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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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"NICE has accredited the process used by the Healthcare Infection Society to produce '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'. The NICE accreditation of HIS methodology is valid for 5 years from March 2015. More information on accreditation can be viewed at http://www.nice.org.uk/about/what-we-do/accreditation"

1. Executive summary:

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) (also referred to as *Clostridioides difficile*[1]), but there is also an emerging evidence base regarding potential applications in non-CDI settings. The main 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): a joint BSG/HIS FMT working group was established. This guideline document is the culmination of that joint dialogue.

2. Lay summary:

Faecal microbiota transplant (FMT) involves the transfer of faeces from a healthy donor to a recipient. There are several different ways to administer the transplant, including endoscopy, enema, nasoenteral tube, or by transferring faecal material into capsules. 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.

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.

3. Introduction:

The aim of the British Society of Gastroenterology (BSG)/Healthcare Infection Society (HIS) faecal microbiota transplant (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 evidence is currently lacking. Relevant guidance published to date includes the interventional procedure guidance from the National Institute for Health and Care Excellence (NICE)[2], UK and European microbiological guidelines on the treatment of *Clostridium difficile* infection (CDI)[3,4], and recent expert consensus documents on FMT in clinical practice[5,6]. Furthermore, there have also been national recommendations regarding FMT produced by working groups in several different countries[7–9]. Principally as a result of randomised studies that have been published in recent years[10–17], FMT has become an accepted treatment for recurrent/refractory CDI.

The unique remit 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[18,19].

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[20]. Previous research has demonstrated that commensal bacteria cultured from the stool of healthy donors[21], and/or spores of *Firmicutes* derived from ethanol-treated stool from healthy donors[22] 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[23]. For the purposes of this guideline, the BSG/HIS working group considered only studies that used the administration of manipulated whole stool (including encapsulated lyophilised 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.

The absence of appropriate protocols[24–27] 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 Team

4.1. Acknowledgements

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4.2. Source of funding

There was no external funding for this work.

4.3. Disclosure of potential conflict of interest

- 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.

4.4. Relationship of authors with sponsor

BSG and HIS commissioned the authors to undertake the Working Party Report. The authors are members of both societies.

4.5. Responsibility for guidelines

The views expressed in this publication are those of the authors, and have been endorsed by BSG and HIS following consultation.

5. Working Party Report

Date of publication: XXX (published online XXX).

5.1. 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 diagnosis and management of *Clostridium difficile* infection in general are outside the remit of these guidelines.

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.

5.2. 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, which are not well-understood by clinicians.

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

The main purpose is to inform clinicians involved in the treatment of recurrent and refractory CDI. 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.

5.4. What is the 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.

5.5. What is the evidence for these guidelines?

Questions for review were derived from the Working Party Group, which included patient representatives in accordance with the PICO process[28]. To prepare these recommendations, the

working group collectively reviewed relevant peer-reviewed research. Methods are described fully below; they were in accordance with SIGN 50[29] and the Cochrane Collaboration[30].

5.6. Who developed these guidelines?

The working group included gastroenterologists, infectious diseases/microbiology clinicians, a clinical scientist, a systematic reviewer, and patient representatives.

5.7. 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.

5.8. 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.

5.9. How frequently are the guidelines reviewed and updated?

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.

5.10. 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.

6. Implementation of these guidelines:

6.1. 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.

6.2. 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[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.

6.3. Summary of audit measures

- 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.
- 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.

6.4. E-learning tools:

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

7. Methodology:

7.1. Evidence appraisal

Questions for review were derived from the Working Party Group, which included patient representatives in accordance with the PICO process[28]. Methods were in accordance with SIGN 50[29] and the Cochrane Collaboration[30].

7.2. 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 **Appendix 2ii** of this document. Free text and MESH/ index terms for faecal microbial transplant and *Clostridium difficile* or inflammatory bowel disease were combined. In addition, conference proceedings from microbiology, infectious disease, and gastroenterology conferences were also searched to identify additional studies.

7.3. 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 RCTs 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.

7.4. Data extraction and quality assessment

The initial search identified 2658 publications, and of these, 802 duplicates were excluded. 1779 studies were subsequently screened, from which 76 studies were assessed by reviewing the full text for eligibility (see **Appendix 2iii** of this document and **Additional Appendix D**). Of these 76 studies, 57 studies were included as the basis of evidence for writing this guideline. In total, 40 were case studies in CDI including at least 10 patients (see **Additional Appendix C.1)**, and ten were randomised studies in CDI (see **Additional Appendix C.2**). Seven were randomised controlled studies for non-CDI indications (see **Additional Appendix C.3**). Studies of which the full text was reviewed (but where there were incomplete methodological or outcome data to allow formal inclusion within the guideline) were noted further by the working group when considering good practice points. 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.

7.5. Rating of evidence and recommendations

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. The strength of evidence was defined by SIGN[29] (**Table 1A**), and the strength of recommendation was adopted from GRADE (Grades of Recommendation Assessment, Development and Evaluation)[35] (**Table 1B**). In addition, where there was no clear evidence or a paucity of evidence, good practice recommendations were made by expert experience and consensus. The section entitled 'Basic requirements for implementing an FMT service' 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 voting by members of the working group.

7.6. Consultation process

Feedback on draft guidelines was received from the Scientific Development Committee (SDC) of HIS, and final changes made. These guidelines were then opened to consultation with relevant

stakeholders (see **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.

8. Rationale for recommendations:

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

8.1.1. Prior to faecal microbiota transplant. Patient selection:

8.1.1.1. 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)[11,17] following previous successful CDI treatment; most studies have also included a requirement for a positive microbiological test[11,13,17,36–46]. Other studies explicitly state that a positive test was not required[47]. Recommendations for CDI testing are beyond the scope of this guideline, and there are already well-established evidence-based guidelines[48]. 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[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)[11,14,15,17,39,40,43,45,47,49], whereas others offered FMT after the second recurrence (third episode)[12,13,36,38,41,42,50,51]. Some protocols offered FMT after three or more recurrences[52], whilst others did not define the point at which it was adminstered[37,53].

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[16]. 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[40], 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 in-patient status is likely a proxy of severity of CDI and/or co-morbidities.

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.

Evidence:

The reviewed literature represents a wide variety of different study designs. However, regardless of design, there is consistent evidence that FMT is an effective therapy for people with recurrent CDI (quality of evidence: 1+).

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 and severe-complicated CDI (strong).

8.1.1.2. 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[16]. 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[15]. Both studies included only small numbers of patients with refractory CDI (4/20 (20%) and between 6/108 (5.6%) and 9/111 (8.1%), 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[45,46,54,59].

Evidence:

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, evidence for the utility of FMT in refractory cases of CDI is lacking. The

standardisation of definitions will allow more robust comparison between patient cohorts (quality of evidence: 1-).

Recommendation:

FMT should be considered in cases of refractory CDI (conditional).

8.1.1.3. 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% (3/16 patients) vs 64.4% (29/45 patients))[60]. However, 37.5% (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[60]. 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% (8/9) patients with vancomycin, compared to 4/7 patients (57.1%) with one FMT, and 5/7 patients (71.4%) after two FMTs[61]. Given the small size of these studies and equivocal results, the working group concluded that the reviewed studies did not support CDI as initial therapy for CDI.

Evidence:

There is very little experience of FMT as use as initial therapy for CDI (quality of evidence: 3).

Recommendation:

FMT should not be administered as initial treatment for CDI *(strong)*.

8.1.1.4. 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 significantly to reduce the risk of recurrence compared with vancomycin[62,63]. There is also some evidence that pulsed/tapered dosing of vancomycin and fidaxomicin (including pulsed fidaxomicin[64]) results in fewer recurrences than with standard dosing of these agents[65,66] (although this finding has not been replicated in all studies[67]). 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)[62]; 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[68]. 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)[63].

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[11]. 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[11,14,15,17].

Evidence:

There is evidence that particular antimicrobial agents reduce the likelihood of recurrence of CDI, but data comparing FMT to antimicrobial therapy is lacking (quality of evidence: 3).

Recommendation:

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. Consider treatment with extended/ pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI (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).

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

8.1.2.1. 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[13,14,16,17,40,43,47,51,54,69,70]. 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 8.1.2.5**). Second FMTs have been offered as soon as 24-72 hours after an initial FMT for presumed non-response[45,71,72]. For FMT failure in patients with pseudomembranous colitis, repeat FMT every three days until resolution of pseudomembranes has been a successful approach[17]. Good outcomes in pseudomembranous disease have also been achieved through a protocol that routinely restarted five days of vancomycin if FMT failed, before offering anther FMT[72]. Other studies have demonstrated potential success in treating initial FMT failure with further antibiotics, including repeat FMT with vancomycin between procedures[39], or anti-CDI antibiotics alone[39,40,42,43,51,69,70]. Patients unresponsive to two FMTs have been offered further FMT or antibiotic therapy[15], or even the administration of intravenous immunoglobulin[43].

