given, to define treatment failure on a case-by-case basis, is the most fair summary of the current literature on this topic.

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	therefore, if negative, no further testing needs to be done. Specifically, they suggest glutamate dehydrogenase (GDH) EIA or NAAT/PCR testing. Our recommendation is GDH EIA as it is less expensive and has a slightly superior NPV at higher CDI prevalence compared with NAAT/PCR (98 vs 96 at hypothetical CDI prevalence of 50%), and an NPV of 100% at lower CDI prevalence. The second test should be a test with a high positive predictive value, such as EIA for toxin A/B. Obtaining CDI testing at each suspected CDI recurrence and working with institutional laboratories to use an appropriate testing algorithm is a key component to ensuring appropriate patient selection for FMT. As currently worded, the recommendations risk encouraging over testing in a context where patients may develop post-infectious IBS. This concept is highlighted by evidence suggesting that up to 25% of patients referred to an FMT center for "C difficile infection" were found to have an alternative diagnosis, with younger patients being more likely to have a non-CDI diagnosis (Jackson 2016). Jackson M, Olefson S, Machan JT, Kelly CR. A high rate of alternative diagnoses in patients referred for presumed clostridium difficile infection. J Clin Gastroenterol. 2016 Oct;50(9):742-6.	
8.2.1. General approach to co-morbidities and FMT:	***FMT should be offered with caution in patients with decompensated chronic liver disease and should be avoided in those with anaphylactic food allergy (strong).*** The authors may want to consider the approach recommended by Allegretti et al (2017). In patients with a severe food allergy, a potential option for FMT could be from a patient identified donor living with the patient (e.g. spouse) who avoids the same allergens.	The working group thought it important to emphasise the 'good practice point' that in patients with true anaphylaxis, the risks of FMT administration were likely to outweigh the benefits. As such, this suggestion has not been incorporated.

Section	Comments	Working group response
	Allegretti JR, Kassam Z, Osman M, Budree S, Fischer M, Kelly CR. The 5D framework: a clinical primer for fecal microbiota transplantation to treat Clostridium difficile infection. Gastrointest Endosc [Internet]. 2017 Jul 26; Available from: http://dx.doi.org/10.1016/j.gie.2017.05.036	
8.2.2. Immunosuppression and FMT:	***FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong).*** We agree.	Thank you for this comment.
8.2.3. Other co-morbidities and FMT:	***Recommendation:*** ***i. FMT should be offered to those with recurrent CDI and inflammatory bowel disease (strong).*** ***ii. FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities (conditional).*** We agree.	Thank you for this comment.
8.3.1. General approach to donor selection:	***Related or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor (conditional).*** We agree.	Thank you for this comment.
8.3.2. Age and BMI restrictions for potential donors:	***People should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of <30 kg/m² (conditional).*** We agree.	Thank you for this comment.
8.3.3. General approach to the donor screening assessment:	***A donor-screening history/ questionnaire is mandatory (Table 2) (strong).*** ***1. Receipt of antimicrobials within the past three months.***	

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	2. *Known prior exposure to HIV and/ or viral hepatitis, and known previous or latent tuberculosis.* 3. *Risk factors for blood-borne viruses - including high risk sexual behaviours, use of illicit drugs, any tattoo/ body piercing/ needlestick injury/ blood transfusion/ acupuncture, all within previous six months.* 4. *Receipt of a live attenuated virus within the past six months.* 5. *Underlying gastrointestinal conditions (e.g. history of IBD, IBS, chronic diarrhoea, chronic constipation, coeliac disease, bowel resection or bariatric surgery).* 6. *Family history of any significant gastrointestinal conditions (e.g. family history of IBD, or colorectal cancer).* 7. *History of atopy (e.g. asthma, eosinophilic disorders).* 8. *Any systemic autoimmune conditions.* 9. *Any metabolic conditions, including diabetes and obesity.* 10. *Any neurological or psychiatric conditions, or known risk of prion disease.* 11. *History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia.* 12. *History of any malignancy.* 13. *Taking particular regular medications, or such medications within the past three months, i.e. antimicrobials, proton pump inhibitors, immunosuppression, chemotherapy* 14. *History of receiving growth hormone, insulin from cows, or clotting factor concentrates.* 15. *History of receiving an experimental medicine or vaccine within the past six months.*	

