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

Supplementary Material 1: General additional information:

1. Additional information:

1.1. Lay summary:

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

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

1.2. Working Party Report

1.2.1. What is the Working Party Report?

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

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

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

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

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

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

1.2.4. Who are these guidelines for?

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

1.2.5. How are the guidelines structured?

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

1.2.6. Aim

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

1.3. Implementation of these guidelines:

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

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

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

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

1.3.3. E-learning tools:

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

2. Appendices

Appendix 1: Glossary

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

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

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

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

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

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

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

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

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

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

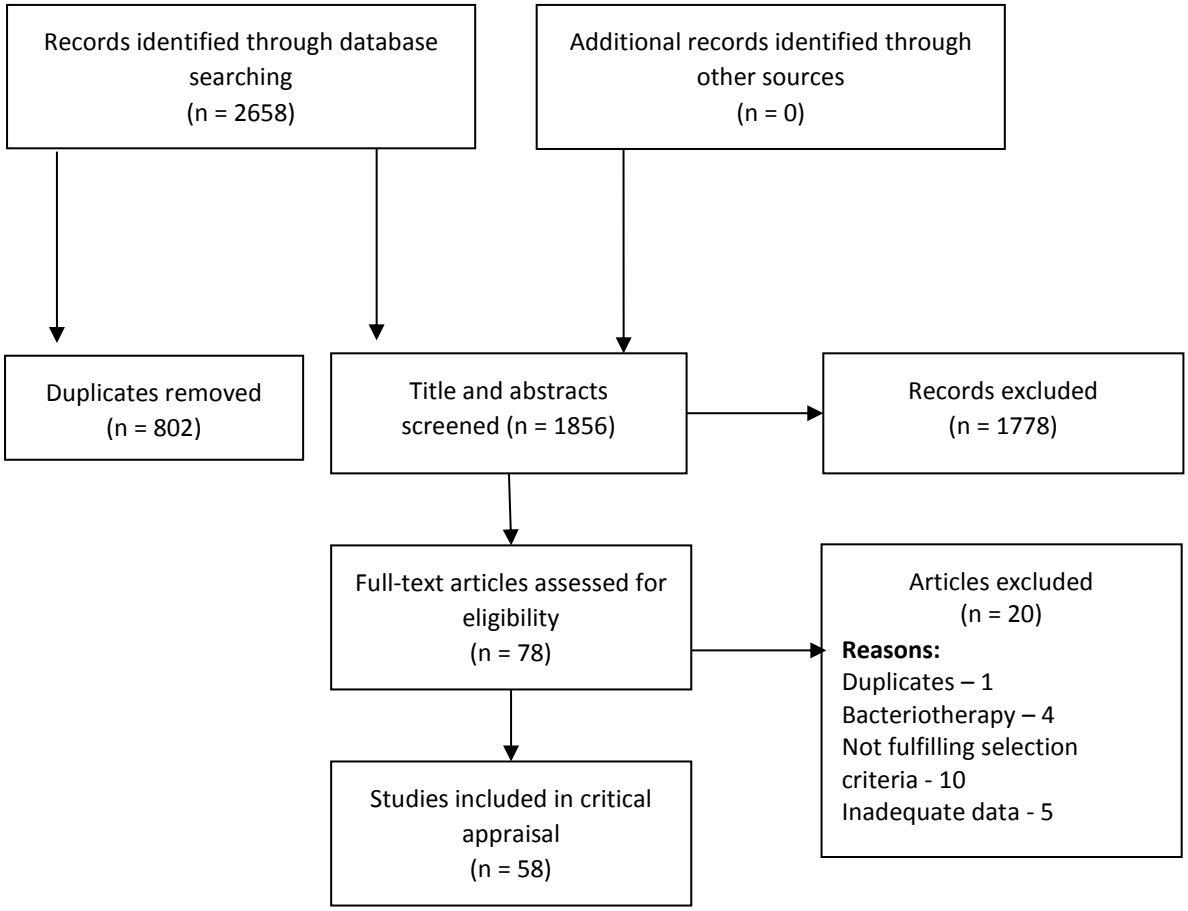
13. limit 12 to (clinical trial or randomized controlled trial or controlled clinical trial)

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 (as well as to provide feedback in stakeholder consultation) included:

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

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

Appendix 4. Continuing Professional Development material

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

Answer: d

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

Answer: c

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

Answer: a

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

Answer: e

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

d) Medical Drugs and Healthcare Products Regulatory Authority

e) None of the above

Answer: b

3. References:

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

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

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

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