Evidence:

Regardless of how failure is defined, there is good evidence that further FMT is efficacious at treating CDI after initial FMT failure (quality of evidence 1++).

Recommendation:

Further FMT should be offered after initial FMT failure (strong).

8.1.2.2. 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[13,40,58,69,73–75], telephone interview[16,36,40,47,58,69,73] and case note/ database review[36,37,39,40,42,43,47,49,51,54,69,70,73]. Follow-up duration has varied from 60 days[42] to 8 years[44], with very different durations used in each study. Once again, however, this variability in follow-up 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 fully to assess efficacy and potential adverse events.

Evidence:

The approach to following up patients after FMT varies considerably between studies, and is often pragmatically designed (quality of evidence: 3).

Recommendation:

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 (strong).

8.1.2.3. 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[49,59], 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[47]). One death occurred due to witnessed aspiration at the time of colonoscopy[59]. Faecal regurgitation and vomiting with temporal association to upper GI FMT administration has also been described (also see Section 8.5.2.2)[76].

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[14], nausea[14,15,49,59], abdominal cramps/ discomfort/ bloating/ pain[14,17,49,59,71], and diarrhoea[14,15,17,59]. One patient with a history of autonomic dysfunction experienced dizziness with diarrhoea after FMT[14]. These symptoms are typically short-lived,

resolving in hours to days[14,15,17,49,71]. Minor subsequent adverse events have included a range of GI side effects including self-limiting abdominal discomfort[13,16,57,75], nausea[13,49,70], flatulence[13,15,16,38,39,49,57], self-limiting irregular bowel movements[38], *C. difficile*-toxin negative diarrhoea[52,55], constipation[13,14,39,55,70] and constitutional symptoms/ temperature disturbance[13,16].

As such, immediately post-endoscopic administration of FMT, most FMT centres typically manage patients using standard protocols for an endoscopic procedure[38,49], 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[14,17]. 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[14]) to prompt post-procedure removal and oral water administration (after nasogastric administration of 90ml of FMT[71]), 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 generally involved significant morbidity necessitating hospital admission and death in the follow up period. Many of these are described as not directly caused by the FMT, including the scenario of post-FMT severe CDI recurrences[71] and probable or certain CDI-related deaths[15,59,70] occurring in the context of FMT failure, or deaths related to patient comorbidities[16,55]. One patient was admitted to hospital with self-limiting abdominal pain post-FMT[59], four patients with flares of inflammatory bowel disease[59]. 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[59]. Other reported serious adverse events include recurrent urinary tract infection[14], fever during haemodialysis[14] 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. 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[14,16,47,55,57,71], stool consistency[13,14,71], abdominal pain or tenderness[55,57], rating of gastrointestinal symptoms[71], general well-being[55,71], days to improvement post-FMT[57], weight change[71], functional status[55], and changes in medication/use of antibiotics[57,71]. Additionally, certain patients have been given specific advice post-FMT to contact their clinical team if there is recurrence of diarrhoea or symptoms[13,38,40,43]. Where patients underwent outpatient clinical evaluation, this was generally undertaken relatively early post-FMT[36,52,75]. 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[40], and counselling on the risk of recurrent CDI with future antibiotic courses[75].

Evidence:

Much of the short-term management of the FMT recipient describes general principles of best practice related to the route of administration. Many adverse events described following FMT are minor, and/or may not directly relate to the transplant itself (quality of evidence: 3).

Recommendations:

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).***

8.1.2.4. 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 four-five days in others[57,69]). 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 three-five days[44] up to six months[39]. 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'[77]. The working group recommended that the definition should be made on a case-by-case basis.

Evidence:

No universal definition exists regarding cure/remission post-FMT for CDI (quality of evidence: 4).

Good practice point:

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).

8.1.2.5. 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[49,52–54,59,71,73]. Some studies have routinely performed CDT testing without specifying any action taken after a positive result[13,14,17,36,38,44], whilst others have tested for *C. difficile* PCR but relied on clinical criteria (even if PCR was positive) post-FMT for evaluating FMT efficacy[13]. 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[78].

Evidence:

No standard definition exists regarding treatment failure/recurrence post-FMT for CDI (quality of evidence: 4).

Good practice point:

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 (strong).

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

8.2.1. General approach to co-morbidities and FMT:

Most published studies had a core set of general recipient exclusions which included: significant/ anaphylactic food allergy[13,16], pregnancy[11–14,16,17], breastfeeding[13], admission to Intensive Care or the requirement for vasopressors[11,14,17], chronic diarrhoea or other infectious cause of diarrhoea[11,13,17,50], inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS)[13,44], immunodeficiency due to recent chemotherapy and/ or neutropenia[11,13–17,50], HIV/AIDS[13,16,17], prolonged use of corticosteroids[14,16,17], graft versus host disease[11], and decompensated cirrhosis[13,14,16,17].

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 this patient group merited a specific 'good practice point', that such individuals should not be offered FMT.

Evidence:

There is a wide range of FMT recipient exclusions listed in different studies, but little evidence on the safety of FMT administration in patients with these excluded conditions (quality of evidence: 4).

Good practice points:

1. FMT should be avoided in those with anaphylactic food allergy (strong).

2. FMT should be offered with caution in patients with CDI and decompensated chronic liver disease (conditional).

8.2.2. Immunosuppression and FMT:

One randomised study[15] included patients with immunodeficiency (treatment with 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 are 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[59]. 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)[59]; however, such adverse events have also been reported in non-immunocompromised patient populations[79]. 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[80]. A further case series[42] 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.

Evidence:

The growing pool of experience in using FMT in CDI patients with a range of causes of immunosuppression demonstrates that it appears to be generally as safe and effective as in patients without immunosuppression (quality of evidence: 1-).

Recommendation:

FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong).

Good practice point:

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 (strong).

8.2.3. 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[11,13,14,17,50]. One randomised study reported the presence of IBD in 10/17 (59%) FMT recipients[15], 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[12]. This study also included 64/72 (89%) patients with cardiac, respiratory, renal, central nervous system or multi-organ system comorbidities[12]; however outcomes were not stratified according to co-morbidity. Kelly and coauthors[59] reported an overall cure rate of 94% in a subset of 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[81].

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[16,50]. Exclusions for lower GI administration have included colostomy/ileostomy[15,50], significant bleeding disorders[11], untreated colorectal cancer[13,44,54], 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.

Evidence:

There is growing evidence that FMT is safe and efficacious as treatment for CDI in people with concomitant inflammatory bowel disease, but that there is the potential for FMT to cause a flare in IBD activity (quality of evidence: 1+).

Recommendation:

i. FMT should be offered to those with recurrent CDI and inflammatory bowel disease, but should be counselled about a small but recognised risk of exacerbation of IBD (strong).

ii. FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities (conditional).

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

8.3.1. General approach to donor selection:

Excellent efficacy has been shown in treating recurrent CDI using FMT derived from both related[13,37,38,42,44,46,47,49,53,54,57,60,82–84] and unrelated[13–16,38,43,45,46,53,57,60,71,73,82–88] donors. To date, there have been no randomised studies exploring 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[11–17,89]. Three case series used donor stool from healthcare professionals[36,60,86]; 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.

Evidence:

Both related and unrelated donors have been shown to be acceptable as donors, but there has been no comparative study of the two groups (quality of evidence: 3).

Recommendation:

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).

8.3.2. Age and BMI restrictions for potential donors:

There are no well-defined age restrictions on donors. Randomised studies have used donors of ≥18[11,71] and ≤60 years old[14,16,17] with satisfactory outcomes. Two of the case series defined age limitations for donors as ≥18 and ≤ 50 years[71,90]. 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; however, there were loss of the phylum *Actinobacteria* and family *Bifidobactericeae* from donors older than 60 years[91]. 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[92], but any association between a donor with a raised BMI and weight gain post-FMT has not been replicated elsewhere in the literature[93]. Whereas most randomised studies did not report donor-specific BMIs, some have excluded those without a 'normal' BMI[12,16]. The working group considered an acceptable BMI as between ≥18 to ≤30 kg/m^2.

Evidence:

There is considerable variability between studies with regards to age and BMI restrictions for donors, and no comparative studies (quality of evidence: 3).

Recommendation:

People should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of <30 kg/m^2 (conditional).