Section	Comments	Working group response
8.3.4. Laboratory screening of potential donors:	***Blood and stool screening of donors is mandatory (Tables 2 and 3) (strong).*** ***Table 3: Recommended blood screening for stool 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*** • ***Cytomegalovirus IgM*** • ***Strongyloides stercoralis IgG*** • ***Entamoeba histolytica serology*** ***General/ metabolic screening:*** • ***Full blood count with differential.*** • ***Creatinine and electrolytes*** • ***Liver enzymes (including albumin, bilirubin, aminotransferases, gamma-glutamyltransferase and alkaline phosphatase).*** • ***C-reactive protein*** ***Table 4: Recommended stool screening for stool donors:*** • ***Clostridium difficile PCR*** • ***Campylobacter, Salmonella, and Shigella by standard stool culture and/ or PCR*** • ***Escherichia coli 0157 H7 by culture and/or PCR***	We agree with the comment regarding matching donors and immunosuppressed recipients for EBV and CMV status, and have updated **Section 8.2.2** and **Section 8.3.4** accordingly. The working group did not think that screening for adenovirus was justified. Whilst vancomycin-resistant *Enterococci* (VRE) carriage is relatively common in the community (probably related to food consumption) (Endtz *et al,* 1997), the form of VRE in the community is genetically distinct from that found nosocomially, with much lower pathogenicity in community forms (Willems *et al,* 2005). As such, the working group strongly opined that routine screening was not justified. However, it was acknowledged that the potential infection risk from VRE (and MRSA) would vary regionally depending on local prevalence and pathogenicity, and as such a local risk assessment has been recommended to decide whether screening for these organisms should be considered.

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	• ***Multi-drug resistant bacteria, specifically carbapenemase-producing Enterobacteriaceae.*** • ***Stool ova, cysts and parasite analysis, including for Microsporidia.*** • ***Faecal antigen for Cryptosporidium and Giardia.*** • ***Acid fast stain for Cyclospora and Isospora.*** • ***Helicobacter pylori faecal antigen.*** • ***Norovirus and Rotavirus PCR.*** We recommend: **CMV and EBV:** Given the high rates of carriage for both EBV and CMV in a healthy, adult population, excluding EBV or CMV positive donors would make it prohibitively difficult to identify suitable donors to provide access to care (Bate et al). Moreover, excluding EBV or CMV positive candidates is not expected to provide a significant benefit to the majority of the patients that would be served by a centralized stool bank, who are not severely immunocompromised. Given the need to ensure a reliable supply of material for the vast majority of rCDI patients while protecting severely immunocompromised patients, until now OpenBiome has chosen not to test for EBV and CMV. Instead, we treat material as presumptively CMV and EBV positive and discourage use in severely immunocompromised patients who are seronegative for CMV or EBV. We are sensitive to the fact that this leaves clinicians with an additional challenge for managing these already difficult cases (severely immunocompromised rCDI patients). Should FMT be indicated then we would suggest that **in the immunocompromised**	

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	patient at risk of CMV or EBV infection either: 1) CMV and EBV testing of the recipient to confirm positive serology, in which case FMT may be considered after extensive discussion of the risks, benefits, and alternatives in the informed consent process; or 2) the use of a directed donor with matching serology. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. Clin Infect Dis. 2010;50:1439–1447. **Adenovirus:** We recommend including adenovirus on stool in addition to norovirus and rotavirus. **Vancomycin resistant enterococcus (VRE):** VRE should be specifically mentioned in "*Multi-drug resistant bacteria*". VRE is a leading cause for donor exclusion despite prospective donors having no known risk factors for colonization.	
8.3.5. Final donor checks prior to donation:	***Further final screening should take place prior to collection of a stool sample for processing into FMT (strong).*** We agree.	Thank you for this comment. In light of this and other comments, the recommendation on repeat screening has been strengthended.
8.4.1. General principles of FMT preparation:	***Recommendation:*** ***i. Donor stool collection should follow a standard protocol (strong).*** ***ii. Donor stool should be processed within 6 hours of defecation (conditional).*** ***iii. Both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI (strong).***	Thank you for this comment.

