**Main Appendix:**

**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***

1. ***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-CDIantibiotics 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

1. ***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.
5. ***Summary of the data extraction and literature review process (includes Q1-6):***

Duplicates removed
(n = 802)

Articles excluded

(n = 20)

**Reasons:**

Duplicates – 1

Bacteriotherapy – 4

Not fulfilling selection criteria - 10

Inadequate data - 5

Records identified through database searching
(n = 2658)

Additional records identified through other sources
(n = 0)

Title and abstracts screened (n = 1856)

Records excluded
(n = 1778)

Full-text articles assessed for eligibility
(n = 78)

Studies included in critical appraisal
(n = 58)

**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?
	1. Immunocompromised patients
	2. Decompensated liver disease
	3. Heart failure
	4. History of anaphylactic food allergy
	5. A previous failed FMT

Answer: d

1. Where is FMT best sourced, if available?
	1. Related healthy donor
	2. Health care professional
	3. Centralised stool bank
	4. Pooled from multiple donors
	5. Any of above

Answer: c

1. What is the maximum recommended length of time between stool donation and stool processing?
	1. 6 hours
	2. 7 hours
	3. 8 hours
	4. 9 hours
	5. 10 hours

Answer: a

1. For which non-CDI condition is FMT currently recommended?
	1. Irritable bowel syndrome
	2. Obesity and metabolic syndrome
	3. Parkinson’s disease
	4. Ulcerative colitis
	5. None of the above

Answer: e

1. When considering setting up an FMT service in the UK, which organisation should be contacted to seek guidance in establishing the service?
	1. Medicines and Healthcare Products and Regulatory Agency
	2. Medicines and Healthcare Products Regulatory Authority
	3. Medical Drugs and Healthcare Products and Regulatory Agency
	4. Medical Drugs and Healthcare Products Regulatory Authority
	5. 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.