8.3.3. 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[94], 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[11–15], questionnaires that focused on previous potential transferable medical conditions[17], and adaptations from the American Association of Blood Banks Donor Questionnaire[13,16]. One randomised study used the OpenBiome questionnaire as a screening questionnaire[95]. 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[36,46,49,52,55,73,82,88]; this is also the protocol employed in randomised studies[13,15,17]. 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[96–99] (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[13,47,53–55,57,60,73] or six month[15–17,36,43,46,49,83,86,100,101] period without antimicrobial use prior to FMT donation.

The working group was of the opinion that a screening process is mandatory; any positive responses should mean exclusion from donation. 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 8.3.5).

Evidence:

Based on the principles derived from blood transfusion, a donor screening questionnaire has become standard practice (quality of evidence: 3).

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 2) (strong).

8.3.4. Laboratory screening of potential donors:

Currently, there are no known 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[36–39,43–45,47,49,52–55,60,71,73,82,83,85,87,88,103]; other studies (including the randomised trials) have a more thorough blood screening process[13–17]. Many studies have also included a 'metabolic/general blood screen', to select out donors with hitherto undiagnosed chronic illness. **Table 3** 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 8.2.2.** 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 4** 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 8.3.5).

Evidence:

Blood and stool screening is performed uniformly as a part of FMT donor selection, but with varying protocols between studies (quality of evidence: 3).

Recommendation:

Blood and stool screening of donors is mandatory (Tables 2 and 3) (strong).

8.3.5. 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.

Evidence:

Repetition of some or all elements of initial donor screening at a later point is standard practice, though the means of assessment differs between studies (quality of evidence: 3).

Recommendation:

1. ***In centres using frozen FMT, before FMT may be used clinically, 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 (strong).***
2. ***In centres using fresh FMT, 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 (strong).***

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

8.4.1. 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 defecation. The period of six hours has been generally applied across many successful studies of FMT treatment in CDI[13,17,36,40,43,52], 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[38,73], 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 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[15,40,43]. 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%[15,38]. 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[73].

A variety of homogenisation and open filtration systems have been used, with no apparent major variation in efficacy. Open filtration systems such as gauze[15,37,45,55], filter paper[36] and strainers/

sieves[16,38] are unpleasant to use and pose a risk of external contamination. In order best to 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.

Evidence:

The mechanics of stool preparation vary widely between different studies. There are almost no comparative data for any of these variables (quality of evidence: 3).

Recommendation:

i. Donor stool collection should follow a standard protocol (strong).

ii. Donor stool should be processed within 6 hours of defecation (strong).

iii. Both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI (strong).

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. Use ≥50g of stool for use in FMT preparation (strong).

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).

8.4.2. 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[15]. 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). These data support the findings of earlier small observational studies[38,43]. Frozen FMT is preferable to fresh FMT on logistical and cost

grounds[15]. Banked frozen FMT also enables the window period for donor screening to be minimised, more closely to meet regulatory requirements (also see **Section 8.3.5**).

Evidence:

There is randomised trial evidence demonstrating that fresh and frozen FMT have comparable efficacy (quality of evidence: 1+).

Recommendation:

The use of banked frozen FMT material should be considered preferable to fresh preparations for CDI (strong).

8.4.3. Use of frozen FMT:

Frozen FMT has been used up to six months after storage at -80^{o}C[16,38,73], 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[73], and as such, the working group agreed that six months was the acceptable limit for freezing of an FMT in glycerol. Storage at -80^{o}C is recommended rather than -20^{o}C to minimise sample degradation.

Warm water baths have been recommended to speed thawing[5]; 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, 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[107].

Evidence:

Frozen FMT remains an efficacious treatment for CDI after six months frozen, but it has not been assessed at longer time points. There are little published data addressing optimal thawing of frozen FMT (quality of evidence: 3).

Recommendation:

FMT material stored frozen at -80^{o}C should be regarded as having a maximum shelf life of six months from preparation (strong).

Good practice points:

1. ***Consider thawing frozen FMT at ambient temperature, and use within six hours of thawing (conditional).***
2. ***Do not thaw FMT in warm water baths, due to the risks of cross contamination with Pseudomonas (and other contaminants) and reduced bacterial viability (strong).***

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

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

8.5.1.1. 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[108–112]. Further, bowel purgatives pre-colonoscopic FMT delivery facilitate safe endoscopy. Various bowel purgatives have been used in colonoscopic FMT studies, including polyethylene glycol (PEG) (often 4L)[13,16,38,43,47,54–56,83,100,113–115], MoviPrep®[38,43], and macrogol[12,14,17,82]. In those studies that used an upper GI route for FMT, PEG[54,55,85] and Klean-Prep®[14,60] 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[15].

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[116,117], and have also been associated with primary and recurrent CDI[118,119]. Some studies advocate the use of PPI prior to receiving FMT via the upper GI route[36,42,45,85,86,120,121], 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[16,88].

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[86]. 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.

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[12,47,49,55,85,121]. 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[122,123], using a sporicidal agent. Best practice for prevention of transmission of healthcare-associated infections, as described in national guidelines[124], should also be applied throughout.

Evidence:

These different classes of medications have all been used variably pre-FMT between different studies. They do not appear to adversely affect the efficacy of FMT, and there are sound reasons to expect that they may be beneficial (quality of evidence: 3)

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).

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).

8.5.1.2. Additional antibiotics pre-FMT:

Many studies have given further courses of conventional antimicrobial *C. difficile* treatment prior to FMT. Regimens have included vancomycin alone[11,13,17,36,43,55,82,87,115], metronidazole or vancomycin[37,38,83,120], or alternatively vancomycin, fidaxomicin or metronidazole[56], with one study using a range of regimens which included rifaximin[121]. The length of treatment was also variable, ranging from 24 hours[54] up to four days prior to receiving FMT[36,42]; however, comparative studies have not been undertaken.

Evidence:

In many studies, additional anti-CDI antibiotics have been used pre-FMT, with the aim of further reducing the burden of *C. difficile* (quality of evidence: 3).

Recommendation:

Administer further antimicrobial treatment for CDI for at least 72 hours prior to FMT (strong).

8.5.1.3. 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[47] or 12 hours[51], up to 72 hours[44]. The majority of studies specified either 24 hours[14,36,37,42,45,54,125] or 48 hours[38,39,49,59], however some allowed a range from 1-3 days[15,41,52,53,55].

One study appeared to allow co-administration of vancomycin with bowel preparation, without a washout period[17].

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)[126]. Similarly, the experience of the large pan-Netherlands stool bank[127] 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.

Evidence:

A washout period between the end of antibiotic use and administration of FMT is usually described. However, no formal trial assessment as to the optimal length of this period has been undertaken (quality of evidence: 3).

Recommendation:

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).

Good practice point:

Consider 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 (conditional).

8.5.2. Route of FMT delivery:

8.5.2.1. 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[125,128–130] 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[129].

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)[16].

8.5.2.2. 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[36,42,45,60,84,121], nasoduodenal tube[14,85,86], enteroscopy[120,121], or via the infusion channel on a gastroscope[37,42]. In a randomised trial, nasoduodenal donor FMT has been shown to be more efficacious than vancomycin in treating recurrent CDI[14]. Furthermore, it has been shown that FMT can also be safely and effective delivered via a percutaneous endoscopic gastrectomy tube[42,84].

Typically, smaller volumes of faecal suspension are administered to the upper GI tract compared to lower GI administration, with quoted volumes ranging from 25ml[36] up to 150ml[85]- 250ml[45,86]. Up to 500ml of suspension has been given safely and effectively via the upper GI route[14,76]. 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[79]. 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[131]. 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[76]. Based on their expert opinion, the working group recommended that upper GI FMT should be used with caution in those with swallowing disorders (although administration via a gastrostomy tube would be acceptable), and also that no more than 50ml of FMT should be administered to the upper GI tract to minimise these risks.

Evidence:

There is randomised trial evidence demonstrating that upper GI administration of FMT for CDI is effective, although there are concerns about the possibility of aspiration and vomiting associated with its use (quality of evidence: 1+).

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, nasoduodenal, or nasojejunal tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate (strong).

Good practice point:

i. It is recommended that no more than 50ml of FMT is administered to the upper GI tract (conditional).

ii. Upper GI administration of FMT should be used with caution in those with swallowing disorders (strong).