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	iv. Sterile 0.9% saline should be considered as an appropriate diluent for FMT production, and cryoprotectant such as glycerol should be added for frozen FMT (strong). ***v. Consider ≥50g of stool for use in FMT preparation (conditional).*** ***Good practice points:*** ***i. Stool should be mixed 1:5 with diluent to make the initial faecal emulsion (conditional).*** ***ii. Homogenisation and filtration of FMT should be undertaken in a closed disposable system (conditional).*** We agree.	
8.4.2. Fresh vs frozen FMT:	***The use of banked frozen FMT material should be considered preferable to fresh preparations for CDI (strong).*** We agree.	Thank you for this comment.
8.4.3. Use of frozen FMT:	***Recommendation:*** ***FMT material stored frozen at -80°C should be regarded as having a maximum shelf life of six months from preparation (strong).*** ***Good practice point:*** ***Consider thawing frozen FMT should at ambient temperature and using within six hours of thawing (conditional).*** We agree.	Thank you for this comment.
8.5.1. Use of specific medications in the period around FMT administration:	***Recommendation:*** ***i. Bowel lavage should be administered prior to FMT via the lower GI route, and bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred (conditional).***	Thank you for this comment.

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8.5.1.1. General principles of FMT administration:	***ii. For upper GI FMT administration, a proton pump inhibitor should be considered, e.g. the evening before and morning of delivery (conditional).*** ***iii. Loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery (conditional).*** ***Good practice point:*** ***i. Prokinetics (such as metoclopramide) should be considered prior to FMT via the upper GI route (conditional).*** ***ii. Best practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc).*** We agree.	
8.5.1.2. Additional antibiotics pre-FMT:	***Consider further antimicrobial treatment for CDI for at least 72 hours prior to FMT (conditional).*** We agree.	Thank you for this comment.
8.5.1.3. Washout period between antibiotic use and FMT:	***To minimise any deleterious effect of antimicrobials on the FMT material, there should be a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT (strong).*** We agree.	Thank you for this comment.
8.5.2.2. Upper gastrointestinal tract administration of FMT:	***Recommendation:*** ***i. Upper GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate (strong).*** ***ii. Where upper GI administration is considered most appropriate, FMT administration should be via nasogastric,***	Thank you for this comment. In light of further discussion by the working group, the maximum volume of FMT recommended by upper GI administration is now 100ml.

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	nasoduodenal, or nasojejunal tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate (strong). ***Good practice point:*** ***It is recommended that no more than 50ml of FMT is administered to the upper GI tract (conditional).*** We agree.	
8.5.2.3. Lower gastrointestinal tract administration of FMT:	***Recommendation:*** ***i. Colonoscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate (strong).*** ***ii. Where colonoscopic administration is employed, consider preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate (conditional).*** ***iii. FMT via enema should be used as a lower GI option when colonoscopic delivery is not possible (strong).*** We recommend rewording point *iii*. Although there is limited data, flexible sigmoidoscopy may be the preferred route of delivery where colonoscopic delivery is not possible. Several experts have advised less invasive modalities such sigmoidoscopy in high risk patients (Brandt 2013; Kelly 2014). This may provide a more effective method for delivering material as proximally as possible and improving retention. We therefore recommend re-wording point *iii* to: ***FMT via enema should be used as a lower GI option when colonoscopic or flexible sigmoidoscopy delivery is not possible (strong).***	We agree with this suggestion, and have updated the guideline accordingly.

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	Brandt LJ, Aroniadis OC. An overview of fecal microbiota transplantation: Techniques, indications, and outcomes. Gastrointest Endosc. 2013 Aug;78(2):240-9. Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, et al. Fecal microbiota transplant for treatment of clostridium difficile infection in immunocompromised patients. Am J Gastroenterol. 2014 Jul;109(7):1065-71.	
8.5.2.4. Capsulised FMT:	***Capsulised FMT holds promise as a treatment option for recurrent CDI, but further evidence regarding its safety and efficacy is awaited, and it should not be considered for use at present (conditional).*** There is a growing body of evidence on encapsulated FMT and the delivery modality presents a potential option in circumstances where it may be inappropriate, contraindicated, or contrary to patient preferences to deliver material via traditional routes of administration for CDI. In terms of patient perceptions, Zipursky and colleagues report that more aesthetically appealing FMT formulations, such as capsules, would both eliminate potential barriers to treatment and reduce the necessity for healthcare resources and procedure time for clinicians. Capsules appear well tolerated. For example, the mean time of 30 capsule administration is approximately 20 minutes (range 10-30 minute) (Allegretti, unpublished data). Although the optimal dose is still under investigation (as with other FMT delivery modalities), there have been several studies that have shown equivalent efficacy rates. Youngster and colleagues reported their experience with a capsule formulation that averaged 1.6 grams	We largely agree with this comment. Whilst the Kao *et al,* 2017 study was not published at the time of initial searches, it has been identified by updated searches and has now been reviewed by the working group. The guideline has been updated accordingly.

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	of stool per capsule in which they dosed 15 capsules on 2 consecutive days. They reported a 70% cure rate after an initial dose in a cohort of 140 patients. Those that failed to achieve cure were re-treated, bringing the cumulative cure rate up to 90%. Similarly, Hirsch and colleagues demonstrated a clinical cure rate of 68% in the 19 participants, using capsules containing purified, concentrated, and cryopreserved fecal bacteria and this increased to 89% with retreatment. Allegretti and colleagues conducted the first dose-finding study for FMT capsules (0.75 grams of stool per capsule with upper GI release) assessing 30 capsules once (low dose) versus 30 capsules on 2 consecutive days (high dose). Efficacy rates between the groups were similar on initial dose (70%) and there were no adverse events reported. Lastly the largest randomized control trial to date of FMT used encapsulated FMT with good safety and efficacy outcomes equivalent to colonoscopy FMT. In Kao et al's non-inferiority randomized clinical trial (cited in the guidelines) that included 116 adults with rCDI, the proportion without recurrence over 12 weeks was 96.2% after a single treatment in a group treated with oral capsules and in a group treated via colonoscopy. Given this 1+ level of evidence, in addition to multiple smaller studies of encapsulated FMT, we feel that there is a good body of evidence to support the short-term safety of encapsulated FMT. We agree that further evidence is needed on optimal dosing and formulation, however this applies to all delivery modalities.	

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	We agree that capsule availability is very limited in the UK at present however this shouldn't preclude guidelines recommending this as a potential FMT delivery option. We therefore recommend rewording the 8.5.2.4 to: ***Capsulised FMT holds promise as a treatment option for recurrent CDI and should be offered to patients as a potential treatment modality. Capsule preparations should follow a standard protocol. Further evidence regarding its optimal dosing and formulation is needed (conditional).*** Allegretti J*, Fischer M*, Papa E, Elliot R, Klank M, Mendolia G, et al. Fecal microbiota transplantation delivered via oral capsules achieves microbial engraftment similar to traditional delivery modalities: Safety, efficacy and engraftment results from a multi-center cluster randomized dose-finding study. Digestive Disease Week 2016. Hirsch BE, Saraiya N, Poeth K, Schwartz RM, Epstein ME, Honig G. Effectiveness of fecal- derived microbiota transfer using orally administered capsules for recurrent clostridium difficile infection. BMC Infect Dis. 2015 Apr 17;15:191,015-0930-z. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing clostridium difficile infection. JAMA. 2014 Nov 5;312(17):1772-8. Zipursky JS, Sidorsky TI, Freedman CA, Sidorsky MN, Kirkland KB. Patient attitudes toward the use of fecal microbiota transplantation	