8.5.2.3. Lower gastrointestinal tract administration of FMT:

FMT via enema: Successful treatment of *C. difficile* with FMT enema has been demonstrated[15,39,46,53,55,84,87] 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[15]. However, resolution rates in both arms only reached >80% after at least three enemas[15]. 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 (9/16 patients with recurrence vs 5/12 respectively)[11]. 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[17]**.** Efficacy is similar whether FMT is fresh or frozen, but modestly reduced when using a lyophilised FMT product[12]. Colonoscopic delivery of donor FMT into the ileum or caecum was associated with a 91% cure rate for recurrent CDI[13]. Observational studies highlighted similar success, describing cure rates of 88% (*n*=14/16)[73] and 91%[47] (*n*=21/23) in response to infusion of donor FMT into the caecum or terminal ileum. Flexible sigmoidoscopy appears to be an feasible option where full colonoscopy cannot be performed e.g. due to severity of colitis[59].

The amount of faecal suspension via enema has varied between 150-500mls[15,39,46,55,87]. 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%[83]. 250ml-400ml had a success rate of 100%[44], whereas infusions of up to 500-700ml were associated with cure rates of 92%[47]. 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.

Evidence:

Randomised trial evidence demonstrates the efficacy of FMT as treatment for CDI when administrated either as enema or via colonoscopy (quality of evidence: 1+).

Recommendation:

i. Colonoscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate (strong).

ii. Where colonoscopic administration is used, 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 delivery using colonoscopy or flexible sigmoidoscopy is not possible (strong).

8.5.2.4. 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[71,90] 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[88,121,132], including when lyophilised stool is used instead of frozen whole FMT[132].

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 [95], 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[95]. 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)[10]. 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.

Evidence:

Case series and RCT evidence demonstrate that capsulised FMT is efficacious in treating recurrent CDI, with comparable efficacy to other modalities of administration. However, capsules are a relatively new modality of administration, and further data are awaited on longer term efficacy and safety, and the optimal mechanics of preparation and administration (quality of evidence: +1).

Recommendation:

Capsulised FMT holds promise as a treatment option for recurrent CDI and 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 (conditional).

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

8.6.1. 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[133]. 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 RCTs involving patients with well-defined conditions and in which there was a primary clinical outcome. To date, there have been a total of 71 studies investigating the role of FMT in IBD; of these, only four are prospective randomised controlled trials, limited to patients with ulcerative colitis[134–137]. Three other studies investigated the use of FMT in irritable bowel syndrome[138], slow transit constipation[139], and hepatic encephalopathy[140]. Another study[141] compared the effect of autologous *vs* healthy donor FMT on people with metabolic syndrome, but this was deemed to be a

pilot scientific study rather than a formal randomised FMT clinical trial, so was not considered further.

8.6.2. Use of FMT for ulcerative colitis:

8.6.2.1. 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)[134]. 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[134,137]. Three of the four studies demonstrated that patients receiving donor FMT were significantly more likely to achieve clinical and endoscopic remission compared to placebo[135–137]. 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[135].

8.6.2.2. 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[135–137]. 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[134]. 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[137]. A further interesting observation in one study was a trend towards higher rates of remission with one particular donor[135].

8.6.2.3. 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[134]. In addition, one patient developed concurrent CDI[135]. No deaths were reported in any of the studies.

8.6.3. 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[138], 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[139]. 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).

8.6.4. Use of FMT in hepatic encephalopathy:

One small study has investigated the role of FMT in the management of hepatic encephalopathy (HE)[140]. 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.

8.6.5. Future directions for RCTs of FMT:

Currently there are a large number of 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.

Evidence:

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 (quality of evidence: 1+). The evidence for the use of FMT in hepatic encephalopathy is currently limited, and further well-designed RCTs are needed to evaluate its potential role (quality of evidence: 1-).

Recommendation:

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).

8.7. 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[127]). This section is therefore based on the working group's expert opinion and experience of developing FMT services.

8.7.1. 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[5], 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)[142] 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[143]. 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. 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.

Evidence:
Working group consensus opinion (quality of evidence: 4).

Good practice point:

i. The development of FMT centres should be encouraged (strong).

ii. FMT centres should work to raise awareness about FMT as a treatment option amongst clinicians caring for patients with CDI.

8.7.2. 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[18]. 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[18].
- 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*'[18], 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[144] and specials[145] 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[147]. 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[148]. 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[146], 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.

Evidence:

Working group consensus opinion and legal requirement (quality of evidence: 4).

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 countires other than the UK, FMT should only be manufactered following appropriate approval from the national authority of that country (strong).

8.7.3. 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.

Evidence:

Working group consensus opinion (quality of evidence: 4).

Recommendation:

A multidisciplinary team should be formed to deliver FMT services (strong).

8.7.4. 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[75]; 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.

Evidence:

Working group consensus opinion (quality of evidence: 4).

Recommendation:

Utilise suitable laboratory facilities and infrastructure for FMT production (strong).

8.7.5. 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[149] and Germany[150] to standardise and improve future clinical practice.

Evidence:

Working group consensus opinion (quality of evidence: 4).

Recommendation:

Ensure traceability of supply (strong).

8.7.6. 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.

Evidence:

Working group consensus opinion and legal requirement (quality of evidence: 4).

Recommendation:

Monitor, notify and investigate all adverse events and reactions related to FMT (strong).

8.7.7. 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.

Evidence:

Working group consensus opinion (quality of evidence: 4).

Recommendation:

Ensure the clinical governance of donor screening (strong).

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.

10. 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.

11. References:

1. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of Clostridium difficile as Clostridioides difficile (Hall and O'Toole 1935) Prévot 1938. *Anaerobe*. 2016;40:95-99.

doi:10.1016/j.anaerobe.2016.06.008.

2. Faecal microbiota transplant for recurrent Clostridium difficile infection | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/ipg485. Accessed October 2, 2017.

3. Health England P. Updated guidance on the management and treatment of Clostridium difficile infection. 2013. http://www.gov.uk/phe. Accessed March 20, 2017.

4. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: Update of the Treatment Guidance Document for Clostridium difficile Infection. *Clin Microbiol Infect*. 2014;20(s2):1-26. doi:10.1111/1469-0691.12418.

5. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut*. 2017;66(4):569-580. doi:10.1136/gutjnl-2016-313017.

6. König J, Siebenhaar A, Högenauer C, et al. Consensus report: faecal microbiota transfer - clinical applications and procedures. *Aliment Pharmacol Ther*. 2017;45(2):222-239. doi:10.1111/apt.13868.

7. Treating Clostridium difficile Infection With Fecal Microbiota Transplantation. *Clin Gastroenterol Hepatol*. 2011;9(12):1044-1049. doi:10.1016/J.CGH.2011.08.014.

8. Kump P, Krause R, Steininger C, et al. Empfehlungen zur Anwendung der fäkalen Mikrobiotatransplantation „Stuhltransplantation“: Konsensus der Österreichischen Gesellschaft für Gastroenterologie und Hepatologie (ÖGGH) in Zusammenarbeit mit der Österreichischen Gesellschaft für Infektiologie und Tropenmedizin (OEGIT). *Z Gastroenterol*. 2014;52(12):1485-1492. doi:10.1055/s-0034-1385562.

9. Faecal microbiota transplantation in recurrent Clostridium difficile infection: Recommendations from the French Group of Faecal microbiota Transplantation. *Dig Liver Dis*. 2016;48(3):242-247. doi:10.1016/J.DLD.2015.08.017.

10. Kao D, Roach B, Silva M, et al. Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection. *JAMA*. 2017;318(20):1985. doi:10.1001/jama.2017.17077.

11. Hota SS, Sales V, Tomlinson G, et al. Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent *Clostridium difficile* Infection: An Open-Label, Randomized Controlled Trial. *Clin Infect Dis*. 2017;64(3):265-271. doi:10.1093/cid/ciw731.

12. Jiang ZD, Ajami NJ, Petrosino JF, et al. Randomised clinical trial: faecal microbiota transplantation for recurrent Clostridum difficile infection – fresh, or frozen, or lyophilised microbiota from a small pool of healthy donors delivered by colonoscopy. *Aliment Pharmacol Ther*. 2017;45(7):899-908. doi:10.1111/apt.13969.

13. Kelly CR, Khoruts A, Staley C, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection. *Ann Intern Med*. 2016;165(9):609. doi:10.7326/M16-0271.

14. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile. *N Engl J Med*. 2013;368(5):407-415. doi:10.1056/NEJMoa1205037.

15. Lee CH, Steiner T, Petrof EO, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent *Clostridium difficile* Infection. *JAMA*. 2016;315(2):142. doi:10.1001/jama.2015.18098.

16. Youngster I, Sauk J, Pindar C, et al. Fecal Microbiota Transplant for Relapsing Clostridium difficile Infection Using a Frozen Inoculum From Unrelated Donors: A Randomized, Open-Label, Controlled Pilot Study. *Clin Infect Dis*. 2014;58(11):1515-1522. doi:10.1093/cid/ciu135.

17. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. *Aliment Pharmacol Ther*. 2015;41(9):835-843. doi:10.1111/apt.13144.

18. 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.

19. Thomas A. HTA Policy on the Regulation of Faecal Microbiota Transplant. 2015. http://www.bsg.org.uk/images/stories/docs/clinical/guidance/hta_pol_030_policy_regulation_of_fmt.pdf. Accessed October 3, 2017.

20. Khoruts A, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. *Nat Rev Gastroenterol Hepatol*. 2016;13(9):508-516. doi:10.1038/nrgastro.2016.98.

21. Petrof EO, Gloor GB, Vanner SJ, et al. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: "RePOOPulating" the gut. *Microbiome*. 2013;1(1):3. doi:10.1186/2049-2618-1-3.

22. Khanna S, Pardi DS, Kelly CR, et al. A Novel Microbiome Therapeutic Increases Gut Microbial

Diversity and Prevents Recurrent *Clostridium difficile* Infection. *J Infect Dis*. 2016;214(2):173-181. doi:10.1093/infdis/jiv766.

23. Martin J, Wilcox M. New and emerging therapies for Clostridium difficile infection. *Curr Opin Infect Dis*. 2016;29(6):546-554. doi:10.1097/QCO.0000000000000320.

24. Quraishi MN, Segal J, Mullish B, et al. National survey of practice of faecal microbiota transplantation for Clostridium difficile infection in the UK. *J Hosp Infect*. 2016. doi:10.1016/j.jhin.2016.10.023.

25. Porter RJ, Fogg C. Faecal microbiota transplantation for Clostridium difficile infection in the United Kingdom. *Clin Microbiol Infect*. 2015;21(6):578-582. doi:10.1016/j.cmi.2015.01.020.

26. Ding NS, Mullish BH, McLaughlin J, Hart A, Marchesi JR. Meeting update: faecal microbiota transplantation—bench, bedside, courtroom? *Frontline Gastroenterol*. November 2016:flgastro-2016-100752. doi:10.1136/flgastro-2016-100752.

27. Prior AR, Kevans D, McDowell L, Cudmore S, Fitzpatrick F. Treatment of Clostridium difficile infection: a national survey of clinician recommendations and the use of faecal microbiota transplantation. *J Hosp Infect*. 2017;95(4):438-441. doi:10.1016/j.jhin.2016.10.004.

28. 1995 - The well-built clinical question: a key to evidence-based decisions (Editorial) | 1995 Nov-Dec : Volume 123, Number 3, Page A12 | ACP Journal Club Archives. https://acpjc.acponline.org/Content/123/3/issue/ACPJC-1995-123-3-A12.htm. Accessed October 18, 2017.

29. SIGN 50. 2015. http://www.sign.ac.uk/assets/sign50_2015.pdf. Accessed October 18, 2017.

30. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training. http://training.cochrane.org/handbook. Accessed October 18, 2017.

31. 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.

32. 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.

33. 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.

34. 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.

35. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD.

36. Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* Colitis: Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube. *Clin Infect Dis*. 2003;36(5):580-585. doi:10.1086/367657.

37. Garborg K, Waagsbø B, Stallemo A, Matre J, Sundøy A. Results of faecal donor instillation therapy for recurrent Clostridium difficile-associated diarrhoea. *Scand J Infect Dis*. 2010;42(11-12):857-861. doi:10.3109/00365548.2010.499541.

38. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent Clostridium difficile Infection. *Am J Gastroenterol*. 2012;107(5):761-767. doi:10.1038/ajg.2011.482.

39. Lee CH, Belanger JE, Kassam Z, et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory Clostridium difficile infection using single to multiple fecal microbiota transplantation via retention enema. *Eur J Clin Microbiol Infect Dis*. 2014;33(8):1425-1428. doi:10.1007/s10096-014-2088-9.

40. Mattila E, Uusitalo-Seppälä R, Wuorela M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. *Gastroenterology*. 2012;142(3):490-496. doi:10.1053/j.gastro.2011.11.037.

41. Rohlke F, Surawicz CM, Stollman N. Fecal Flora Reconstitution for Recurrent Clostridium difficile Infection: Results and Methodology. *J Clin Gastroenterol*. 2010;44(8):567-570. doi:10.1097/MCG.0b013e3181dadb10.

42. Rubin TA, Gessert CE, Aas J, Bakken JS. Fecal microbiome transplantation for recurrent Clostridium difficile infection: Report on a case series. *Anaerobe*. 2013;19:22-26. doi:10.1016/j.anaerobe.2012.11.004.

43. Satokari R, Mattila E, Kainulainen V, Arkkila PET. Simple faecal preparation and efficacy of frozen inoculum in faecal microbiota transplantation for recurrent *Clostridium difficile*

infection - an observational cohort study. *Aliment Pharmacol Ther*. 2015;41(1):46-53. doi:10.1111/apt.13009.

44. Yoon SS, Brandt LJ. Treatment of Refractory/Recurrent C. difficile-associated Disease by Donated Stool Transplanted Via Colonoscopy. *J Clin Gastroenterol*. 2010;44(8):562-566. doi:10.1097/MCG.0b013e3181dac035.

45. Zainah H, Hassan M, Shiekh-Sroujieh L, Hassan S, Alangaden G, Ramesh M. Intestinal microbiota transplantation, a simple and effective treatment for severe and refractory Clostridium difficile infection. *Dig Dis Sci*. 2014;60(1):181-185. doi:10.1007/s10620-014-3296-y.

46. Kassam Z. Fecal Transplant via Retention Enema for Refractory or Recurrent <emph type=“ital”>Clostridium difficile</emph> Infection. *Arch Intern Med*. 2012;172(2):191. doi:10.1001/archinte.172.2.191.

47. Patel NC, Griesbach CL, DiBaise JK, Orenstein R. Fecal Microbiota Transplant for Recurrent Clostridium difficile Infection: Mayo Clinic in Arizona Experience. *Mayo Clin Proc*. 2013;88(8):799-805. doi:10.1016/j.mayocp.2013.04.022.

48. Crobach MJT, Planche T, Eckert C, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection. *Clin Microbiol Infect*. 2016;22 Suppl 4:S63-81. doi:10.1016/j.cmi.2016.03.010.

49. Ray A, Smith R, Breaux J. Fecal Microbiota Transplantation for Clostridium difficile Infection: The Ochsner Experience. *Ochsner J*. 2014;14(4):538-544. http://www.ncbi.nlm.nih.gov/pubmed/25598718. Accessed October 9, 2017.

50. Kao, D., Roach B., Hotte, N., Silva, M., Madsen, K., Beck, P., Louie T, Canadian Association for the Study of the Liver. A Prospective, Dual Center, Randomized Trial Comparing Colonoscopy versus Capsule Delivered Fecal Microbiota Transplantation (FMT) in the Management of Recurrent Clostridium Difficile Infection (RCDI). In: *Canadian Journal of Gastroenterology and Hepatology*. Vol 2016. Hindawi; 2016:1-204. doi:10.1155/2016/4792898.

51. MacConnachie AA, Fox R, Kennedy DR, Seaton RA. Faecal transplant for recurrent Clostridium difficile-associated diarrhoea: a UK case series. *QJM*. 2009;102(11):781-784. doi:10.1093/qjmed/hcp118.

52. Kelly CR, de Leon L, Jasutkar N. Fecal Microbiota Transplantation for Relapsing Clostridium difficile Infection in 26 Patients. *J Clin Gastroenterol*. 2012;46(2):145-149.

doi:10.1097/MCG.0b013e318234570b.

53. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-Term Follow-Up of Colonoscopic Fecal Microbiota Transplant for Recurrent Clostridium difficile Infection. *Am J Gastroenterol*. 2012;107(7):1079-1087. doi:10.1038/ajg.2012.60.

54. Pathak R, Enuh HA, Patel A, Wickremesinghe P. Treatment of relapsing Clostridium difficile infection using fecal microbiota transplantation. *Clin Exp Gastroenterol*. 2013;7:1-6. doi:10.2147/CEG.S53410.

55. Agrawal M, Aroniadis OC, Brandt LJ, et al. The Long-term Efficacy and Safety of Fecal Microbiota Transplant for Recurrent, Severe, and Complicated Clostridium difficile Infection in 146 Elderly Individuals. *J Clin Gastroenterol*. 2015;50(5):1. doi:10.1097/MCG.0000000000000410.

56. Fischer M, Kao D, Kelly C, et al. Fecal Microbiota Transplantation is Safe and Efficacious for Recurrent or Refractory Clostridium difficile Infection in Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2016;22(10):2402-2409. doi:10.1097/MIB.0000000000000908.