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	in the treatment of recurrent clostridium difficile infection. Clin Infect Dis. 2012 Dec;55(12):1652-8.	
8.6. What is the clinical effectiveness of faecal microbiota transplant in treating conditions other than Clostridium difficile infection?	***FMT is not currently recommended as treatment for inflammatory bowel disease. There is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease (strong).*** We agree.	Thank you for this comment.
8.7. Basic requirements for implementing a FMT service	***The development of FMT centres should be encouraged (strong).*** We agree.	Thank you for this comment.
8.7.5. FMT manufacturing:	***Ensure traceability of supply (strong).*** We agree.	Thank you for this comment.
FMT in patients with IBD	We recommend emphasizing the importance of counselling patients with IBD on the risk of flare or worsening IBD activity post-FMT.	We agree with this comment, and have updated **Section 8.2.3.** accordingly.
FMT in paediatric populations	A recommendation on paediatric FMT should be include. The evidence base is limited but safety and efficacy appears comparable to adult FMT. Patients and caregivers should be counselled on the unknown long-term risks of FMT. Recommendation: ***i. FMT should be offered to paediatric patients with recurrent CDI.*** ***ii. Paediatric patients and caregivers should be counselled on the unknown short and long-term risks of FMT.***	FMT in the paediatric setting is outside of the remit of this working group. We have updated **Section 5.4** to clarify this.

Closing date: Please forward this electronically by 5pm on January 2018 at the very latest to consultations@his.org.uk

Supplementary Material 3 for *Gut*

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

Supplementary Material 3: Basic requirements for implementing a FMT service:

1. Basic requirements for implementing a FMT service:

1.1. General considerations:

Although it is possible to prepare and administer FMT on an individual patient basis in a single hospital, the regulatory requirements are more readily fulfilled by a specialist centre approach for the production of a safe FMT product. This particularly applies to record keeping and staff expertise in quality control and production. Recent European consensus advice suggests that FMT should be administered in a referral centre[1], however an alternative approach which limits the need for patient transfer is to undertake controlled production in a large centre and transport treatment to the patient, a supply model which has been well established in the USA (OpenBiome)[2] and has also been successfully replicated in the UK in a large centre in Birmingham, which has supplied FMT to nine NHS Trusts across three regions[3]. This service design only requires that a responsible clinician is capable of administering the FMT safely at the satellite clinical site. It also eliminates the need for patient transfer between clinical sites, which in the case of severe CDI may not be practical.

The working group encouraged the use of frozen FMT material supplied from a carefully controlled production site. This allows donor screening more closely to meet regulatory requirements, ensuring that the window period between donor testing and FMT production is maintained to a minimum. The costs of donor screening are substantially reduced using this supply model, as a single donor can provide multiple FMT donations under a single screening period.

The working group also noted that given the novelty of FMT, awareness of this as a potential treatment option for recurrent or refractory CDI may be low amongst certain groups of clinicians. For instance, clinicians working in primary care, or those whose practice is not located near to an FMT centre, are likely to have less knowledge about the potential suitability of FMT for patients with CDI, or be unaware of referral pathways. As such, there is a responsibility for FMT centres to raise awareness and educate as wide a range of clinicians as possible about the potential role for FMT.

Supplementary Material 3 for *Gut*

Furthermore, microbiology staff processing stool samples for *C difficile* assays from the community should proactively liaise with primary care teams where recurrent positive tests are received from a single patient to raise awareness and suggest the option of FMT.

Similarly, given the expectation that FMT and/ or other 'microbiome therapeutics' are likely to play an increasing role within medicine over future years, there is also an expectation for FMT centres to not only educate about the potential role for FMT, but also to train relevant healthcare professionals in the practicalities of delivering an FMT service, to enable longer-term ongoing provision of services. This is likely to be most of relevance to specialty trainee and consultant physicians specialising in gastroenterology, infectious diseases and/ or medical microbiology, but potentially to other healthcare professionals too, including infection prevention and control nurses, infectious diseases pharmacists, etc.

Recommendations:

i. The development of FMT centres should be encouraged (GRADE of evidence: very low; strength of recommendation: strong).

ii. We suggest that FMT centres should work to raise awareness about FMT as a treatment option amongst clinicians caring for patients with CDI, and provide training to relevant healthcare professionals on the practicalities of delivering an FMT service (GRADE of evidence: very low; strength of recommendation: weak).