57. 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. *J Clin Gastroenterol*. 2015;50(5):1. doi:10.1097/MCG.0000000000000374.

58. Fischer M, Kao D, Mehta SR, et al. Predictors of Early Failure After Fecal Microbiota Transplantation for the Therapy of Clostridium Difficile Infection: A Multicenter Study. *Am J Gastroenterol*. 2016;111(7):1024-1031. doi:10.1038/ajg.2016.180.

59. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. *Am J Gastroenterol*. 2014;109(7):1065-1071. doi:10.1038/ajg.2014.133.

60. Lagier J-C, Delord M, Million M, et al. Dramatic reduction in Clostridium difficile ribotype 027-associated mortality with early fecal transplantation by the nasogastric route: a preliminary report. *Eur J Clin Microbiol Infect Dis*. 2015;34(8):1597-1601. doi:10.1007/s10096-015-2394-x.

61. Camacho-Ortiz A, Gutiérrez-Delgado EM, Garcia-Mazcorro JF, et al. Randomized clinical trial to evaluate the effect of fecal microbiota transplant for initial Clostridium difficile infection in intestinal microbiome. Green J, ed. *PLoS One*. 2017;12(12):e0189768. doi:10.1371/journal.pone.0189768.

62. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus Vancomycin for *Clostridium*

difficile Infection. *N Engl J Med*. 2011;364(5):422-431. doi:10.1056/NEJMoa0910812.

63. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection. *N Engl J Med*. 2017;376(4):305-317. doi:10.1056/NEJMoa1602615.

64. Guery B, Menichetti F, Anttila V-J, et al. Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis*. December 2017. doi:10.1016/S1473-3099(17)30751-X.

65. McFarland L V., Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. *Am J Gastroenterol*. 2002;97(7):1769-1775. doi:10.1111/j.1572-0241.2002.05839.x.

66. Sirbu BD, Soriano MM, Manzo C, Lum J, Gerding DN, Johnson S. Vancomycin Taper and Pulse Regimen With Careful Follow-up for Patients With Recurrent Clostridium difficile Infection. *Clin Infect Dis*. 2017;65(8):1396-1399. doi:10.1093/cid/cix529.

67. Gentry CA, Giancola SE, Thind S, Kurdgelashvili G, Skrepnek GH, Williams RJ. A Propensity-Matched Analysis Between Standard Versus Tapered Oral Vancomycin Courses for the Management of Recurrent Clostridium difficile Infection. *Open Forum Infect Dis*. 2017;4(4):ofx235. doi:10.1093/ofid/ofx235.

68. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012;12(4):281-289. doi:10.1016/S1473-3099(11)70374-7.

69. Khan MA, Sofi AA, Ahmad U, et al. Efficacy and safety of, and patient satisfaction with, colonoscopic-administered fecal microbiota transplantation in relapsing and refractory community- and hospital-acquired Clostridium difficile infection. *Can J Gastroenterol Hepatol*. 2014;28(8):434-438. http://www.ncbi.nlm.nih.gov/pubmed/25014180. Accessed October 9, 2017.

70. Tauxe WM, Haydek JP, Rebolledo PA, et al. Fecal microbiota transplant for Clostridium difficile infection in older adults. *Therap Adv Gastroenterol*. 2016;9(3):273-281. doi:10.1177/1756283X15622600.

71. 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;312(17):1772. doi:10.1001/jama.2014.13875.

72. 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.

73. Costello SP, Conlon MA, Vuaran MS, Roberts-Thomson IC, Andrews JM. Faecal microbiota transplant for recurrent Clostridium difficile infection using long-term frozen stool is effective: Clinical efficacy and bacterial viability data. *Aliment Pharmacol Ther*. 2015;42(8):1011-1018. doi:10.1111/apt.13366.

74. Hui J, Kench JG, Chitturi S, et al. Long-Term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. *Hepatology*. 2003;38(2):420-427. doi:10.1053/jhep.2003.50320.

75. Allegretti JR, Korzenik JR, Hamilton MJ. Fecal microbiota transplantation via colonoscopy for recurrent C. difficile Infection. *J Vis Exp*. 2014;(94). doi:10.3791/52154.

76. van Beurden YH, de Groot PF, van Nood E, Nieuwdorp M, Keller JJ, Goorhuis A. Complications, effectiveness, and long term follow-up of fecal microbiota transfer by nasoduodenal tube for treatment of recurrent Clostridium difficile infection. *United Eur Gastroenterol J*. 2017;5(6):868-879. doi:10.1177/2050640616678099.

77. Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile Infection With Fecal Microbiota Transplantation. *Clin Gastroenterol Hepatol*. 2011;9(12):1044-1049. doi:10.1016/j.cgh.2011.08.014.

78. Allegretti JR, Allegretti AS, Phelps E, Xu H, Kassam Z, Fischer M. Asymptomatic Clostridium difficile carriage rate post-fecal microbiota transplant is low: a prospective clinical and stool assessment. *Clin Microbiol Infect*. November 2017. doi:10.1016/J.CMI.2017.10.022.

79. Baxter M, Colville A. Adverse events in faecal microbiota transplant: a review of the literature. *J Hosp Infect*. 2016;92(2):117-127. doi:10.1016/j.jhin.2015.10.024.

80. Hefazi M, Patnaik MM, Hogan WJ, Litzow MR, Pardi DS, Khanna S. Safety and Efficacy of Fecal Microbiota Transplant for Recurrent Clostridium difficile Infection in Patients With Cancer Treated With Cytotoxic Chemotherapy: A Single-Institution Retrospective Case Series. *Mayo Clin Proc*. 2017;92(11):1617-1624. doi:10.1016/j.mayocp.2017.08.016.

81. Qazi T, Amaratunga T, Barnes EL, Fischer M, Kassam Z, Allegretti JR. The risk of inflammatory

bowel disease flares after fecal microbiota transplantation: Systematic review and meta-analysis. *Gut Microbes*. July 2017:1-15. doi:10.1080/19490976.2017.1353848.

82. Ianiro G, Valerio L, Masucci L, et al. Predictors of failure after single faecal microbiota transplantation in patients with recurrent Clostridium difficile infection: results from a 3-year, single-centre cohort study. *Clin Microbiol Infect*. 2017;23(5):337.e1-337.e3. doi:10.1016/j.cmi.2016.12.025.

83. Fecal Transplantation, Through Colonoscopy, Is Effective Therapy for Recurrent Clostridium difficile Infection. *Gastroenterology*. 2012;142(3):490-496. doi:10.1053/J.GASTRO.2011.11.037.

84. Meighani A, Hart BR, Mittal C, Miller N, John A, Ramesh M. Predictors of fecal transplant failure. *Eur J Gastroenterol Hepatol*. 28:826-830. doi:10.1097/MEG.0000000000000614.

85. Alrabaa S, Jariwala R, Zeitler K, Montero J. Fecal microbiota transplantation outcomes in immunocompetent and immunocompromised patients: A single-center experience. *Transpl Infect Dis*. 2017;19(4):e12726. doi:10.1111/tid.12726.

86. Cohen NA, Livovsky DM, Yaakobovitch S, et al. A Retrospective Comparison of Fecal Microbial Transplantation Methods for Recurrent Clostridium Difficile Infection. *Isr Med Assoc J*. 2016;18(10):594-599.

87. 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. doi:10.1093/cid/civ938.

88. 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;15(1):191. doi:10.1186/s12879-015-0930-z.

89. Kao D, Roach B, Beck P, Hotte N, Madsen K, Louie T. 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. doi:http://dx.doi.org/10.1038/ajg.2015.294.

90. Youngster I, Mahabamunuge J, Systrom HK, et al. Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent Clostridium difficile infection. *BMC Med*. 2016;14(1):134. doi:10.1186/s12916-016-0680-9.

91. Anand R, Song Y, Garg S, et al. Effect of Aging on the Composition of Fecal Microbiota in

Donors for FMT and Its Impact on Clinical Outcomes. *Dig Dis Sci*. 2017;62(4):1002-1008. doi:10.1007/s10620-017-4449-6.

92. Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. *Open forum Infect Dis*. 2015;2(1):ofv004. doi:10.1093/ofid/ofv004.

93. Fischer M, Kao D, Kassam Z, et al. Stool Donor Body Mass Index Does Not Affect Recipient Weight After a Single Fecal Microbiota Transplantation for C. difficile Infection. *Clin Gastroenterol Hepatol*. December 2017. doi:10.1016/J.CGH.2017.12.007.

94. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier. *Gut*. 2016;65(2):330-339. doi:10.1136/gutjnl-2015-309990.

95. Allegretti JR, Fischer M, Papa E, et al. Su1738 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. *Gastroenterology*. 2016;150(4):S540. doi:10.1016/S0016-5085(16)31855-8.

96. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Med*. 2016;8(1):39. doi:10.1186/s13073-016-0294-z.

97. Lange K, Buerger M, Stallmach A, Bruns T. Effects of Antibiotics on Gut Microbiota. *Dig Dis*. 2016;34(3):260-268. doi:10.1159/000443360.

98. Becattini S, Taur Y, Pamer EG. Antibiotic-Induced Changes in the Intestinal Microbiota and Disease. *Trends Mol Med*. 2016;22(6):458-478. doi:10.1016/j.molmed.2016.04.003.

99. Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. *Gut*. 2016;65(11):1906-1915. doi:10.1136/gutjnl-2016-312297.

100. J.R. A, J.R. K, M.J. H. Intestinal microbiome restoration for recurrent clostridium difficile infection in patients with concurrent inflammatory bowel disease. *Gastroenterology*. 2015;148(4 SUPPL. 1):S869.

101. Boostrom SY, Mathis KL, Pendlimari R, et al. Burden of Clostridium difficile on the healthcare system. *Inflamm Bowel Dis*. 2012;18(1):994-1002. doi:10.1126/science.1241214.

102. London: TSO Guidelines for the Blood Transfusion Services in the United Kingdom 7 th Edition 2005 TSO Accredited Agents Web Access.

103. Emanuelsson F, Claesson BEB, Ljungström L, Tvede M, Ung K-A. Faecal microbiota

transplantation and bacteriotherapy for recurrent Clostridium difficile infection: A retrospective evaluation of 31 patients. *Scand J Infect Dis*. 2014;46(2):89-97. doi:10.3109/00365548.2013.858181.

104. Endtz HP, van den Braak N, van Belkum A, et al. Fecal carriage of vancomycin-resistant enterococci in hospitalized patients and those living in the community in The Netherlands. *J Clin Microbiol*. 1997;35(12):3026-3031. http://www.ncbi.nlm.nih.gov/pubmed/9399488. Accessed February 15, 2018.

105. Willems RJL, Top J, van Santen M, et al. Global spread of vancomycin-resistant Enterococcus faecium from distinct nosocomial genetic complex. *Emerg Infect Dis*. 2005;11(6):821-828. doi:10.3201/eid1106.041204.

106. Gough E, Shaikh H, Manges AR. Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent Clostridium difficile Infection. *Clin Infect Dis*. 2011;53(10):994-1002. doi:10.1093/cid/cir632.

107. Sleight SC, Wigginton NS, Lenski RE. Increased susceptibility to repeated freeze-thaw cycles in Escherichia coli following long-term evolution in a benign environment. *BMC Evol Biol*. 2006;6(1):104. doi:10.1186/1471-2148-6-104.

108. O'Brien CL, Allison GE, Grimpen F, Pavli P. Impact of colonoscopy bowel preparation on intestinal microbiota. *PLoS One*. 2013;8(5):e62815. doi:10.1371/journal.pone.0062815.

109. Mai V, Stine OC. Bowel preparation for colonoscopy: relevant for the gut's microbiota? *Gut*. 2015;64(10):1504-1505. doi:10.1136/gutjnl-2014-308937.

110. Jalanka J, Salonen A, Salojärvi J, et al. Effects of bowel cleansing on the intestinal microbiota. *Gut*. 2015;64(10):1562-1568. doi:10.1136/gutjnl-2014-307240.

111. Mai V, Greenwald B, Glenn Morris J, Raufman J-P, Stine OC. Effect of bowel preparation and colonoscopy on post-procedure intestinal microbiota composition. *Gut*. 2006;55(12):1822-1823. doi:10.1136/gut.2006.108266.

112. Harrell L, Wang Y, Antonopoulos D, et al. Standard Colonic Lavage Alters the Natural State of Mucosal-Associated Microbiota in the Human Colon. Singh SR, ed. *PLoS One*. 2012;7(2):e32545. doi:10.1371/journal.pone.0032545.

113. Chin SM, Sauk J, Mahabamunuge J, Kaplan JL, Hohmann EL, Khalili H. Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection in Patients With Inflammatory Bowel Disease: A Single-Center Experience. *Clin Gastroenterol Hepatol*. 2017;15(4):597-599.

doi:10.1016/j.cgh.2016.11.028.

114. Wang S, Xu M, Wang W, et al. Systematic Review: Adverse Events of Fecal Microbiota Transplantation. *PLoS One*. 2016;11(8):e0161174. doi:10.1371/journal.pone.0161174.

115. Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. *Clin Gastroenterol Hepatol*. 2016;14(10):1433-1438. doi:10.1016/j.cgh.2016.02.018.

116. de Jager CPC, Wever PC, Gemen EFA, et al. Proton pump inhibitor therapy predisposes to community-acquired *Streptococcus pneumoniae* pneumonia. *Aliment Pharmacol Ther*. 2012;36(10):941-949. doi:10.1111/apt.12069.

117. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. *Gut*. 2016;65(5):740-748. doi:10.1136/gutjnl-2015-310376.

118. McDonald EG, Milligan J, Frenette C, Lee TC. Continuous Proton Pump Inhibitor Therapy and the Associated Risk of Recurrent *Clostridium difficile* Infection. *JAMA Intern Med*. 2015;175(5):784. doi:10.1001/jamainternmed.2015.42.

119. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-Associated Diarrhea and Proton Pump Inhibitor Therapy: A Meta-Analysis. *Am J Gastroenterol*. 2012;107(7):1001-1010. doi:10.1038/ajg.2012.179.

120. Girotra M, Garg S, Anand R, Song Y, Dutta SK. Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection in the Elderly: Long-Term Outcomes and Microbiota Changes. *Dig Dis Sci*. 2016;61(10):3007-3015. doi:10.1007/s10620-016-4229-8.

121. Hagel S, Fischer A, Ehlermann P, et al. Fecal Microbiota Transplant in Patients With Recurrent Clostridium Difficile Infection. *Dtsch Arztebl Int*. 2016;113(35-36):583-589. doi:10.3238/arztebl.2016.0583.

122. Department of Health (UK). Management and decontamination of flexible endoscopes (HTM 01-06) - GOV.UK. https://www.gov.uk/government/publications/management-and-decontamination-of-flexible-endoscopes. Accessed December 19, 2017.

123. British Society of Gastroenterology. Guidance on Decontamination of Equipment for Gastrointestinal Endoscopy: 2017 Edition. https://www.bsg.org.uk/resource/guidance-on-decontamination-of-equipment-for-gastrointestinal-endoscopy-2017-edition.html. Accessed December 19, 2017.

124. Loveday HP, Wilson JA, Pratt RJ, et al. epic3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England. *J Hosp Infect*. 2014;86(1):S1-S70. doi:10.1016/S0195-6701(13)60012-2.

125. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal Microbiota Transplantation for Clostridium difficile Infection: Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2013;108(4):500-508. doi:10.1038/ajg.2013.59.

126. Allegretti JR, Kao D, Sitko J, Fischer M, Kassam Z. Early antibiotic use post-fecal microbiota transplantation increases the risk of treatment failure. *Clin Infect Dis*. August 2017. doi:10.1093/cid/cix684.

127. Terveer EM, van Beurden YH, Goorhuis A, et al. How to: Establish and run a stool bank. *Clin Microbiol Infect*. 2017;23(12):924-930. doi:10.1016/j.cmi.2017.05.015.

128. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2017;46(5):479-493. doi:10.1111/apt.14201.

129. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. *J Clin Gastroenterol*. 2014;48(8):693-702. doi:10.1097/MCG.0000000000000046.

130. D. D, J. R, S. G, et al. Fecal microbiota transplantation for clostridium difficile infection a systematic review. *Ann Intern Med*. 2015;162(9):630-638.

131. Baxter M, Ahmad T, Colville A, Sheridan R. Fatal Aspiration Pneumonia as a Complication of Fecal Microbiota Transplant. *Clin Infect Dis*. 2015;61(1):136-137. doi:10.1093/cid/civ247.

132. Hecker MT, Obrenovich ME, Cadnum JL, et al. Fecal Microbiota Transplantation by Freeze-Dried Oral Capsules for Recurrent Clostridium difficile Infection. *Open forum Infect Dis*. 2016;3(2):ofw091. doi:10.1093/ofid/ofw091.

133. Ni J, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol*. 2017;14(10):573-584. doi:10.1038/nrgastro.2017.88.

134. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology*. 2015;149(1):110-118.e4. doi:10.1053/j.gastro.2015.03.045.

135. Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in

Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology*. 2015;149(1):102-109.e6. doi:10.1053/j.gastro.2015.04.001.

136. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet (London, England)*. 2017;389(10075):1218-1228. doi:10.1016/S0140-6736(17)30182-4.

137. Costello S, Waters O, Bryant R. Short Duration, Low Intensity, Pooled Fecal Microbiota Transplantation Induces Remission in Patients with Mild-Moderately Active Ulcerative Colitis: A Randomised Controlled Trial. (Abstract). *Gastroenterology*. 152(5):S198-S199.

138. Johnsen PH, Hilpüsch F, Cavanagh JP, et al. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *lancet Gastroenterol Hepatol*. 2018;3(1):17-24. doi:10.1016/S2468-1253(17)30338-2.

139. Tian H, Ge X, Nie Y, et al. Fecal microbiota transplantation in patients with slow-transit constipation: A randomized, clinical trial. Green J, ed. *PLoS One*. 2017;12(2):e0171308. doi:10.1371/journal.pone.0171308.

140. Bajaj JS, Kassam Z, Fagan A, et al. Fecal Microbiota Transplant from a Rational Stool Donor Improves Hepatic Encephalopathy: A Randomized Clinical Trial. *Hepatology*. June 2017. doi:10.1002/hep.29306.

141. Vrieze A, Van Nood E, Holleman F, et al. Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome. *Gastroenterology*. 2012;143(4):913-916.e7. doi:10.1053/j.gastro.2012.06.031.

142. Home — OpenBiome. http://www.openbiome.org/home/. Accessed October 19, 2017.

143. Quraishi MN, Segal J, Mullish B, et al. National survey of practice of faecal microbiota transplantation for Clostridium difficile infection in the UK. *J Hosp Infect*. 2017;95(4):444-445. doi:10.1016/j.jhin.2016.10.023.

144. Medicines and Healthcare products Regulatory Agency. Apply for manufacturer or wholesaler of medicines licences - GOV.UK. https://www.gov.uk/guidance/apply-for-manufacturer-or-wholesaler-of-medicines-licences#apply-for-a-manufacturerimporter-licence. Accessed February 15, 2018.

145. 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.

146. Great Britain. Medicines and Healthcare products Regulatory Agency. *Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017*.

147. Edelstein CA, Kassam Z, Daw J, Smith MB, Kelly CR. The regulation of fecal microbiota for transplantation: An international perspective for policy and public health. *Clin Res Regul Aff*. 2015;32(3):99-107. doi:10.3109/10601333.2015.1046602.

148. Human Tissue Authority Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment. 2010. https://www.hta.gov.uk/sites/default/files/Annex_-_Guide_to_Quality_and_Safety_Assurance_for_Tissues_and_Cells_for_Patient_Treatment.pdf. Accessed October 9, 2017.

149. Kelly CR, Kim AM, Laine L, Wu GD. The AGA's Fecal Microbiota Transplantation National Registry: An Important Step Toward Understanding Risks and Benefits of Microbiota Therapeutics. *Gastroenterology*. 2017;152(4):681-684. doi:10.1053/j.gastro.2017.01.028.

150. Vehreschild M. MicroTrans - A Multicenter Registry of Fecal Microbiota Transplantation (MicroTrans). doi:10.1016/j.cmi.2015.06.027.

12. Figure legends and tables:

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

Table 1: Evidence statements and recommendations. A. Levels of evidence for intervention studies; B. Recommendation grading.

A. Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series.
4	Expert opinion
B. Recommendations	
Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations	

than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation. Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.
For **'strong'** recommendations on interventions that 'should' be used, the working group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For 'strong' recommendations on interventions that 'should not' be used, the working group is confident that, for the vast majority of people, the intervention (or interventions) will do more harm than good. For **'conditional'** recommendations on interventions that should be 'considered', the working group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
Good practice points are recommended best practice based on the clinical experience of the guideline working group.

Table 2: Recommended donor history/ questionnaire: A positive response to any of these questions should result in exclusion from further consideration as a donor.

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 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.

Table 3: 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 4: 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 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.

13.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.

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

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)

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

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

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

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.

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.

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

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.

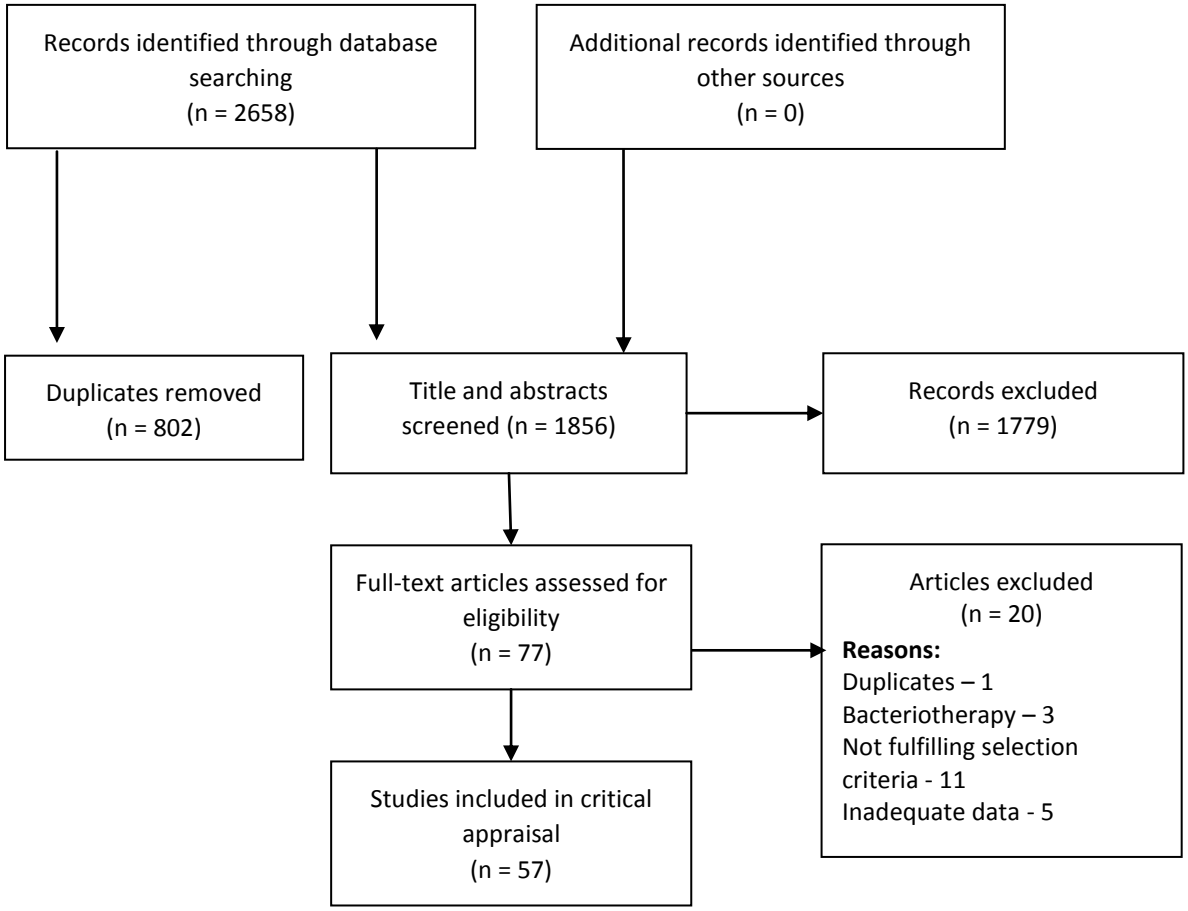
12. 10 not 11

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

Limits:

1. After 1980.
2. Studies in English only.
3. Human studies only.
4. Randomised trials only.

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 included:

- HRPA (Ireland) (Eadaoin Griffin)
- ESCMID
- OpenBiome
- NHS Wales
- NHS Scotland
- ECDC
- Royal College of Pathologists
- Royal College of General Practitioners
- Infection Prevention Society

- Public Health England
- Royal College of Physicians
- Royal College of Nursing
- Royal College of Surgeons
- MRSA Action
- HSCNI
- Sally Cudmore
- Ngozi Elimogo
- Vanya Gant
- Bram Goorguis
- Robert Porter
- Laura Prtak
- Ray Sheridan
- Robert Watson
- Mark Wilks

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

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

Additional Appendices:

A: Scope.

B: Declarations of interest.

C: Clinical evidence tables.

D: Excluded clinical studies.

E: Peer review.