1.2. Legal aspects and clinical governance:

In the United Kingdom, FMT is now considered a medicinal product based on the definitions of purpose and efficacy, in The Medicines Directive 2001/83 and The Human Medicines Regulations[4]. As the competent authority for medicines regulation, the Medicines and Healthcare products Regulatory Agency (MHRA) has indicated that the approach to regulation will be proportionate, depending on factors such as supply being within or outside a legal entity and FMT production scale. Specifically:

- When FMT is supplied on prescription on a named patient basis, then supply under a pharmacy exemption may be used subject to ensuring proper governance and traceability[4].
- If production scale reaches an '*industrial*' level, defined '*by virtue of the batch sizes, the extent of processing and/ or whether potential use includes supply between legal entities*'[4], the route to regulation is via adherence to HMR and formal Manufacturer's 'Specials' (MS) license.

- If a supply is to a clinical trial, then an MIA (IMP) manufacturing license is required (further information on license applications[5] and specials[6] is available online).

Centres establishing an FMT service should undertake steps to ensure practice meets the required compliance levels and seek guidance from the MHRA. If pharmacy exemption is applied, there should be justifiable processes in place to ensure traceability, health and safety, governance and to prevent cross-contamination. FMT is regulated as a medicine, rather than a tissue, but no products have been licensed following an assessment against the criteria of safety, quality and efficacy, for there is a possible risk that donor screening protocols will not be sufficiently considered, a step which is critical to the quality of the product and therefore safety of the patient[7]. To mitigate this, it is advisable that donor screening protocols are under regularly review and risk assessment, and to ensure that consideration is also given to the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment, particularly Annex B related to donor testing[8]. When formal licencing is sought, this is overseen by a Production Manager and Quality Control Manager if under an MS, or by a Qualified Person if under an MIA (IMP). Both should follow the Good Manufacturing Practice (GMP) guidelines, found within The Orange Guide Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017[9], or at: https://ec.europa.eu/health/documents/eudralex/vol-4_en .

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The working group noted that outside the UK, the legal and regulatory framework relating to FMT was highly variable between different countries. They agreed that FMT should only be administered after appropriate approval from the competent body of each country.

Recommendation:

In the UK, FMT must be manufactured in accordance with MHRA guidance for human medicines regulation. When FMT is supplied on a named patient basis, within a single organisation, a pharmacy exemption may be used, subject to ensuring proper governance and traceability. All centres that are processing and distributing FMT should seek guidance from the MHRA and where necessary obtain appropriate licenses prior to establishing an FMT service. This is a legal requirement. In countries other than the UK, FMT should only be manufactured following appropriate approval from the national authority of that country (GRADE of evidence: very low; strength of recommendation: strong).

1.3. Multidisciplinary teams:

To promote safe and high quality FMT supply, it is strongly recommended that providers adopt a multidisciplinary team approach. The choice of the team required is subject to the scale of production, but should involve as a minimum a clinical gastroenterologist, microbiologist/infectious diseases clinician, state-registered experienced healthcare scientist and pharmacist. Governance and quality expertise will be required, which may be provided by consultation. If FMT production is to be under a 'specials' licence, the team should be expanded to include a Qualified Person, Quality Manager and Production Manager, all with GMP training.

Recommendation:

We recommend that a multidisciplinary team should be formed to deliver FMT services (GRADE of evidence: very low; strength of recommendation: strong).

1.4. Infrastructure:

Dedicated laboratory facilities for FMT production are recommended to ensure that the process adheres to Health and Safety requirements, to reduce the risk of cross-contamination, and to facilitate standardisation of the production process. In some studies, FMT has been prepared in a clinical environment[10]; however, this may not be advisable because of the risks of cross-contamination. The manipulation of human stool should be conducted in a Containment Level 2 laboratory according to current Health and Safety guidance (Health and Safety at Work Act 1974, COSHH Control of Substances Hazardous to Health Regulations, 2002), and at least within a microbiological safety cabinet which provides user protection (Class I) or, ideally, user and product protection (Class II). To meet the requirements of GMP, this facility should be sole use or be risk assessed for multipurpose use with adequate separation of different activities. The working group recommend that the facility complies with the new GMP production facility classification of 'clean not sterile'. The use of personal protective equipment - such as laboratory coat, gloves and face mask - is also recommended to prevent production contamination. It is essential to risk assess the process and develop control measures to reduce microbial ingress into the facility and monitor the microbiological cleanliness of the production suite. FMT preparation under a 'specials' licence should ensure that the production process is integrated into a Quality Management System, to safeguard production and maintain the minimum criteria for audit, monitoring, standard operating procedures, document control, training, facilities, equipment and storage. With regard to storage, it is essential that the freezer system has real-time temperature monitoring which provides notification outside pre-set limits.

Recommendation:

We recommend utilisation of suitable laboratory facilities and infrastructure for FMT production (GRADE of evidence: very low; strength of recommendation: strong).

1.5. FMT manufacturing:

It is strongly recommended to employ a batch numbering system to track FMT preparations from production to use. It should be possible from records to identify an individual FMT aliquot, trace it to a specific donation, and identify all other FMT aliquots prepared from the same donation. It must also be clear which FMT aliquots patients have received, which should be verifiable from the donor to the patient and vice-versa. It is therefore strongly recommended that a treatment directory be maintained documenting all production and use of FMT, and that an unambiguous record is created in the patients' clinical notes to identify the specific FMT batch number. Further to this, it is also recommended that treatment directories also record clinical outcome, such as that developed in the USA[11] and Germany[12] to standardise and improve future clinical practice.

Recommendation:

We recommend ensuring the traceability of supply (GRADE of evidence: very low; strength of recommendation: strong).

1.6. FMT production quality control:

Safety and clinical governance is a central responsibility for FMT centres, particularly in light of the absence of phase III licensing trials for FMT, which would normally be required for a novel medicinal product. Reporting and investigating adverse events and reactions contributes to knowledge of the FMT safety profile, while also identifying previously unknown safety issues. Governance structures and processes must be in place to monitor, notify and investigate all FMT-related adverse events or reactions locally, and FMT users are encouraged to use the MHRA Yellow Card Scheme for formal notification. FMT supply should be suspended if serious adverse events or reactions occur which are directly attributable to FMT, and there should be a clear documented pathway to achieve this. To facilitate a 'look-back exercise' if required, it is advisable to store documentation and reference samples, both product-based and donor/ patient-based. Specifically, retention of production documentation should be for at least five years after the use of the batch; retention of reference FMT

samples (and stool samples from donors and recipients) should be for at least one year after the last use. Retention of excipient samples should be for at least one year after expiry of the excipient.

Recommendation:

We recommend monitoring, notification and investigation of all adverse events and reactions related to FMT (GRADE of evidence: very low; strength of recommendation: strong).

1.7. Donor screening governance:

The testing requirements for donor screening have been discussed previously; however, it is worth noting here the pertinent clinical governance issues which should be addressed. Donor anonymity should be maintained at all times. The laboratory undertaking testing of donor samples should be competent for such activity, demonstrable by accreditation with the United Kingdom Accreditation Service (UKAS). The results of donor testing should remain confidential. There should be appropriate standard operating procedures to ensure that the outcome of donor screening is built into a robust FMT batch release process. To ensure unbiased autonomy during donor screening, it is suggested that a clinician independent to the FMT production team is responsible for ratifying FMT donors prior to donation. Finally, the duration of donor follow-up should be considered and extend beyond the period of active donation to capture acute and chronic health changes.

Recommendation:

We recommend ensuring the clinical governance of donor screening (GRADE of evidence: very low; strength of recommendation: strong).

2. References:

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transplantation for Clostridium difficile infection in the UK. *J Hosp Infect*. 2016. doi:10.1016/j.jhin.2016.10.023.

4. Faecal Microbiota Transplantation (FMT) MHRA's position. http://www.bsg.org.uk/images/stories/docs/clinical/guidance/fmt_mhra_position_june2015.pdf. Accessed October 3, 2017.

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6. Medicines and Healthcare products Regulatory Agency. Supply unlicensed medicinal products (specials) - GOV.UK. https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials. Accessed February 15, 2018.

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